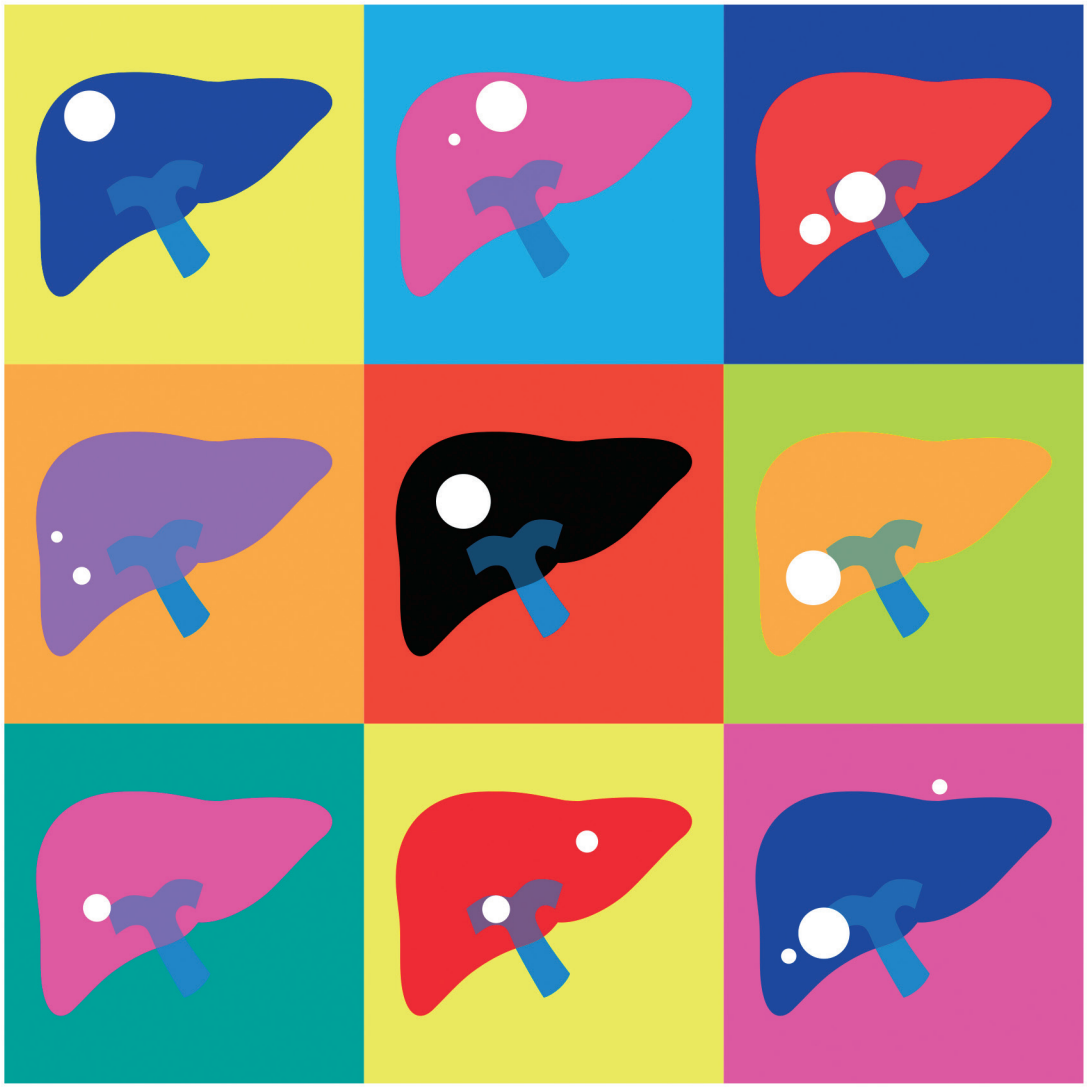
VOLUME 28 NUMBER 4 OCTOBER 2022

pISSN 2287-2728
eISSN 2387-285X

CLINICAL and MOLECULAR HEPATOLOGY

The forum for latest knowledge of hepatobiliary diseases



2022 KLCA-NCC HCC practice guideline

Insulin resistance index and NAFLD

Auranofin inhibits NAFLD

Depression and anxiety in HCC

KASL

pISSN 2287-2728
eISSN 2287-285X

CLINICAL and MOLECULAR HEPATOLOGY

https://doi.org/10.3350/cmh.2022.0087
Clinical and Molecular Hepatology 2022;28:890-911

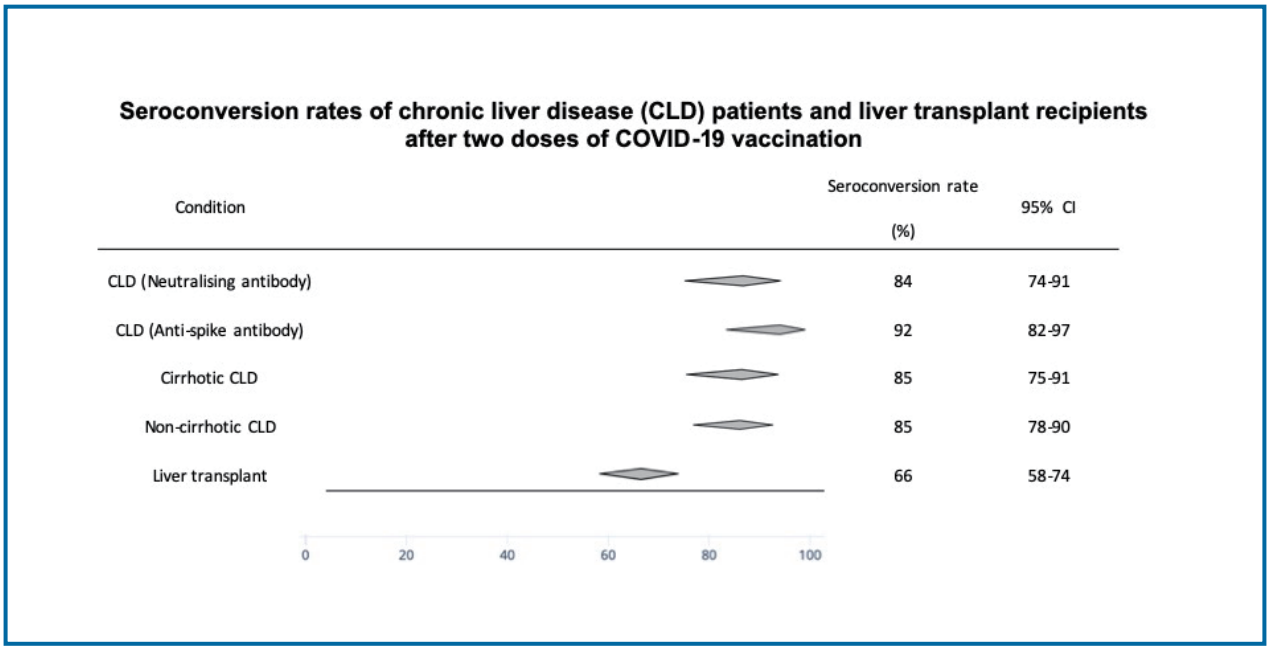
Original Article

COVID-19 vaccine immunogenicity among chronic liver disease patients and liver transplant recipients: A meta-analysis

Ka Shing Cheung[1,2,*], Chiu Hang Mok[3,*], Xianhua Mao[1], Ruiqi Zhang[1], Ivan FN Hung[1], Wai Kay Seto[1,2,4], and Man Fung Yuen[1,4]

[1]Department of Medicine, Queen Mary Hospital, School of Clinical Medicine, The University of Hong Kong, Hong Kong; [2]Department of Medicine, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China; [3]School of Clinical Medicine, The University of Hong Kong, Hong Kong; [4]State Key Laboratory of Liver Research, The University of Hong Kong, Hong Kong

Graphical Abstract



Study Highlights

- Chronic liver disease patients, either cirrhotic or non-cirrhotic, have good humoral response to inactivated or mRNA COVID-19 vaccine
- Liver transplant recipients have lower humoral response to mRNA vaccine and hence early booster dose should be considered
- COVID-19 vaccine has good safety profile in both chronic liver disease patients and liver transplant recipients

Background/Aims: Data of coronavirus disease 2019 (COVID-19) vaccine immunogenicity among chronic liver disease (CLD) and liver transplant (LT) patients are conflicting. We performed meta-analysis to examine vaccine immunogenicity regarding etiology, cirrhosis status, vaccine platform and type of antibody.

Methods: We collected data via three databases from inception to February 16, 2022, and reported pooled seroconversion rate, T cell response and safety data after two vaccine doses.

Results: Twenty-eight (CLD only: 5; LT only: 18; both: 2; LT with third dose: 3) observational studies of 3,945 patients were included. For CLD patients, seroconversion rate ranged between 84% (95% confidence interval [CI], 76–90%) and 91% (95% CI, 83–95%), based predominantly on neutralizing antibody and anti-spike antibody, respectively. Seroconversion rate was 81% (95% CI, 76–86%) in chronic hepatitis B, 96% (95% CI, 93–97%) in non-alcoholic fatty liver disease, 85% (95% CI, 75–91%) in cirrhosis and 85% (95% CI, 78–90%) in non-cirrhosis, 86% (95% CI, 78–92%) for inactivated vaccine and 89% (95% CI, 71–96%) for mRNA vaccine. The pooled seroconversion rate of anti-spike antibody was 66% (95% CI, 55–75%) after two doses of mRNA vaccines and 88% (95% CI, 58–98%) after third dose among LT recipients. T cell response rate was 65% (95% CI, 30–89%). Prevalence of adverse events was 27% (95% CI, 18–38%) and 63% (95% CI, 39–82%) among CLD and LT groups, respectively.

Conclusions: CLD patients had good humoral response to COVID-19 vaccine, while LT recipients had lower response. **(Clin Mol Hepatol 2022;28:890-911)**

Keywords: COVID-19; SARS-CoV-2; Liver transplant; Chronic hepatitis B; Non-alcoholic fatty liver disease

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has affected over 400 million people and caused near nearly 6 million deaths globally as of March 2022.[1] Vaccination has high efficacy profile against COVID-19 infection using different vaccine platforms, such as mRNA (e.g., BNT162b2,[2] mRNA-1273[3]), adenoviral vector (e.g., ChAdOx1 nCov-19/AZD1222[4]), and inactivated vaccines (e.g., CoronaVac,[5] BBIBP-CorV[6]). However, these trials had limited data on patients with chronic liver disease (CLD).

CLD is associated with higher risk of adverse outcomes following COVID-19 infection, especially those with liver cirrhosis.[7,8] Immunogenicity and safety of COVID-19 vaccine is a concern in this group of patients, as cirrhosis affects innate and adaptive immune response.[9] A study of 581 subjects receiving inactivated vaccines revealed that the seroconversion rates of neutralizing antibody (Nab) were 76.8%, 78.9%, and 76.7% among non-cirrhosis, compensated and decompen-

Corresponding author : **Man-Fung Yuen**
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Pokfulam Road, Hong Kong
Tel: +852-22553984, Fax: +852-28162863, E-mail: mfyuen@hkucc.hku.hk
https://orcid.org/0000-0001-7985-7725

Wai-Kay Seto
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Pokfulam Road, Hong Kong
Tel: +852-22556979, Fax: +852-28725828, E-mail: wkseto@hkucc.hku.hk
https://orcid.org/0000-0002-9012-313X

*The two authors share co-first authorship.

Editor: Eun Sun Jang, Seoul National University Bundang Hospital, Korea

Received : Apr. 5, 2022 / **Revised :** May 25, 2022 / **Accepted :** May 31, 2022

Abbreviations:

CHB, chronic hepatitis B; CI, confidence interval; CLD, chronic liver disease; CLIA, chemiluminescence immunoassays; COVID-19, coronavirus disease 2019; ECLIA, electrochemiluminescence immunoassay analyzer; ELISA, enzyme-linked immunosorbent assay; IgG, immunoglobulin G; IQR, interquartile range; LT, liver transplant; Nab, neutralising antibody; NAFLD, non-alcoholic fatty liver disease; NOS, Newcastle-Ottawa scale; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RBD, receptor binding domain

sated cirrhosis groups respectively, in comparison with healthy subjects (90.3%).[10] However, other studies reported a higher seroconversion rate of at least 90% among CLD patients.[11,12]

Due to use of immunosuppressants, liver transplant (LT) recipients are at higher risk of severe infection,[13] and have attenuated response to vaccinations against other diseases.[14] Lower immunogenicity was reported in LT recipients (73.9%) comparing with cirrhotic patients (100%) and controls (100%).[15] An even lower seroconversion rate of <50% was reported in some studies.[16-21]

The conflicting data of COVID-19 vaccine immunogenicity among CLD patients and LT recipients could be related to significant heterogeneity among studies in terms of CLD etiology, cirrhosis status, vaccine platform and type of antibody measured (including Nab, anti-spike receptor binding domain [RBD] antibody and anti-spike antibody). Currently, Nab level is a surrogate marker of vaccine effectiveness[22] and is predictive of protection from symptomatic COVID-19 infection.[23,24] Although levels of anti-spike antibody correlate with Nab, seropositivity is lower upon measurement of Nab than anti-spike antibody.[11,25,26]

We therefore performed a systematic review and meta-analysis to summarize data on vaccine immunogenicity and reactogenicity among patients with liver diseases with stratification according to etiology, cirrhosis status, vaccine platform and type of antibody measured.

MATERIALS AND METHODS

Data sources and searches

We searched electronic databases MEDLINE (OVID), EMBASE, and Cochrane Library from inception to February 16, 2022. Keywords include liver disease, LT, organ transplant, COVID-19, vaccination. The search details can be found in Appendix 1. This review was conducted and reported in consonance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Study selection

Two reviewers (KSC, CHM) screened the titles and abstracts independently for inclusion. Full texts were retrieved if they met the inclusion criteria and assessed independently, and dissonance was resolved by WKS and MFY. Inclusion criteria included (1) study population: CLD patients and LT recipients; (2) intervention: COVID-19 vaccines (including CoronaVac, BBIBP-CorV, WIBP-CorV, BNT162b2, mRNA-1273, AZD1222); (3) study design: randomized controlled trials and observational studies; and (4) primary outcome: seroconversion rate of either Nab or anti-spike antibody. Secondary outcomes are T cell immune response and frequency of adverse events.

Exclusion criteria included (i) age <18 years; (ii) history of COVID-19 infection; and (iii) non-original studies, such as systematic reviews, meta-analysis, review articles, or guidelines. A summary of studies identified, included, and excluded is shown in PRISMA flow diagram (Supplementary Fig. 1).

Data extraction and quality assessment

For eligible studies, we recorded the first author, site of study, study duration, sample size, age, sex, causes of CLD and LT, COVID-19 vaccine type administered, antibody type measured, time interval of antibody measurement from second dose of vaccination, method of antibody test, and cut-off of antibody level regarded as seropositive (Table 1).

The quality of observational studies was assessed using Newcastle-Ottawa scale (NOS). Risk of bias was categorized into three groups: low risk (7–9 points), moderate risk (4–6 points), and high risk (<4 points).[27]

Data analysis

All statistical analyses were conducted in R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) statistical software. Continuous variables were expressed as median (interquartile range [IQR]) or mean±standard deviation). The pooled rate of seroconversion and adverse events were expressed as proportion and 95% confidence interval (95% CI) using random effects model, and was presented as Forest plot. A *P*-value of <0.05 was used to define statistical significance. We used Cochran Q test to detect heterogeneity among studies, with a *P*-value <0.10 indicating significant heterogeneity. We calculated I^2 statistic to measure proportion of total variation in study estimates attributed to heterogeneity. I^2 values of ≥50% and ≥75% indicate substantial and considerable heterogeneity, respectively.[28] Meta-regression analysis was used to examine association between back-

https://doi.org/10.3350/cmh.2022.0087

https://doi.org/10.3350/cmh.2022.0087

Table 1. Background characteristics of the included studies

Study	Country	Study duration	Participants	Age (years)	Male	Liver disease	Immunosuppressants used	Vaccine type	Antibody type	Time interval of antibody measurement from second dose of vaccination	Method of antibody test	Cut-off of antibody level regarded as seropositive
Chronic liver disease												
Ai et al.[10]	China	January to August 2021	437	Median (IQR): 47.0 (38.0–56.0)	278 (63.6%)	Non-cirrhotic chronic liver disease: HBV, 260 (91.5%); HCV, 8 (2.82%); NAFLD, 9 (3.17%); ALD, 1 (0.35%); AIH/PBC/PSC, 1 (0.35%); others, 5 (1.76%) Cirrhosis: HBV, 124 (81.0%); HCV, 12 (7.84%); NAFLD. 3 (1.96%); AIH/PBC/PSC, 7 (4.58%); others, 7 (4.58%)	NA	CoronaVac: NA BBIBP-CorV: NA WIBP-CorV: NA	Neutralising Ab	≥14 days	CLIA	>10.0 AU/mL
Bakasis et al.[11]	Greece	March to May 2021	87	Median (range): cirrhosis, 67.0 (27–86); non-cirrhotic liver disease, 65.0 (35–81)	43 (49.4%)	Non-cirrhotic chronic liver disease: HBV, 23 (46.9%); HCV, 1 (2.04%); NAFLD, 7 (14.3%); AIH, 6 (12.2%); PBC, 11 (22.4%); PSC, 1 (2.04%) Cirrhosis: HBV, 7 (18.4%); HCV, 1 (2.63%); NAFLD, 9 (23.7%); ALD, 6 (15.8%); AIH, 8 (21.1%); PBC, 1 (2.63%); PSC, 3 (7.89%); HSC, 1 (2.63%); BCS, 1 (2.63%); DILI, 1 (2.63%)	MTX: 5 (5.75%) AZA: 7 (8.05%) RTX: 4 (4.60%) MMF: 6 (6.90%) TNFI: 4 (4.60%) S: 14 (16.1%)	BNT162b2: 81 (93.1%) mRNA-1273: 6 (6.90%)	Anti-spike Ab, neutralising Ab	Cirrhosis: 24 days (IQR, 14–57) Non-cirrhotic liver disease: 25 days (IQR, 15–45)	ELISA	Anti-spike Ab: >1.1 OD ratio Neutralising Ab: >30% inhibitory concentration

Table 1. Continued

Study	Country	Study duration	Participants	Age (years)	Male	Liver disease	Immunosuppressants used	Vaccine type	Antibody type	Time interval of antibody measurement from second dose of vaccination	Method of antibody test	Cut-off of antibody level regarded as seropositive
He et al.[26]	China	July to August 2021	362	Median (range): 45.0 (19.0–78.0)	223 (61.6%)	HBV, 362 (100%); cirrhosis, 48 (13.3%)	NA	CoronaVac: NA BBIBP-CorV: NA	Anti-spike Ab, anti-spike RBD Ab, neutralising Ab	≥21 days (range, 21–105)	ELISA	Anti-spike Ab, anti-spike RBD Ab: ≥2.1 OD ratio Neutralising Ab: ≥20% inhibitory concentration
Ruether et al.[15]	Germany	NA	48	Mean±SD: 53.8±9.5	108 (58.1%)	Cirrhosis: ALD, 23 (47.9%); VH, 3 (6.30%); AIH, 11 (22.9%); NAFLD, 4 (8.30%); CC, 5 (10.4%); ALF, 1 (2.10%); others, 1 (2.10%); HCC, 5 (10.4%)*	NA	mRNA/mRNA: 44 (91.6%) BNT162b2: 38 (79.2%) mRNA-1273: 6 (12.4%) AZD1222/AZD1222: 1 (2.08%) AZD1222/mRNA: 3 (6.25%)	Anti-spike RBD Ab, anti-spike trimer Ab	Median (IQR): 28 days (21–41)	CLIA ECLIA	Anti-spike RBD Ab: >100 U/mL Anti-spike trimer Ab: >100 BAU/mL
Thuluvath et al.[21]	USA	NA	171	Mean±SD: non-cirrhotic chronic liver disease, 60.4±13.9; liver cirrhosis, 63.8±11.1	Non-cirrhotic chronic liver disease: 37 (40.2%) Liver cirrhosis: 40 (50.6%)	Non-cirrhotic chronic liver disease: AIH/PBC/PSC, 36 (39.1%); ALD, 2 (2.17%); HBV/HCV, 20 (21.7%); NAFLD, 36 (39.1%); others, 8 (8.70%) Cirrhosis: AIH/PBC/PSC, 17 (21.5%); ALD, 17 (21.5%); HBV/HCV, 17 (21.5%); NAFLD, 33 (41.8%); others, 8 (10.1%)	AZA: 25 (14.6%) S: 19 (11.1%) TAC: 0 (0.00%) Others: 11 (6.43%)	BNT162b2: 80 (46.8%) mRNA-1273: 77 (45.0%) JNJ-78436735: 14 (8.19%)	Anti-spike Ab	Mean±SD: non-cirrhotic chronic liver disease, 40.8±19.6; liver cirrhosis, 40.9±23.9	ECLIA	>250 U/mL

https://doi.org/10.3350/cmh.2022.0087

Table 1. Continued

Study	Country	Study duration	Participants	Age (years)	Male	Liver disease	Immunosuppressants used	Vaccine type	Antibody type	Time interval of antibody measurement from second dose of vaccination	Method of antibody test	Cut-off of antibody level regarded as seropositive
Wang et al.[12]	China	October 2020 to March 2021	381	Median (IQR): 39.0 (33.0–48.0)	179 (47.0%)	NAFLD: 381 (100%)	NA	BBIBP-CorV: 381 (100%)	Neutralising Ab	14 days	CLIA	NA
Xiang et al.[25]	China	March to September 2021	149	Median (IQR): 41.0 (33.0–49.0)	108 (72.5%)	HBV: 284 (100%)	NA	CoronaVac: NA BBIBP-CorV: NA WIBP-CorV: NA	Anti-spike RBD Ab, neutralising Ab	Median (IQR): 33 days (24–48)	CLIA	Anti-spike RBD Ab: 1 AU/mL Neutralising Ab: 0.05 AU/mL
Liver transplant												
Rashidi-Alavijeh et al.[44]	Germany	February to March 2021	43	Median (IQR): 47.0 (36.0–54.0)	26 (60.5%)	HCC: 10 (23.3%); PSC: 7 (16.3%); AC: 6 (14.0%); HCV: 3 (6.98%); ALF: 3 (6.98%); WD: 3 (6.98%); CC: 2 (4.65%); AAD: 2 (4.65%); others: 7 (16.3%)	TAC+EVE: 22 (51.2%) TAC+MMF: 11 (25.6%) TAC: 7 (16.3%) CSA: 2 (4.65%) EVE: 1 (2.33%)	BNT162b2: 43 (100%)	Anti-spike Ab	15 days (IQR: 12–24)	CLIA	≥13.0 AU/mL
Boyarsky et al.[45]	USA	December 2020 to March 2021	129	NA	NA	NA	NA	BNT162b2: NA mRNA-1273: NA	Anti-spike Ab	Median (IQR): 29 days (28–31)	ECLIA	≥0.8 U/mL
Cholankeril et al.[16]	USA	January to February 2021	69	Median (IQR): 63.0 (51–68)	48 (69.6%)	ALD: 24 (34.8%); NAFLD: 13 (18.8%); HCC: 21 (30.4%)	TAC: 64 (92.8%) MMF: 23 (33.3%) S: 22 (31.9%)	BNT162b2: 69 (100%)	Anti-spike Ab	30–75 days	ELISA	Titer ≥1

Table 1. Continued

Study	Country	Study duration	Participants	Age (years)	Male	Liver disease	Immunosuppressants used	Vaccine type	Antibody type	Time interval of antibody measurement from second dose of vaccination	Method of antibody test	Cut-off of antibody level regarded as seropositive
Davidov et al.[46]	Israel	January to May 2021	76	Mean±SD: 59.0±15	43 (56.6%)	HBV: 7 (9.30%); HCV: 19 (25.3%); NAFLD: 13 (17.3%); PSC: 11 (14.7%); PBC: 3 (4.00%); others: 23 (30.3%)	CNI (TAC/CSA): 40 (52.6%) CNI+MMF: 12 (15.8%) CNI+EVE: 10 (13.2%) CNI+S: 9 (11.8%) CNI+MMF+S: 4 (5.26%) SRL: 1 (1.32%)	BNT162b2: 76 (100%)	Anti-spike RBD Ab	Mean±SD: 38±24 days	ELISA	Titer ≥1.1
Erol et al.[47]	Turkey	April to June 2021	10	NA	NA	NA	NA	BNT162b2: 4 (40.0%) CoronaVac: 6 (60.0%)	Anti-spike Ab	28–42 days	CLIA	≥50 AU/mL
Fernández-Ruiz et al.[37]	Spain	April to June 2021	13	NA	NA	NA	NA	mRNA-1273: 13 (100%)	Anti-spike Ab	14 days	ELISA	OD ≥1.1
Guarino et al.[48]	Italy	May to August 2021	444	Median (IQR): seronegative, 65.6 (59.4-71.0); seropositive, 65.2 (56.9-70.1)	332 (74.8%)	VH: 342 (77.0%); ALD: 34 (7.66%); NAFLD: 8 (1.80%); AIH: 18 (4.05%); others: 43 (9.68%)	TAC/CSA: 357 (80.4%) MMF: 151 (34.0%) EVE/SRL: 118 (26.6%)	BNT162b2: 444 (100%)	Anti-spike Ab	Median (IQR): 1st collection, 28 days (28–31); 2nd collection, 88 days (86–91)	CLIA	>25 AU/mL

https://doi.org/10.3350/cmh.2022.0087

Table 1. Continued

Study	Country	Study duration	Participants	Age (years)	Male	Liver disease	Immunosuppressants used	Vaccine type	Antibody type	Time interval of antibody measurement from second dose of vaccination	Method of antibody test	Cut-off of antibody level regarded as seropositive
Hall et al.[35]	Canada	March to April 2021	11	NA	NA	NA	NA	mRNA-1273: 11 (100%)	Anti-spike RBD Ab, neutralising Ab	28–42 days	ECLIA ELISA	Anti-spike RBD Ab: ≥0.8 U/mL Neutralising Ab: >30% inhibitory concentration
Herrera et al.[36]	Spain	NA	58	Median (range): 61.5 (18.0–88.0)	40 (69.0%)	NA	CNI: 53 (91.4%) MMF: 15 (25.9%) S: 13 (22.4%) mTORI: 13 (22.4%)	mRNA-1273: 58 (100%)	Anti-spike RBD Ab	≥28 days	CLIA	NA
Holden et al.[17]	Denmark	From January 2021	13	NA	NA	NA	NA	BNT162b2: NA	Anti-spike Ab	Median (IQR): 5.6 weeks (5.1–6.3)	ELISA	Titer ≥1.1
Huang et al.[18]	USA	January to April 2021	87	NA	NA	NA	NA	BNT162b2: NA mRNA-1273: NA	Anti-spike Ab	≥14 days	ELISA	Titer >1:50
Marion et al.[19]	France	January to April 2021	58	NA	NA	NA	NA	BNT162b2: NA mRNA-1273: NA	Anti-spike Ab	28 days	ELISA	NA
Mazzola et al.[49]	France	January to April 2021	58	Median (IQR): 64.0 (58.0–68.2)	43 (74.1%)	NA	S: 15 (25.9%) CNI: 45 (77.6%) MMF: 33 (56.9%) mTORI: 13 (22.4%)	BNT162b2: 58 (100%)	Anti-spike Ab	28 days	CLIA	≥50 AU/mL

Table 1. Continued

Study	Country	Study duration	Participants	Age (years)	Male	Liver disease	Immunosuppressants used	Vaccine type	Antibody type	Time interval of antibody measurement from second dose of vaccination	Method of antibody test	Cut-off of antibody level regarded as seropositive
Mulder et al.[50]	Netherlands	March to July 2021	476	Median (IQR): BNT162b2, 71.0 (59.0–79.0); mRNA-1273, 59.0 (49.0–66.0); AZD1222, 63.0 (60.0–64.0)	286 (60.1%)	PSC: 101 (21.2%); HCC: 103 (21.6%); ALF: 46 (9.66%); PBC/SSC/CBD: 37 (7.77%); NAFLD/ALD: 42 (8.82%); CC: 22 (4.62%); VH: 24 (5.04%); DC: 20 (4.20%); others: 50 (10.5%); retransplant: 31 (6.51%)	TAC: 243 (51.1%) MMF: 27 (5.67%) CSA: 5 (1.05%) SRL: 2 (0.42%) EVE: 1 (0.21%) AZA: 1 (0.21%) S: 39 (8.19%) TAC+MMF: 113 (23.7%) TAC+S: 27 (5.67%) TAC+SRL: 16 (3.36%) CSA+EVE: 6 (1.26%) TAC+AZA: 7 (1.46%) TAC+EVE: 5 (1.05%) MMF+EVE: 3 (0.63%) MMF+SRL: 2 (0.42%) AZA+S: 1 (0.21%) CSA+AZA: 1 (0.21%) MMF+S: 1 (0.21%) TAC+MMF+S: 8 (1.68%) TAC+SRL+S: 1 (0.21%)	BNT162b2: 25 (5.25%) mRNA-1273: 430 (90.3%) AZD1222: 21 (4.41%)	Anti-spike Ab	Median (IQR): BNT162b2, 31 (29.0–40.0); mRNA-1273, 43.0 (33.0–56.3); AZD1222, 31.0 (26.0–38.0)	CLIA	NA

https://doi.org/10.3350/cmh.2022.0087

Table 1. Continued

Study	Country	Study duration	Participants	Age (years)	Male	Liver disease	Immunosuppressants used	Vaccine type	Antibody type	Time interval of antibody measurement from second dose of vaccination	Method of antibody test	Cut-off of antibody level regarded as seropositive
Nazaruk et al.[51]	Poland	January to June 2021	55	Mean±SD: 58.4±13.3	44 (80.0%)	NA	S: 20 (36.4%) MMF: 16 (29.1%) AZA: 5 (9.10%) CSA: 11 (20.0%) TAC: 43 (78.2%) SRL: 2 (3.60%) EVR: 2 (3.60%) CNI/MMF: 24 (43.6%) CNI+S/MMF/AZA/mTORI: 18 (32.7%) CNI/mTORI+S+MMF/AZA: 13 (23.6%)	BNT162b2: 55 (100%)	Anti-spike Ab	28–56 days	CLIA	>50 AU/mL
Rabinowich et al.[20]	Israel	From December 2020	80	Mean±SD: 60.1±13.3	56 (70.0%)	HBV: 13 (16.3%); HCV: 26 (32.5%); NAFLD: 16 (20.0%); ALD: 3 (3.75%); AIH: 6 (7.50%); PBC: 3 (3.75%); PSC: 7 (8.75%); ALF: 2 (2.50%); CC: 3 (3.75%); WD: 1 (1.25%); SSC: 1 (1.25%); CHF: 1 (1.25%); HCC: 26 (32.5%)*	S: 24 (30.0%) TAC: 65 (81.3%) CSA: 10 (12.5%) EVE: 18 (22.5%) AZA: 4 (5.00%) MMF: 40 (50.0%)	BNT162b2: 80 (100%)	Anti-spike Ab	10–20 days	CLIA	≥15 AU/mL

Table 1. Continued

Study	Country	Study duration	Participants	Age (years)	Male	Liver disease	Immunosuppressants used	Vaccine type	Antibody type	Time interval of antibody measurement from second dose of vaccination	Method of antibody test	Cut-off of antibody level regarded as seropositive
Ruether et al.[15]	Germany	NA	138	Mean±SD: 55.0±13.2	79 (57.2%)	ALD: 28 (20.3%); VH: 17 (12.3%); AIH: 40 (29.0%); NAFLD: 7 (5.10%); PLD: 5 (3.60%); CC: 13 (9.4%); ALF: 5 (3.60%); others: 23 (16.7%); HCC: 25 (18.1%)*	S: 43 (31.2%) TAC: 95 (68.8%) CSA: 33 (23.9%) CNI: 33 (23.9%) CNI+S: 19 (13.8%) CNI+mTORI: 17 (12.3%) CNI+MMF: 48 (34.8%) CNI+AZA: 9 (6.50%) Biologics: 8 (5.8%)	mRNA/mRNA: 121 (87.7%) BNT162b2: 110 (79.7%) mRNA-1273: 11 (7.97%) AZD1222/AZD1222: 6 (4.35%) AZD1222/mRNA: 11 (7.97%)	Anti-spike RBD Ab, anti-spike trimer Ab	Median (IQR): 29 days (25–39)	CLIA ECLIA	Anti-spike RBD Ab: >100 U/mL Anti-spike trimer Ab: >100 BAU/mL
Strauss et al.[52]	USA	January to April 2021	161	Median (IQR): 64.0 (48.0–69.0)	69 (42.9%)	NA	TAC: 81 (50.3%) MMF: 35 (21.7%) S: 22 (13.7%) SRL: 11 (6.83%) CSA: 8 (4.97%) AZA: 6 (3.73%) ERL: 3 (1.86%)	BNT162b2: 85 (52.8%) mRNA-1273: 76 (47.2%)	Anti-spike Ab, anti-spike RBD Ab	Median (IQR): 30 days (28–31)	ECLIA	>250 U/mL
Thuluvath et al.[21]	USA	NA	62	Mean±SD: 65.7±8.7	41 (66.1%)	AIH/PBC/PSC: 8 (12.9%); ALD: 13 (21.0%); HBV/HCV: 26 (41.9%); NAFLD: 15 (24.2%); others: 16 (25.8%)	AZA: 2 (3.23%) S: 8 (12.9%) TAC: 41 (66.1%) Others: 29 (46.8%)	BNT162b2: 24 (38.7%) mRNA-1273: 33 (53.2%) JNJ-78436735: 5 (8.06%)	Anti-spike Ab	Mean±SD: 38.9±19.6 days	ECLIA	>250 U/mL

https://doi.org/10.3350/cmh.2022.0087

Table 1. Continued

Study	Country	Study duration	Participants	Age (years)	Male	Liver disease	Immunosuppressants used	Vaccine type	Antibody type	Time interval of antibody measurement from second dose of vaccination	Method of antibody test	Cut-off of antibody level regarded as seropositive
Timmermann et al.[53]	Germany	May to July 2021	118	Mean (range): 66.1 (28.0–89.0)	75 (63.6%)	ALD: 25 (21.1%); VH: 28 (23.7%); LT: 26 (22.0%); AIH: 18 (15.3%); CC: 4 (3.4%); other: 17 (14.4%)	TAC: 42 (35.6%) MMF: 16 (13.6%) TAC+MMF: 24 (20.3%) TAC+EVE: 15 (12.7%) EVR: 1 (0.85%) CSA+MMF: 3 (2.54%) CSA: 2 (1.69%) TAC+AZA: 1 (0.85%)	BNT162b2: 114 (96.6%) mRNA-1273: 3 (2.54%) JNJ-78436735: 1 (0.85%)	Anti-spike Ab	Mean (range): 44.6 days (21–132)	ELISA	NA

IQR, interquartile range; HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, non-alcoholic fatty liver disease; ALD, alcoholic liver disease; AIH, autoimmune hepatitis; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; NA, not available; Ab, anti-body; CLIA, chemiluminescence immunoassays; HSC, hepatic sarcoidosis; BCS, Budd-Chiari syndrome; DILI, drug induced liver injury; MTX, methotrexate; AZA, azathioprine; RTX, rituximab; MMF, mycophenolate mofetil; TNFI, tumour necrosis factor inhibitor; S, steroid; OD, optical density; RBD, receptor binding domain; ELISA, enzyme-linked immunosorbent assay; SD, standard deviation; VH, viral hepatitis; CC, cryptogenic cirrhosis; ALF, acute liver failure; HCC, hepatocellular carcinoma; ECLIA, electrochemiluminescence immunoassay analyzer; TAC, tacrolimus; AC, alcoholic cirrhosis; WD, Wilson's disease; AAD, α-1 antitrypsin deficiency; EVE, everolimus; CSA, cyclosporin A; CNI, calcineurin inhibitors; SRL, sirolimus; mTORI, mTOR inhibitors; SSC, secondary sclerosing cholangitis; CBD, congenital biliary disease; DC, dysmetabolic cirrhosis; CHF, congenital hepatic fibrosis; PLD, pediatric liver disease; LT, liver tumour.
*Concomitant condition.

ground characteristics of the included studies and pooled seroconversion rates.[29]

We assessed publication bias by funnel plot and Egger regression. Publication bias was considered significant if *P*-value of Egger regression is <0.1.[30] The trim-and-fill method was used to adjust for publication bias, if present, which re-estimated the effect size after imputing potentially missing studies.

Subgroup analysis was performed according to type of antibody tested, method of antibody test (electrochemiluminescence immunoassay analyzer [ECLIA], enzyme-linked immunosorbent assay [ELISA], and chemiluminescence immunoassays [CLIA]), age (with a cut-off of 60 years), etiology of CLD, cirrhosis status, vaccine platform, individual vaccine type, use of multiple immunosuppressants, and region, where applicable.

RESULTS

Study characteristics of meta-analysis

Supplementary Figure 1 depicts the study selection process. Of the 3,590 studies identified, 28 (CLD only: 5, LT only: 18, both CLD and LT: 2; LT with third dose vaccine: 3) are included in the meta-analysis with 3,945 subjects. The characteristics of included studies are shown in Table 1 (for CLD patients and LT recipients receiving two doses of vaccine) and Supplementary Table 1 (for LT recipients receiving third dose). For CLD patients, the median age was 53.8 years (IQR, 43.0–64.4 years), and 62.1% were male. For LT recipients, the median age was 63.0 years (IQR, 59.0–65.6 years), and 64.0% were male. All studies scored at least six stars in NOS, indicating low to moderate risk of bias with satisfactory quality (Supplementary Table 1).

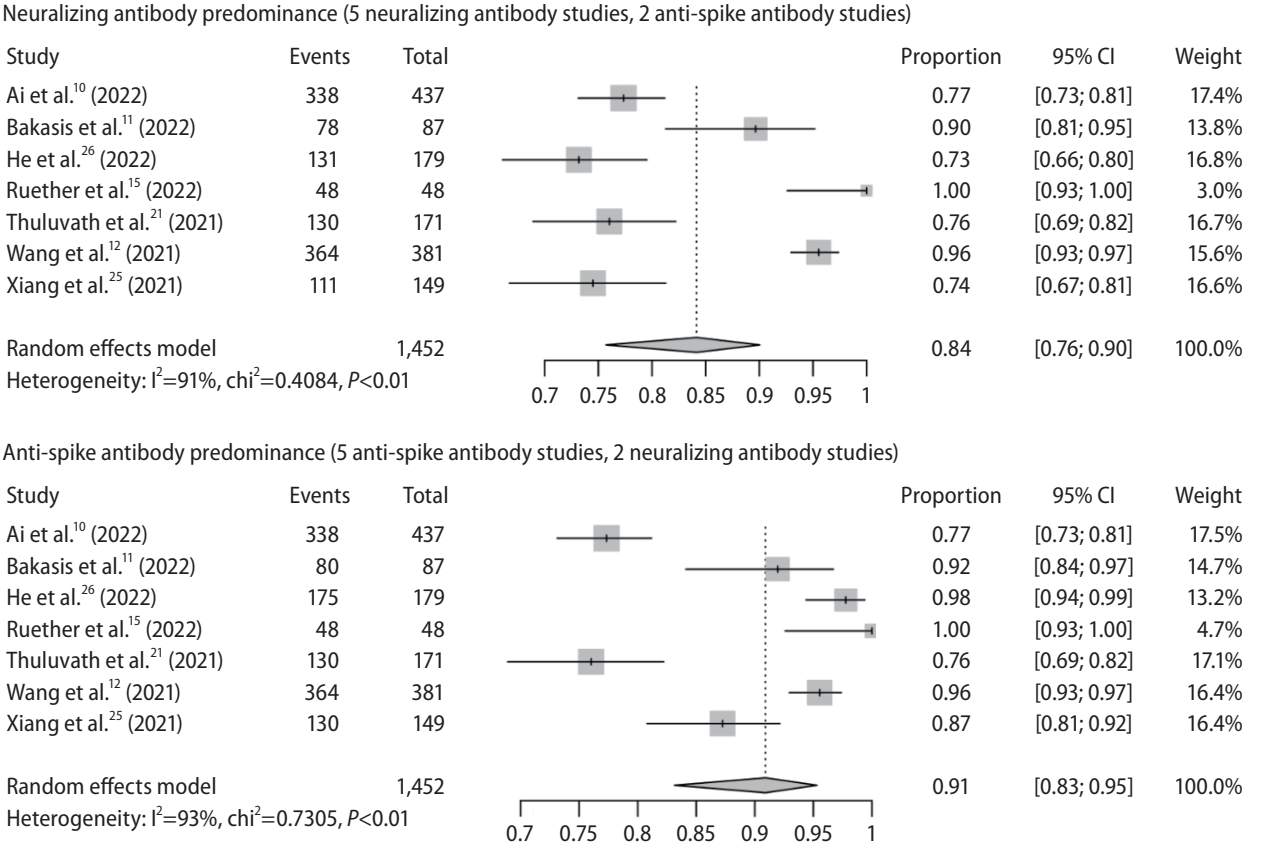


Figure 1. Pooled seroconversion rate in chronic liver disease. CI, confidence interval.

https://doi.org/10.3350/cmh.2022.0087

Meta-analysis for CLD patients

Humoral immune response

There are seven observational studies with 1,452 subjects (studies reporting both Nab and anti-spike antibody: 3; Nab only: 2; anti-spike antibody only: 2) (Table 1). In Nab predominance forest plot (Nab: 5; anti-spike antibody: 2), pooled seroconversion rate was 84% (95% CI, 76–90%) with considerable heterogeneity among the studies (P<0.01; I^2=91%) (Fig. 1). In anti-spike antibody predominance forest plot (anti-spike antibody: 5; Nab: 2), pooled seroconversion rate was 91% (95% CI, 83–95%) with considerable hereogeneity (P<0.01; I^2=93%) (Fig. 1).

The funnel plot appeared to be have some asymmetry for studies with either anti-spike antibody (P=0.038 by Egger test) or neutralizing antibody predominance (P=0.012 by Egger test), indicating publication bias (Supplementary Fig. 2). Trim and fill-method was used to adjust for publication bias, and the pooled seroconversion rate was 83% (95% CI, 71–90%) for Nab predominance analysis and 82% (95% CI, 61–93%) for anti-spike antibody predominance analysis.

Meta-regression analysis showed significant association between seroconversion of Nab and etiology of liver disease (P<0.001) and a trend for method of antibody test (P=0.053 for ECLIA vs. ELISA) but not other factors (Supplementary Fig. 3).

Antibody type

Pooled seroconversion rate of Nab and anti-spike antibody was 84% (95% CI, 74–91%) and 92% (95% CI, 82–97%), respectively (Fig. 2).

Method of antibody test

There were four studies on CLIA, two on ELISA and one on ECLIA. Seroconversion rate was 89% (95% CI, 77–95%), 88% (95% CI, 82–92%), 76% (95% CI, 69–82%) in CLIA, ELISA and ECLIA, respectively (Supplementary Fig. 4).

Age

There were two studies with median age ≥60 years and five studies with median age <60 years. Seroconversion rate was 85% (95% CI, 64–94%) and 88% (95% CI, 79–93%) in the older and younger age group, respectively (Supplementary Fig. 5).

Etiology of liver disease and cirrhosis status

We used 80% as cut-off for classifying the major etiology of a study. There were three studies on chronic hepatitis B (CHB)

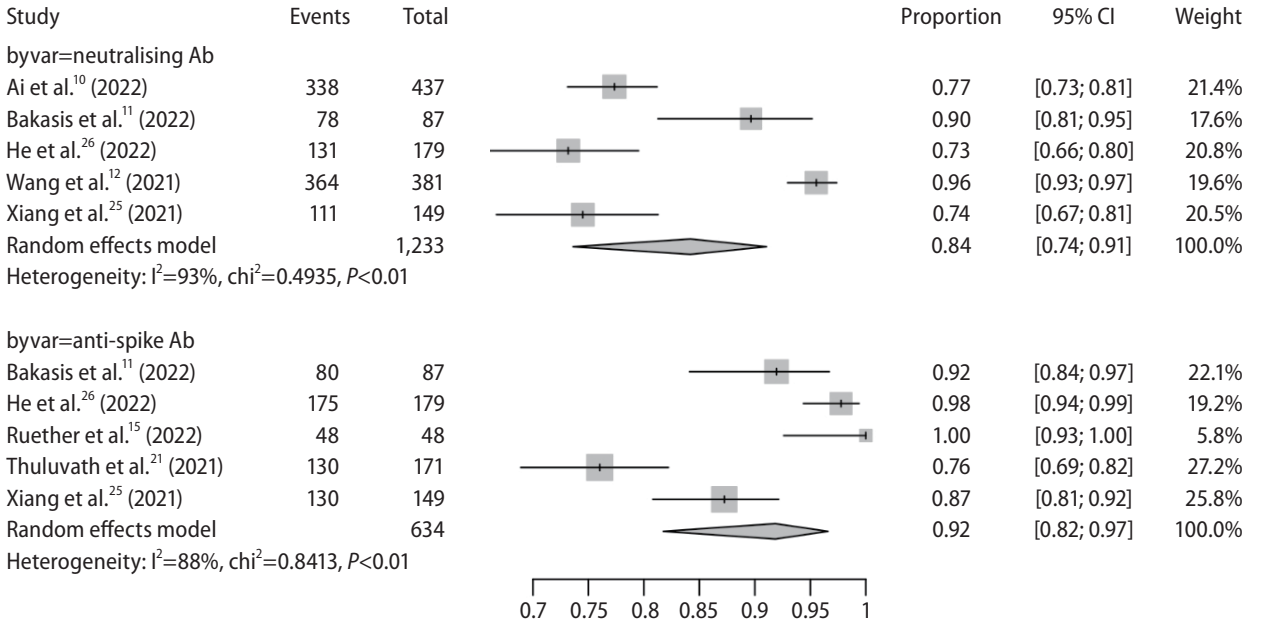


Figure 2. Pooled seroconversion rate in chronic liver disease according to antibody type. CI, confidence interval; Ab, antibody.

 https://doi.org/10.3350/cmh.2022.0087

infection (two studies with 100% CHB[25,26] and one with 87.9%[10]) and one study on non-alcoholic fatty liver disease (NAFLD) (Table 1).[12] Other studies recruited a heterogeneous population of CLD patients of various etiologies without available individual data, and therefore were excluded from subgroup analysis. Seroconversion rate was 81% (95% CI, 76–86%) and 96% (95% CI, 93–97%) in CHB and NAFLD patients, respectively (Fig. 3).

There were five studies on cirrhosis and six studies on non-cirrhosis CLD, four of which reported both outcomes. Seroconversion rate was 85% (95% CI, 75–91%) and 85% (95% CI, 78–90%) in patients with cirrhosis and those without cirrhosis, respectively (Fig. 3). Only one study reported seroconversion rate regarding cirrhosis severity (compensated cirrhosis: 78.9%; decompensated cirrhosis: 76.7%).[10]

Vaccine platform

There were four studies on inactivated vaccine and three on mRNA vaccine. Seroconversion rate was 86% (95% CI, 78–

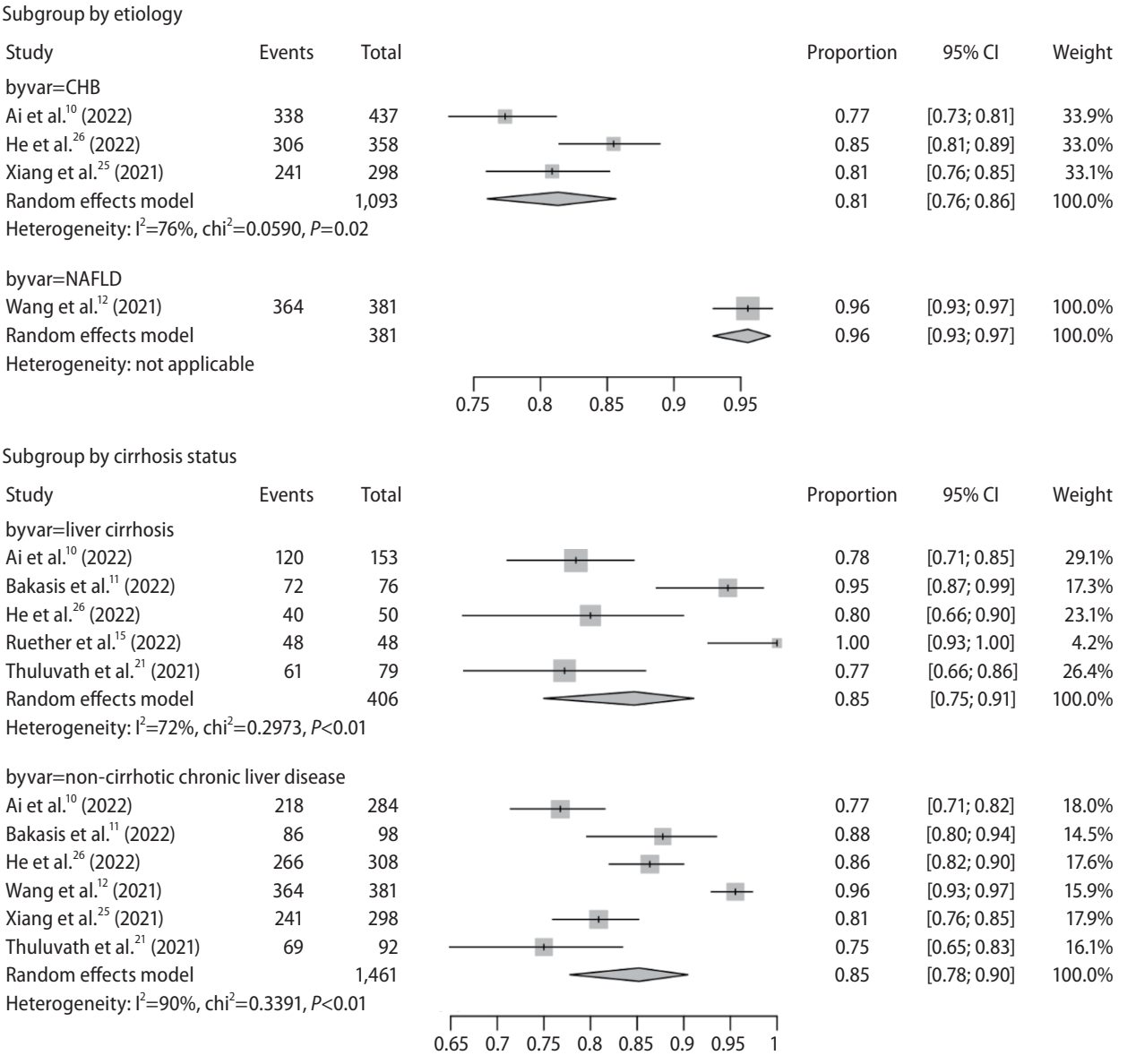


Figure 3. Pooled seroconversion rate in chronic liver disease according to etiology and cirrhosis status. CI, confidence interval; CHB, chronic hepatitis B; NAFLD, non-alcoholic fatty liver disease.

https://doi.org/10.3350/cmh.2022.0087

92%) and 89% (95% CI, 71–96%) in inactivated and mRNA vaccine, respectively (Supplementary Fig. 6).

Individual vaccine type

We used 80% as cut-off for classifying vaccine type of a study. There were two studies using BNT162b2[11,15] and one using BBIBP-CorV[12] with 516 subjects. Other studies recruited a heterogeneous population of patients with various vaccine types without available individual data, and therefore were excluded from subgroup analysis. Seroconversion rate was 95% (95% CI, 72–99%) and 96% (95% CI, 93–97%) in BNT162b2 and BBIBP-CorV subgroups, respectively (Supplementary Fig. 7).

Region

There were four studies from the East and three from the West. Seroconversion rate was 86% (95% CI, 78–92%) and 89% (95% CI, 1–96%) in the East and West subgroups, respectively (Supplementary Fig. 8).

Cell-mediated vaccine immunogenicity

Only one study reported T-cell immune response among cirrhosis patients.[15] A T cell response was observed in 65% of cirrhosis patients, 37% of LT recipients and 100% of control subjects, with a strong response being present in 46%, 32%, and 100% in the three groups, respectively.

Adverse events

There were five studies (inactivated vaccine: 4; mRNA vaccine: 1) reporting adverse events with 1,360 subjects. Prevalence of adverse events was 27% (95% CI, 18–38%) with considerable heterogeneity (P<0.01; I^2=88%) (Supplementary Fig. 9). Ai et al.[10] reported three subjects having grade 3 laboratory abnormalities with raised alanine transaminase five times above upper limit of normal, one of whom developed trend of acute liver failure requiring hospitalization (grade 4). Ruether et al.[15] reported two subjects with severe systemic side effects or requiring medications (grade 3) and one requiring hospitalization (grade 4). Supplementary Table 2 showed pooled prevalence of local and systemic adverse events among inactivated vaccine recipients. The most com-

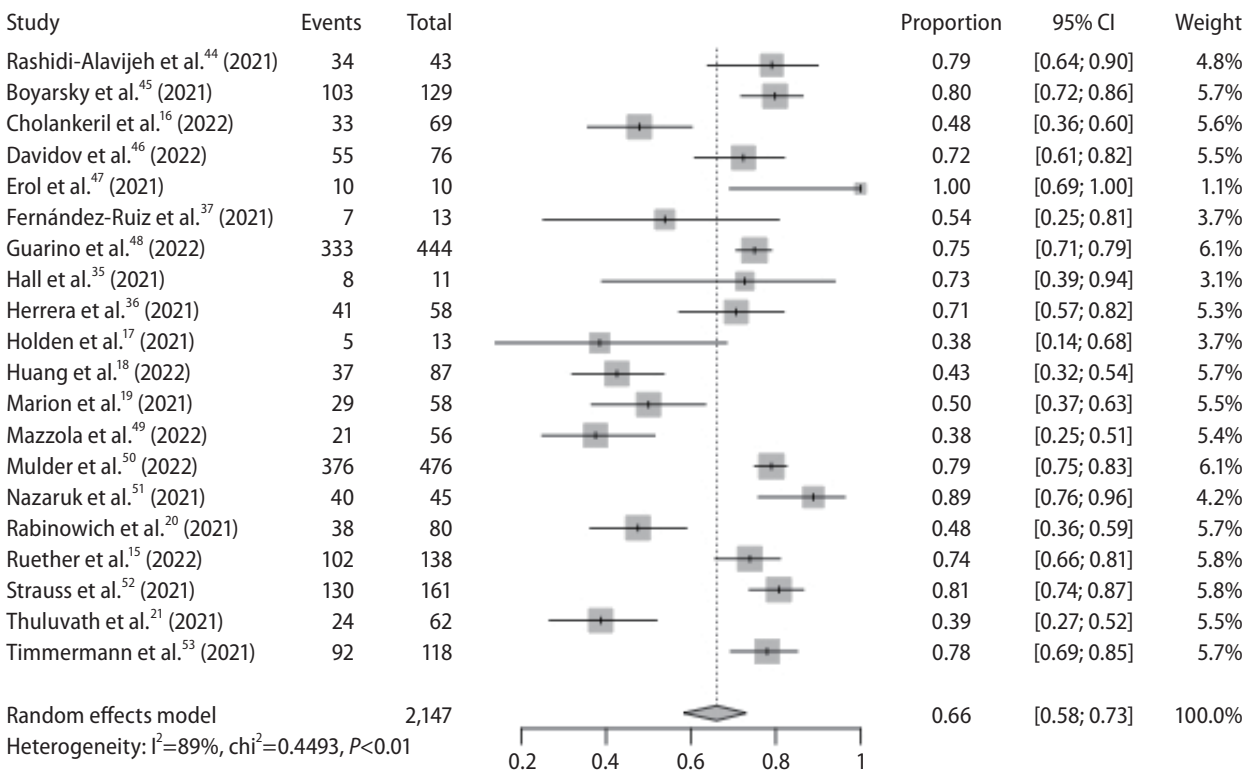


Figure 4. Pooled seroconversion rate in liver transplant recipients. CI, confidence interval.

mon local and systemic adverse event was pain (13%; 95% CI, 7–23%) and fatigue (3%; 95% CI, 2–5%), respectively. The study using mRNA vaccine did not report detailed data on individual adverse events.

Liver transplant recipients

Humoral immune response

There were 20 observational studies with 2,147 subjects. All studies were conducted in the West. Pooled seroconversion rate was 66% (95% CI, 58–73%) with considerable heterogeneity (P<0.01; I^2=89%) (Fig. 4). The funnel plot appeared to be have some asymmetry (P=0.059 by Egger test), indicating publication bias (Supplementary Fig. 10). Trim and fill-method was used to adjust for publication bias, and the pooled seroconversion rate was 69% (95% CI, 61–76%).

Meta-regression analysis showed a trend for association between seroconversion of Nab and age (P=0.085) and method of antibody test (P=0.066 for CLIA vs. ECLIA) but not other factors (Supplementary Fig. 11).

Subgroup analysis

Method of antibody test

There were nine studies on CLIA, seven on ELISA, and four on ECLIA. Seroconversion rate was 71% (95% CI, 61–79%), 56% (95% CI, 43–69%), 70% (95% CI, 47–86%) in CLIA, ELISA and ECLIA, respectively (Supplementary Fig. 12).

Age

There were nine studies with median age ≥60 years and four studies with median age <60 years. A total of 1,826 subjects were included. Seroconversion rate was 64% (95% CI, 52–74%) and 77% (95% CI, 70–83%) in the older and younger age groups, respectively (Supplementary Fig. 13).

Individual vaccine type

All studies used mRNA vaccines (BNT162b2: 10; mRNA-1273: 4) with 1,640 subjects. We used 80% as cut-off for classifying vaccine type of a study. Seroconversion rate was 66% (95% CI, 55–75%) and 73% (95% CI, 63–81%) in BNT162b2 and mRNA-1273 subgroups, respectively (Fig. 5).

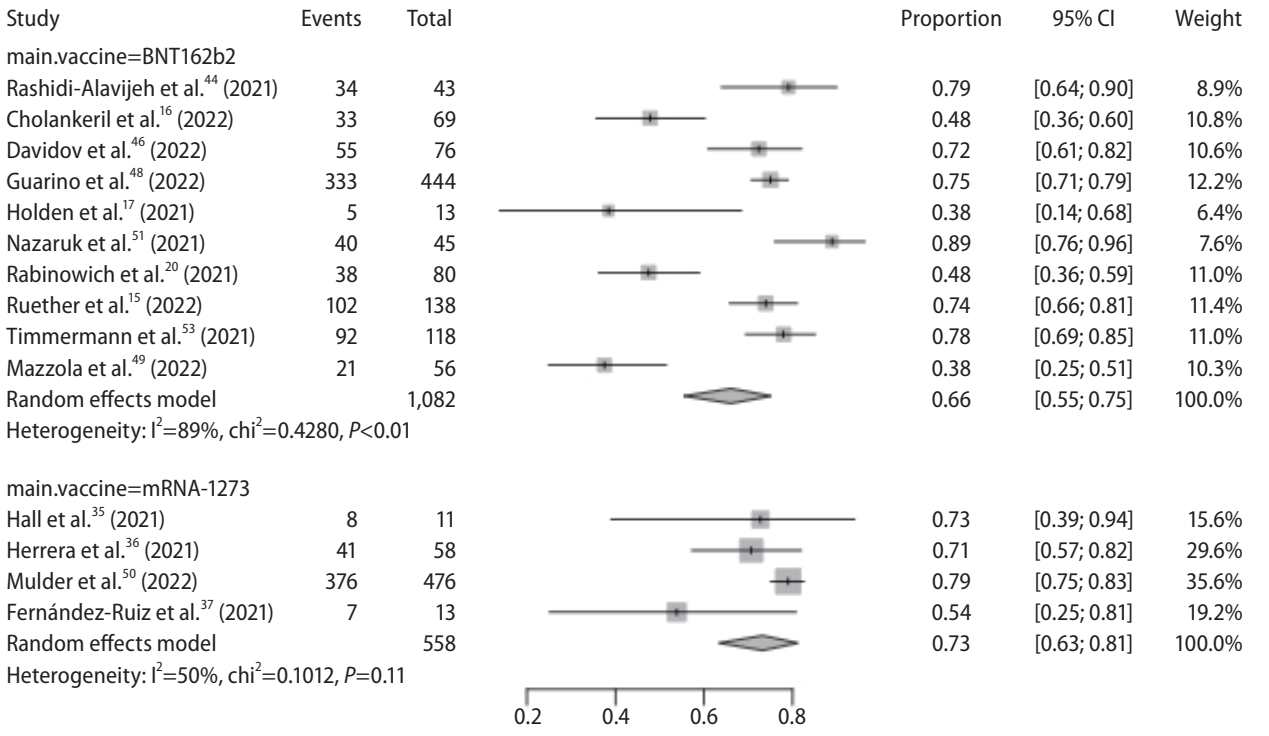


Figure 5. Pooled seroconversion rate in liver transplant recipients according to individual vaccine type. CI, confidence interval.

https://doi.org/10.3350/cmh.2022.0087

Number of immunosuppressants

Four studies reported data on use of ≥2 immunosuppressants with 274 subjects. Seroconversion rate was 62% (95% CI, 43–79%) (Supplementary Fig. 14).

Cell-mediated vaccine immunogenicity

Four studies reported cell-mediated immune response in 157 LT recipients. T cell response rate was 65% (95% CI, 30–89%) with considerable heterogeneity (P<0.01; I^2=90%) (Supplementary Fig. 15). Among those with negative humoral response in two studies, T cell response rate was 52% (95% CI, 12–90%) (Supplementary Fig. 15).

Adverse events

Three studies reported adverse events with 251 subjects. Pooled prevalence of adverse events was 63% (95% CI, 39–82%) with considerable heterogeneity (P<0.01; I^2=92%) (Supplementary Fig. 16). Ruether et al.[15] reported 17 subjects with severe systemic side effects or requiring medications (grade 3) and one subject requiring hospitalization (grade 4). Data on individual adverse events were not reported in these studies.

Seroconversion rate among LT recipients receiving third dose

Three observational studies with 151 subjects were conducted in the West. Pooled seroconversion rate was 88% (95% CI, 58–98%) with considerable heterogeneity (P<0.01; I^2=83%) (Supplementary Fig. 17).

DISCUSSION

This is the first meta-analysis to report COVID-19 vaccine immunogenicity and reactogenicity among CLD patients and LT recipients. Overall seroconversion rate ranges between 84% (based predominantly on Nab) and 91% (based predominantly on anti-spike antibody) among CLD patients; similar immunogenicity is noted regardless of cirrhosis status. Seroconversion rate of anti-spike antibody is 68% after two doses and 88% after third dose among LT recipients.

CLD

CLD patients are at a higher risk of developing severe COVID-19 disease and acute decompensation[31] with mortality reaching 14%.[31,32] Owing to immune dysregulation, CLD patients had lower immunologic response rate to inactivated vaccines like influenza or hepatitis vaccines.[33] CLD and fibrosis hamper production of innate immunity proteins and pattern recognition receptors, and adversely influence B- and T-lymphocytes in terms of absolute counts and functions via various mechanisms. However, the pooled seroconversion rate is good, ranging from 84% to 91% in our meta-analysis. Notably, although seroconversion rate is similar among CLD patients compared with healthy controls, their titer is generally lower.[11,15] A lower seroconversion rate of Nab of 77% was noted in the study by Ai et al.[10] recruiting subjects (87.8% CHB) who received inactivated vaccines. Another study of CHB patients receiving inactivated vaccines also found a seroconversion rate of Nab at 64.0–78.9%, dependent on HBV activity and cirrhosis status.[26] Our meta-analysis showed a numerical difference in seroconversion rate for CHB and NAFLD patients (81% vs. 96%). Nonetheless, a firm conclusion could not be drawn as there were only three studies on CHB (using three different inactivated vaccines) and one on NAFLD (using BBIBP-CorV only), and the difference could be due to different vaccine platforms used in each study. The seroconversion rate appears to be similar among younger and older subjects (85% vs. 88%).

There is also no difference in seroconversion rate between cirrhotic and non-cirrhotic groups (both 85%). There is only one study reporting no difference in vaccine immunogenicity as regards cirrhosis severity (compensated cirrhosis: 78.9%; decompensated cirrhosis: 76.7%).[10] Subgroup analysis showed no difference in seroconversion rate between inactivated and mRNA vaccines.

Measuring anti-spike immunoglobulin G (IgG) or anti-RBD IgG results in a slightly higher seroconversion rate than Nab (91% vs. 84%). This difference is exemplified by one study showing seroconversion rate of 64.0–78.9% for Nab (dependent on HBV replication and cirrhosis status) and 96–100% for anti-spike IgG or anti-RBD IgG.[26] Nab level is a surrogate marker of vaccine effectiveness against symptomatic infection.[22-24] Anti-spike and anti-RBD IgG levels correlate with Nab[34] but not equate Nab. Using ECLIA to measure antibody level also results in slightly lower seroconversion rate compared with CLIA and ELISA (76% vs. 89% vs. 88%).

LT

Pooled seroconversion rate is less satisfactory (66%) among LT recipients, in particular for older than younger patients (64% vs. 77%). However, when compared with other organ transplant recipients (e.g., kidney, heart), LT recipients have higher seroconversion rate.[19,35] This may be related to stricter and higher levels of immunosuppression in other organ transplant recipients. However, all studies except one[35] reported seroconversion rate of anti-spike antibody but not Nab. Hall et al.[35] noted that 28.5% of organ transplant recipients with anti-RBD did not have Nab. Seroconversion rate of anti-spike IgG varied from 38% to 100%, likely related to variance in immunosuppression regimen. Known risk factors for seronegativity include high-dose steroid, triple immunosuppression, mycophenolate mofetil,[20,36] low B-lymphocytes,[15] hypogammaglobulinemia,[36] vaccination during the first year post-transplantation,[36] low estimated glomerular filtration rate,[20] old age and alcohol-related liver disease.[12] Our meta-analysis showed that pooled seroconversion rate of patients receiving ≥2 immunosuppressants is slightly lower (62%) than that of whole cohort (66%). Subgroup analysis also shows the seroconversion rate of mRNA-1273 is slightly higher than that of BNT162b2 (73% vs. 66%). Importantly, pooled seroconversion rate increases to 88% after booster dose. Data on immunogenicity of inactivated vaccines in LT recipients are currently lacking. Notably, using ELISA to measure antibody level also results in slightly lower seroconversion rate compared with CLIA and ECLIA (56% vs. 71% vs. 70%).

There are four studies reporting T-cell immune response, with a pooled response rate of 65%.[15,35-37] Similar to the phenomenon observed in humoral response, level of T cell response is higher in LT recipients than other organ transplant recipients, e.g., heart transplant.[36] Our meta-analysis shows 52% have T-cell response despite seronegativity. Vaccine-induced T-cell response may offer protection via suppressing viral replication and supporting long-term memory of the immune system,[38] hence protecting against severe infection despite seronegativity.[23]

Concerning vaccine reactogenicity, pooled prevalence of adverse reactions is 27% among CLD patients receiving mainly inactivated vaccines, which is similar among healthy subjects (23% in a meta-analysis of randomized controlled trials).[39] There is only one study reporting no significant difference in frequency of adverse events as regards cirrhosis status (non-cirrhosis: 15.5%; compensated cirrhosis: 16.3%; decompensated cirrhosis: 20.0%).[10] As for LT recipients receiving mRNA vaccines, pooed prevalence of adverse reactions is 63%, compared with 48% among healthy subjects.[39]

Our study findings support current international recommendation on COVID-19 vaccination in CLD patients and LT recipients.[13,40] LT recipients should receive vaccine platforms with more data (e.g., mRNA vaccine) and third-dose booster. Another strategy may be heterologous vaccination,[41] in which seroconversion rate of 81.8% was reported for 8% of LT cohort who had heterologous vaccination in the study by Ruether et al.[15]

Limitations of the current study should be acknowledged. First, some studies did not measure Nab level, and the test kits differed among different studies. Second, the optimal antibody thresholds for protection is still unknown. Titers above the cut-off should protect against severe disease for the majority of vaccine recipients, but not against asymptomatic infection.[23,42,43] Third, only three studies reported vaccine immunogenicity among CHB patients and one on NAFLD; others recruited a heterogeneous population of CLD patients without available data for individual disease etiology (e.g., chronic viral hepatitis, NAFLD, autoimmune hepatitis) which may have different vaccine immunogenicity, in particular among autoimmune liver diseases which require immunosuppressants. Similarly, the LT recipients were comprised of a heterogeneous population of various disease etiology and different immunosuppressive regimen. Individual studies did not provide the seroconversion rate according to disease etiology and immunosuppressive regimen, and therefore subgroup analysis could not be performed according to these factors. Fourth, we did not include studies with general population that might enrol CLD recipients for comparison.

While an excellent safety profile is demonstrated in CLD and LT patients, the former group has good humoral response and the latter has lower response. Third-dose booster or heterologous vaccination may be considered in LT recipients, although more studies with larger sample size are warranted before this practice is widely recommended.

Authors' contribution

Dr. Ka-Shing Cheung and Mr. Chiu Hang Mok were involved with study concept and design; acquisition of data; analysis and interpretation of data; drafting of manuscript; Mr. Xianhua Mao, Dr. Ricky Zhang and Prof. Ivan FN Hung were in-

https://doi.org/10.3350/cmh.2022.0087

volved with analysis and interpretation of data; and critical revision of the manuscript for important intellectual content. Profs. Wai-Kay Seto and Man-Fung Yuen were involved with the study concept and design; analysis and interpretation of data; drafting of manuscript; critical revision of the manuscript for important intellectual content; and study supervision. The corresponding author had full access to all data, and was fully responsible for the data integrity and statistical analysis. All authors revised the manuscript and approved the final version of this article.

Conflicts of Interest

The authors have no conflicts to disclose.

REFERENCES

1. Johns Hopkins University Coronavirus Resource Center. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). Johns Hopkins University web site, <https://coronavirus.jhu.edu/map.html>. Accessed 5 Mar 2022.
2. 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.
3. 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.
4. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 2021;397:99-111.
5. Palacios R, Patiño EG, de Oliveira Piorelli R, Conde MTRP, Batista AP, Zeng G, et al. Double-blind, randomized, placebo-controlled phase III clinical trial to evaluate the efficacy and safety of treating healthcare professionals with the adsorbed COVID-19 (inactivated) vaccine manufactured by sinovac - PROFISCOV: a structured summary of a study protocol for a randomised controlled trial. Trials 2020;21:853.
6. Xia S, Zhang Y, Wang Y, Wang H, Yang Y, Gao GF, et al. 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.
7. Marjot T, Moon AM, Cook JA, Abd-Elsalam S, Aloman C, Armstrong MJ, et al. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: an international registry study. J Hepatol 2021;74:567-577.
8. Bajaj JS, Garcia-Tsao G, Biggins SW, Kamath PS, Wong F, McGeorge S, et al. Comparison of mortality risk in patients with cirrhosis and COVID-19 compared with patients with cirrhosis alone and COVID-19 alone: multicentre matched cohort. Gut 2021;70:531-536.
9. Bonnel AR, Bunchorntavakul C, Reddy KR. Immune dysfunction and infections in patients with cirrhosis. Clin Gastroenterol Hepatol 2011;9:727-738.
10. Ai J, Wang J, Liu D, Xiang H, Guo Y, Lv J, et al. Safety and immunogenicity of SARS-CoV-2 vaccines in patients with chronic liver diseases (CHESS-NMCID 2101): a multicenter study. Clin Gastroenterol Hepatol 2022;20:1516-1524.e2.
11. Bakasis AD, Bitzogli K, Mouziouras D, Pouliakis A, Roumpoutsou M, Goules AV, et al. Antibody responses after SARS-CoV-2 vaccination in patients with liver diseases. Viruses 2022;14:207.
12. Wang J, Hou Z, Liu J, Gu Y, Wu Y, Chen Z, et al. Safety and immunogenicity of COVID-19 vaccination in patients with non-alcoholic fatty liver disease (CHESS2101): a multicenter study. J Hepatol 2021;75:439-441.
13. 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;74:944-951.
14. Chong PP, Avery RK. A comprehensive review of immunization practices in solid organ transplant and hematopoietic stem cell transplant recipients. Clin Ther 2017;39:1581-1598.
15. Ruether DF, Schaub GM, Duengelhoef PM, Haag F, Brehm TT, Fathi A, et al. SARS-CoV2-specific humoral and T-cell immune response after second vaccination in liver cirrhosis and transplant patients. Clin Gastroenterol Hepatol 2022;20:162-172.e9.
16. Cholankeril G, Al-Hillan A, Tarlow B, Abrams D, Jacobs JS, Flores NP, et al. Clinical factors associated with lack of serological response to SARS-CoV-2 messenger RNA vaccine in liver transplantation recipients. Liver Transpl 2022;28:123-126.
17. Holden IK, Bistrup C, Nilsson AC, Hansen JF, Abazi R, Davidsen JR, et al. Immunogenicity of SARS-CoV-2 mRNA vaccine in solid organ transplant recipients. J Intern Med 2021;290:1264-1267.
18. Huang HJ, Yi SG, Mobley CM, Saharia A, Bhimaraj A, Moore LW, et al. Early humoral immune response to two doses of severe acute respiratory syndrome coronavirus 2 vaccine in a diverse group of solid organ transplant candidates and recipients. Clin Transplant 2022;36:e14600.

19. Marion O, Del Bello A, Abravanel F, Couat C, Faguer S, Esposito L, et al. Safety and immunogenicity of anti-SARS-CoV-2 messenger RNA vaccines in recipients of solid organ transplants. Ann Intern Med 2021;174:1336-1338.
20. Rabinowich L, Grupper A, Baruch R, Ben-Yehoyada M, Halperin T, Turner D, et al. Low immunogenicity to SARS-CoV-2 vaccination among liver transplant recipients. J Hepatol 2021;75:435-438.
21. Thuluvath PJ, Robarts P, Chauhan M. Analysis of antibody responses after COVID-19 vaccination in liver transplant recipients and those with chronic liver diseases. J Hepatol 2021;75:1434-1439.
22. Earle KA, Ambrosino DM, Fiore-Gartland A, Goldblatt D, Gilbert PB, Siber GR, et al. Evidence for antibody as a protective correlate for COVID-19 vaccines. Vaccine 2021;39:4423-4428.
23. Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat Med 2021;27:1205-1211.
24. Bergwerk M, Gonen T, Lustig Y, Amit S, Lipsitch M, Cohen C, et al. Covid-19 breakthrough infections in vaccinated health care workers. N Engl J Med 2021;385:1474-1484.
25. Xiang T, Liang B, Wang H, Quan X, He S, Zhou H, et al. Safety and immunogenicity of a SARS-CoV-2 inactivated vaccine in patients with chronic hepatitis B virus infection. Cell Mol Immunol 2021;18:2679-2681.
26. He T, Zhou Y, Xu P, Ling N, Chen M, Huang T, et al. Safety and antibody response to inactivated COVID-19 vaccine in patients with chronic hepatitis B virus infection. Liver Int 2022;42:1287-1296.
27. Zeng X, Zhang Y, Kwong JS, Zhang C, Li S, Sun F, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. J Evid Based Med 2015;8:2-10.
28. Deeks JJ, Higgins JPT, Altman DG, Group obotCSM. Chapter 10: analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, eds. Cochrane Handbook for systematic reviews of interventions. London: Cochrane, 2019:241-284.
29. van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. Stat Med 2002;21:589-624.
30. Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;343:d4002.
31. Kovalic AJ, Satapathy SK, Thuluvath PJ. Prevalence of chronic liver disease in patients with COVID-19 and their clinical outcomes: a systematic review and meta-analysis. Hepatol Int 2020;14:612-620.
32. Kim D, Adeniji N, Latt N, Kumar S, Bloom PP, Aby ES, et al. Predictors of outcomes of COVID-19 in patients with chronic liver disease: US multi-center study. Clin Gastroenterol Hepatol 2021;19:1469-1479.e19.
33. Alukal JJ, Naqvi HA, Thuluvath PJ. Vaccination in chronic liver disease: an update. J Clin Exp Hepatol 2022;12:937-947.
34. Zost SJ, Gilchuk P, Case JB, Binshtein E, Chen RE, Nkolola JP, et al. Potently neutralizing and protective human antibodies against SARS-CoV-2. Nature 2020;584:443-449.
35. Hall VG, Ferreira VH, Ierullo M, Ku T, Marinelli T, Majchrzak-Kita B, et al. Humoral and cellular immune response and safety of two-dose SARS-CoV-2 mRNA-1273 vaccine in solid organ transplant recipients. Am J Transplant 2021;21:3980-3989.
36. Herrera S, Colmenero J, Pascal M, Escobedo M, Castel MA, Sole-González E, et al. Cellular and humoral immune response after mRNA-1273 SARS-CoV-2 vaccine in liver and heart transplant recipients. Am J Transplant 2021;21:3971-3979.
37. Fernández-Ruiz M, Almendro-Vázquez P, Carretero O, Ruiz-Merlo T, Laguna-Goya R, San Juan R, et al. Discordance between SARS-CoV-2-specific cell-mediated and antibody responses elicited by mRNA-1273 vaccine in kidney and liver transplant recipients. Transplant Direct 2021;7:e794.
38. Le Bert N, Tan AT, Kunasegaran K, Tham CYL, Hafezi M, Chia A, et al. SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls. Nature 2020;584:457-462.
39. Chen M, Yuan Y, Zhou Y, Deng Z, Zhao J, Feng F, et al. Safety of SARS-CoV-2 vaccines: a systematic review and meta-analysis of randomized controlled trials. Infect Dis Poverty 2021;10:94.
40. Fix OK, Blumberg EA, Chang KM, Chu J, Chung RT, Goacher EK, et al. American Association for the Study of Liver Diseases Expert Panel Consensus Statement: vaccines to prevent coronavirus disease 2019 infection in patients with liver disease. Hepatology 2021;74:1049-1064.
41. Schmidt T, Klemis V, Schub D, Mihm J, Hielscher F, Marx S, et al. Immunogenicity and reactogenicity of heterologous ChAdOx1 nCoV-19/mRNA vaccination. Nat Med 2021;27:1530-1535.
42. Feng S, Phillips DJ, White T, Sayal H, Aley PK, Bibi S, et al. Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. Nat Med 2021;27:2032-2040.
43. Gilbert PB, Montefiori DC, McDermott A, Fong Y, Benkeser D,

https://doi.org/10.3350/cmh.2022.0087

Deng W, et al. Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy trial. medRxiv. 2021 Aug 15. doi: 10.1101/2021.08.09.21261290.
44. Rashidi-Alavijeh J, Frey A, Passenberg M, Korth J, Zmudzinski J, Anastasiou OE, et al. Humoral response to SARS-Cov-2 vaccination in liver transplant recipients-a single-center experience. Vaccines (Basel) 2021;9:738.
45. Boyarsky BJ, Werbel WA, Avery RK, Tobian AAR, Massie AB, Segev DL, et al. Antibody response to 2-Dose SARS-CoV-2 mRNA vaccine series in solid organ transplant recipients. JAMA 2021;325:2204-2206.
46. Davidov Y, Tsaraf K, Cohen-Ezra O, Likhter M, Ben Yakov G, Levy I, et al. Immunogenicity and adverse effects of the 2-dose BNT162b2 messenger RNA vaccine among liver transplantation recipients. Liver Transpl 2022;28:215-223.
47. Erol Ç, Yanık Yalçın T, Sarı N, Bayraktar N, Ayvazoğlu Soy E, Yavuz Çolak M, et al. Differences in antibody responses between an inactivated SARS-CoV-2 vaccine and the BNT162b2 mRNA vaccine in solid-organ transplant recipients. Exp Clin Transplant 2021;19:1334-1340.
48. Guarino M, Esposito I, Portella G, Cossiga V, Loperto I, Tortora R, et al. Humoral response to 2-dose BNT162b2 mRNA COVID-19 vaccination in liver transplant recipients. Clin Gastroenterol Hepatol 2022;20:1534-1541.e4.
49. Mazzola A, Todesco E, Drouin S, Hazan F, Marot S, Thabut D, et al. Poor antibody response after two doses of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine in transplant recipients. Clin Infect Dis 2022;74:1093-1096.
50. Mulder MB, van der Eijk AA, GeurtsvanKessel CH, Erler NS, de Winter BCM, Polak WG, et al. High antibody response in relation to immunosuppressive blood levels in liver transplant recipients after SARS-CoV-2 vaccination: an observational, cohort study. Gut. 2022 Jan 31. doi: 10.1136/gutjnl-2021-326755.
51. Nazaruk P, Monticolo M, Jędrzejczak AM, Krata N, Moszczuk B, Sańko-Resmer J, et al. Unexpectedly high efficacy of SARS-CoV-2 BNT162b2 vaccine in liver versus kidney transplant recipients-is it related to immunosuppression only? Vaccines (Basel) 2021;9:1454.
52. Strauss AT, Hallett AM, Boyarsky BJ, Ou MT, Werbel WA, Avery RK, et al. Antibody response to severe acute respiratory syndrome-coronavirus-2 messenger RNA vaccines in liver transplant recipients. Liver Transpl 2021;27:1852-1856.
53. Timmermann L, Globke B, Lurje G, Schmelzle M, Schöning W, Öllinger R, et al. Humoral immune response following SARS-CoV-2 vaccination in liver transplant recipients. Vaccines (Basel) 2021;9:1422.