

# Immunogenicity of COVID-19 vaccines in chronic liver disease patients and liver transplant recipients: A systematic review and meta-analysis

De Luo<sup>1,2</sup>  | Xinpei Chen<sup>3,4</sup> | Juan Du<sup>5</sup> | Bingjie Mei<sup>6</sup> | Ankang Wang<sup>7</sup> | Fei Kuang<sup>8</sup> | Cheng Fang<sup>1</sup> | Yu Gan<sup>1</sup> | Fangyi Peng<sup>1</sup> | Xiaoli Yang<sup>1</sup> | Uta Dahmen<sup>4</sup> | Bo Li<sup>1</sup> | Su Song<sup>1</sup>

<sup>1</sup>Department of Hepatobiliary Surgery, The Affiliated Hospital of Southwest Medical University, Luzhou, China

<sup>2</sup>Department of Nephrology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany

<sup>3</sup>Department of Hepatobiliary Surgery, People's Hospital of Deyang City, Deyang, China

<sup>4</sup>Department of General, Visceral and Vascular Surgery, Jena University Hospital, Jena, Germany

<sup>5</sup>Department of Clinical Medicine, Southwest Medical University, Luzhou, China

<sup>6</sup>Sichuan Cancer Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China

<sup>7</sup>Department of General Surgery, Nanchong Central Hospital, The Second Clinical College of North Sichuan Medical College, Nanchong, China

<sup>8</sup>Institute of Immunology, Medical Faculty, University of Duisburg-Essen, Essen, Germany

## Correspondence

Uta Dahmen, Department of General, Visceral and Vascular Surgery, Jena University Hospital, Jena, Germany.

Email: [uta.dahmen@med.uni-jena.de](mailto:uta.dahmen@med.uni-jena.de) Bo Li and Su Song, Department of Hepatobiliary Surgery, The Affiliated Hospital of Southwest Medical University, Luzhou, China.

Email: [liboer2002@swmu.edu.cn](mailto:liboer2002@swmu.edu.cn) and [susong1978@swmu.edu.cn](mailto:susong1978@swmu.edu.cn)

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## Abstract

**Background and aims:** Chronic liver disease (CLD) patients and liver transplant (LT) recipients have an increased risk of morbidity and mortality from coronavirus disease 2019 (COVID-19). The immunogenicity of COVID-19 vaccines in CLD patients and LT recipients is poorly understood. The present study aimed to evaluate the immunogenicity of COVID-19 vaccines in CLD patients and LT recipients.

**Methods:** We searched electronic databases for eligible studies. Two reviewers independently conducted the literature search, extracted the data and assessed the risk of bias of included studies. The rates of detectable immune response were pooled from single-arm studies. For comparative studies, we compared the rates of detectable immune response between patients and healthy controls. The meta-analysis was conducted using the Stata software with a random-effects model.

**Results:** In total, 19 observational studies involving 4191 participants met the inclusion criteria. The pooled rates of detectable humoral immune response after two doses of COVID-19 vaccination in CLD patients and LT recipients were 95% (95% confidence interval [CI] = 88%–99%) and 66% (95% CI = 57%–74%) respectively. After two doses of vaccination, the humoral immune response rate was similar in CLD patients and

**Abbreviations:** CI, confidence interval; CLD, chronic liver disease; COVID-19, coronavirus disease 2019; GRADE, grading of recommendations assessment, development and evaluation; LT, liver transplant; MMF, mycophenolate mofetil; mRNA, messenger RNA; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio; RR, risk ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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healthy controls (risk ratio [RR] = 0.96; 95% CI = 0.90–1.02;  $p = .14$ ). In contrast, LT recipients had a lower humoral immune response rate after two doses of vaccination than healthy controls (RR = 0.68; 95% CI = 0.59–0.77;  $p < .01$ ).

Conclusions: Our meta-analysis demonstrated that COVID-19 vaccination induced strong humoral immune responses in CLD patients but poor humoral immune responses in LT recipients.

#### KEYWORDS

chronic liver disease, COVID-19, immunogenicity, liver transplantation, vaccine

## 1 | INTRODUCTION

Coronavirus 19 disease (COVID-19), caused by infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to high levels of morbidity and mortality and is dramatically affecting healthcare systems all over the world.<sup>1</sup> Chronic liver disease (CLD) patients and liver transplantation (LT) recipients have well-recognized deficiencies in humoral and cellular immunity, the so-called immune dysfunction, which predisposes to infections.<sup>2,3</sup> CLD patients and LT recipients are reported to have an increased risk of SARS-CoV-2 infection and worse outcomes compared to the general population.<sup>4–8</sup>

COVID-19 vaccines have been considered to be the most effective means of controlling the COVID-19 pandemic.<sup>9</sup> Growing evidence indicates that COVID-19 vaccines are safe and effective in the general population.<sup>10,11</sup> However, immunocompromised and immunosuppressed individuals may have reduced immune responses to COVID-19 vaccines. To date, studies on immune responses of COVID-19 vaccines in CLD patients and LT recipients have been lacking, because these populations were excluded from regulatory vaccine trials. The integration of findings across studies can offer a better understanding of the immunogenicity of COVID-19 vaccines in these populations. Therefore, we conducted the first systematic review and meta-analysis to assess the immunogenicity of COVID-19 vaccines in CLD patients and LT recipients.

## 2 | METHODS

This systematic review and meta-analysis was performed according to the PRISMA guidelines<sup>12</sup> and was registered with the international prospective register of systematic reviews (PROSPERO)<sup>13</sup> with the registration number CRD42021296904.

### 2.1 | Search strategy

We searched PubMed, Embase, Web of Science and Cochrane Library using predefined search terms for eligible studies published in English from December 2019 to April 2022. The main search terms included “COVID-19”, “SARS-CoV-2”, “vaccine”, “liver transplantation”, “liver disease”, “cirrhosis”, “chronic liver diseases”,

### Lay Summary

The immunogenicity of coronavirus disease 2019 (COVID-19) vaccines in chronic liver disease (CLD) patients and liver transplant (LT) recipients is poorly understood. We demonstrated that COVID-19 vaccination elicited strong humoral responses in CLD patients but poor humoral immune responses in LT recipients. The findings indicate that CLD patients and LT recipients should complete the full vaccine schedule without delay and support the administration of a third dose of vaccine to LT recipients.

“non-alcoholic fatty liver disease”, “immunogenicity”, “antibody”, “seroconversion”, “humoral immune response”, and “cellular immune response”. References from the included studies were also manually searched to identify additional studies. Two investigators (B.J.M. and A.K.W.) performed independently the search. Search strategy details for PubMed are provided in Table S1.

### 2.2 | Outcomes of interest

The primary outcomes were the rates of detectable humoral immune response in CLD patients and LT recipients and the comparison of humoral immune responses between these populations and healthy controls. The secondary outcomes were the rates of detectable cellular immune response and risk factors for poor antibody responses.

### 2.3 | Study selection

The eligibility of the studies was determined independently by two investigators (B.J.M. and A.K.W.). The inclusion criteria were: (i) participants: patients were CLD patients or LT recipients without previous COVID-19 infection. If a study enrolled participants with and without previous infection, only participants without previous infection were included in this meta-analysis; (ii) intervention: two doses of COVID-19 vaccination; (iii) at least one of the outcomes of interest was reported; (iv) randomized controlled trial and cohort study were

eligible. Any study that met one of the following conditions was excluded: (i) inadequate description of CLD patients or LT recipients from these studies on solid organ transplantation; (ii) if the number of patients in the study was below 10. Disagreements were resolved by discussion or consultation with the third investigator (F.K.).

## 2.4 | Data extraction

Two independent investigators (F.K. and C.F.) extracted data and recorded them on the predefined form. The extracted information included the first author, year of publication, participant characteristics (gender, age, comorbidity and proportion of cirrhosis), sample size, details of the vaccination (type of vaccine and time interval between transplantation and first vaccination), assay used to assess antibody response, time interval between second vaccination and antibody measurement, immunosuppressive regimen and outcomes of interest. The authors of the studies were contacted for missing information, if necessary. Two investigators compared the data, and discrepancies were decided through discussion.

## 2.5 | Quality assessment

Two independent investigators (Y.G. and X.L.Y.) assessed the risk of bias of included studies using the Newcastle–Ottawa scale (NOS).<sup>14</sup>

According to the scale, the quality of each study was assessed by awarding participant selection a maximum of 4 points, outcome 3 points and comparability 2 points, yielding a maximum total of 9 points. The overall study quality was classified as good (7–9 points), moderate (4–6 points), or poor (0–3 points). The quality of the evidence was determined by the grading of recommendations assessment, development and evaluation (GRADE) approach.<sup>15</sup> Certainty levels (very low, low, moderate or high) were assigned to each result, based on risk of bias, publication bias, inconsistency, indirectness, intransitivity, imprecision and incoherence (difference between direct and indirect effects). Disagreements among investigators were settled by consensus.

## 2.6 | Statistical methods

We conducted the meta-analysis using Stata version 16.0. The meta-analysis was conducted separately based on the patient type (CLD or LT). In the single-armed meta-analysis, the data from the studies were transformed using the double arcsine method to achieve normality of distribution before being pooled. The risk ratio (RR) with 95% confidence interval (CI) was used to compare the humoral immune responses between patients and healthy controls. The  $I^2$  statistic was used as a measure of heterogeneity across studies. Heterogeneity was defined as high (>75%), moderate (25%–75%) and low (<25%).<sup>16</sup> Heterogeneity was determined using Cochran's

**FIGURE 1** Flow chart of the assessment of the studies identified in the meta-analysis.

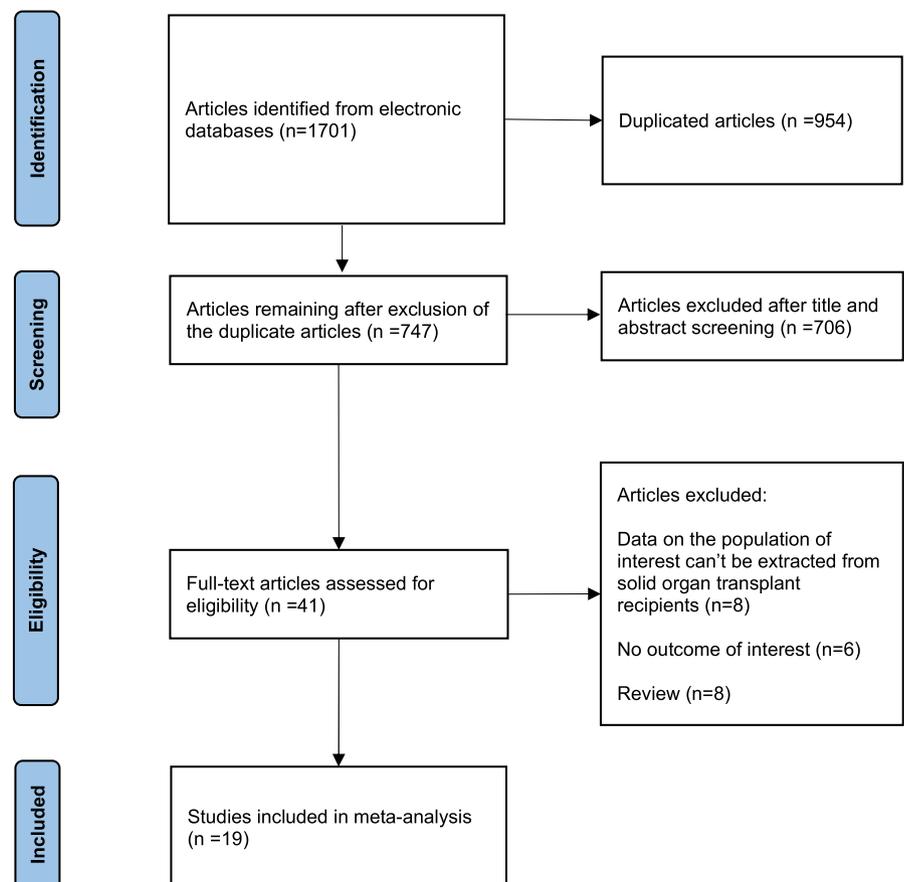


TABLE 1 Characteristics of the included studies

Study	Population	Sample size	Male (%)	Age, years, mean ± SD/median (IQR/range)	Comorbidity	Time after LT, years, mean ± SD/median (IQR/Range)
Ai 2021 <sup>18</sup>	CLD (cirrhosis 35.0%)	437	63.6%	Median: 47.0 (IQR 38.0–56.0)	Diabetes (5.3%) Hypertension (8.7%)	–
	HC	144	NA	Median: 35.0 (IQR 29.0–42.0)	NA	
Boyarsky 2021 <sup>19</sup>	LT	129	NA	NA	NA	NA
Cholankeril 2022 <sup>20</sup>	LT	69	69.6%	Median: 63.0 (IQR 51.0–68.0)	Diabetes (48%)	Median: 3.3 (IQR 1.7–8.3)
Davidov 2022 <sup>21</sup>	LT	76	56.6%	59.0 ± 15.0	CKD (35.2%); diabetes (42%); hypertension (48.6%)	Median: 7.0 (IQR 4.0–16.0)
	HC	174	49.4%	59.0 ± 13.0		–
Fernández-Ruiz 2021 <sup>22</sup>	LT	13	NA	NA	NA	NA
Guarino 2022 <sup>23</sup>	LT	365	76.4%	62.5 ± 13.0	NA	14.08 ± 8.84
	HC	340	64.1%	57.9 ± 8.3	–	–
He 2022 <sup>24</sup>	CLD (cirrhosis 13.3%)	362	61.6%	Median: 45.0 (range 19–78)	NA	–
	HC	87	50.6%	Median: 44.0 (range 25–75)	NA	NA
Herrera 2021 <sup>25</sup>	LT	58	69.0%	Median: 61.5 (IQR 18–88)	CKD (26%) Lymphopenia (20.7%) Hypogammaglobulinemia (14%)	Median: 4.6 (IQR 0.3–26.8)
Huang 2022 <sup>26</sup>	LT	274	NA	NA	NA	NA
	CLD	76	NA	NA	NA	–
Marion 2021 <sup>27</sup>	LT	58	NA	NA	NA	NA
Mazzola 2022 <sup>28</sup>	LT	56	76.8%	Median: 64.0 (IQR 58.0–68.2)	Diabetes (41.4%) Pulmonary diseases (3.4%) Cardiovascular disease (44.8%)	Median: 2.2 (IQR 1.3–4.9)
	HC	25	28.0%	Median: 55.0 (IQR 38.0–62.0)	–	–
Rabinowich 2021 <sup>29</sup>	LT	80	70%	60.1 ± 12.8	Diabetes (32.5%) Hypertension (56.2%)	Median: 5 (range 0.42–37)
	HC	25	32%	52.7 ± 11.5	–	–
Rashidi-Alavijeh 2021 <sup>30</sup>	LT	43	60.5%	NA	NA	Median: 8 (IQR 4–12)
	HC	20	45%	NA	–	–

Type of vaccine	Type of antibody	Assay of antibody testing	Cut-off for positive antibody response	Time interval between second vaccination and antibody measurement	Immunosuppressive regimen	NOS
CoronaVac BBIBP-CorV WIBP-CorV	Neutralizing Ab	CLIA	>10 AU/ml	≥2 weeks	—	8
mRNA-1273 BNT162B2	Anti-spike Ab	ECLIA	≥0.80 U/ml	Median: 29 days (IQR 28–31)	NA	6
BNT162B2 (100%)	Anti-spike Ab	ELISA	Titre >20.0	Range 30–75 days	MMF (36%); tacrolimus (90%); two agents (36%); three agents (12%)	6
BNT162B2 (100%)	Anti-spike RBD Ab	ELISA	Titre >1.1	38 ± 24 days  36 ± 22 days	MMF (21.3%); CNI monotherapy (53%); everolimus (14.7%); prednisone (16%); two agents (41%); three agents (5.3%)  —	8
mRNA-1273 (100%)	Anti-spike Ab	ELISA	OD value ≥1.1	2 weeks	Tacrolimus monotherapy; two agents; three agents	6
BNT162B2 (100%)	Anti-spike Ab	CLIA	>25 AU/ml	4 weeks	CNI (81.9%); steroid (7.6%); antimetabolite (36.2%); mTOR inhibitor (23.3%); single agent (59.7%); ≥two agents (40.3%)  —	6
CoronaVac BBIBP-CorV	Anti-spike RBD Ab	ELISA	OD value ≥2.1	1, 2 and 3 months	—	7
mRNA-1273 (100%)	Anti-spike RBD Ab	CLIA	NA	4 weeks	CNI (91%); MMF (26%); prednisone (22%); mTOR inhibitor (22%); monotherapy (47%); two agents (40%); three agents (12%)	6
mRNA-1273 BNT162B2	Anti-spike Ab	ELISA	Titre >1:50	Median: 63 days (IQR 53–77)	CNI; antimetabolites; mTOR inhibitor  — —	6
mRNA-1273 BNT162B2	Anti-spike Ab	ELISA	NA	4 weeks	CNI; MMF; mTOR inhibitor; steroid	5
BNT162B2 (100%)	Anti-spike RBD Ab	CLIA	≥50 AU/ml	4 weeks	CNI (77.6%); MMF (56.9%); steroid (25.9%); mTOR inhibitor (22.4%)  —	5
BNT162B2 (100%)	Anti-spike Ab	CLIA	≥15 AU/ml	14.8 ± 3.2 days  15.8 ± 2.9 days	CNI (93.7%); MMF (50%); prednisone (30%); everolimus, (22.5%); azathioprine (5%)  —	5
BNT162B2 (100%)	Anti-spike Ab	CLIA	≥13 AU/ml	Median: 15 days (IQR 12–24)  13 days	MMF (28%); tacrolimus (93%); tacrolimus monotherapy (18%); tacrolimus+everolimus (55%); tacrolimus+cyclosporine A (5%); everolimus (2%)  —	6

(Continues)

TABLE 1 (Continued)

Study	Population	Sample size	Male (%)	Age, years, mean ± SD/median (IQR/range)	Comorbidity	Time after LT, years, mean ± SD/median (IQR/Range)
Ruether 2022 <sup>31</sup>	LT	138	27.2%	55.0 ± 13.2	Diabetes (21.0%) Hypertension (61.6%)	Median: 7 (IQR 2–17)
	CLD (cirrhosis 100%)	48	60.4%	53.8 ± 9.5	Diabetes (25.0%) Hypertension (37.5%)	NA
	HC	52	36.5%	50.9 ± 11.6	–	–
Strauss 2021 <sup>32</sup>	LT	161	42.9%	Median: 64.0 (IQR 48.0–69.0)	NA	Median: 6.9 (IQR 2.9–15.0)
Thuluvath 2021 <sup>33</sup>	LT	62	66.1%	65.7 ± 8.7	COPD (13%) Hypertension (81.0%) Hyperlipidemia (56%) Renal impairment (65%) Coronary artery disease (19%)	NA
	CLD (cirrhosis 79%)	171	45.0%	60.4 ± 13.9	COPD (8.2%) Hypertension (63.7%) Hyperlipidemia (57.3%) Renal impairment (14.6%) Coronary artery disease (12.3%)	–
Timmermann 2021 <sup>34</sup>	LT	118	63.6%	Mean: 66.1 (range 28–89)	NA	Mean: 14.4 (range 0–37)
Wang 2021 <sup>35</sup>	NAFLD	381	47.0%	Median: 39 (IQR 33–48)	Diabetes (3.7%) Hypertension (11%)	–
Xiang 2021 <sup>36</sup>	CLD	149	72.5%	Median: 41 (IQR 33–49)	COPD (0.7%) Diabetes (2.7%) Hypertension (0.6%) Cardiovascular disease (1.3%)	–

Abbreviations: CKD, chronic kidney disease; CLD, chronic liver disease; CLIA, chemiluminescence analysis; CNI, calcineurin inhibitor; COPD, chronic obstructive pulmonary disease; ECLIA, electrochemiluminescence immunoassay analyser; ELISA, enzyme-linked immunosorbent assay; HC, healthy controls; IQR, interquartile range; LT, liver transplantation; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin; NA, not available; NAFLD, non-alcoholic fatty liver disease; NOS, Newcastle–Ottawa scale; OD, optical density; RBD, receptor binding domain; SD, standard deviation.

Type of vaccine	Type of antibody	Assay of antibody testing	Cut-off for positive antibody response	Time interval between second vaccination and antibody measurement	Immunosuppressive regimen	NOS
mRNA-1273 (8%) BNT162B2 (79.7%) AZD1222 (12.3%)	Anti-spike RBD Ab	ECLIA	≥0.80 U/mL	Median: 29 days (IQR 25–39)	CNI (92.8%); CNI monotherapy (23.9%); prednisone (31.2%); CNI + prednisone (13.8%); CNI + mTOR inhibitor (12.3%); CNI + MMF (34.8%); CNI + azathioprine (6.5%); biologicals (5.8%); ≥three agents (13%)	8
mRNA-1273 (12.4%) BNT162B2 (79.2%) AZD1222 (8.4%)				Median: 28 days (IQR 21–41)	–	
mRNA-1273 (5.8%) BNT162B2 (69.2%) AZD1222 (25%)				Median: 49 days (IQR 28–74)	–	
mRNA-1273 (47%) BNT162B2 (53%)	Anti-spike RBD Ab	ECLIA	≥0.80 U/ml	Median: 30 days (IQR 28–31)	MMF (35%); tacrolimus (81%); steroid (22%); sirolimus (11%); cyclosporine (8%); azathioprine (6%); everolimus (3%)	5
mRNA-1273 (53%) BNT162B2 (39%) JNJ-78436735 (8%)	Anti-spike RBD Ab	ECLIA	≥0.4 U/ml	38.9 ± 19.6 days	Azathioprine (3%); prednisone (13%); tacrolimus (66%)	6
mRNA-1273 (52%) BNT162B2 (39%) JNJ-78436735 (9%)				40.9 ± 23.9 days	Azathioprine (10%); prednisone (13%)	
BNT162b2 (96.7%) mRNA-1273 (2.5%) JNJ-78436735 (0.8%)	Anti-spike Ab	ELISA	NA	Mean: 44.6 days (range 21–132)	MMF monotherapy (13.6%); tacrolimus monotherapy (35.6%); tacrolimus+MMF (20.3%); tacrolimus+everolimus (12.7%); everolimus monotherapy (0.8%); ciclosporin+MMF (2.5%); ciclosporin monotherapy (1.7%); tacrolimus+Azathioprine (0.8%)	5
BBIBP-CorV (100%)	Neutralizing Ab	CLIA	NA	2 weeks	–	6
CoronaVac BBIBP-CorV WIBP-CorV	Anti-spike RBD Ab	CLIA	>1 AU/ml	Median: 33 days (IQR 24–48)	–	7

Q-statistics with a significance threshold of  $p < .1$ .<sup>17</sup> To mitigate the effects of between-study heterogeneity on the findings of the analysis, we conducted the meta-analysis using a random-effects model. We performed the sensitivity analysis by removing one study at a time to observe the effects on the outcomes. Subgroup analyses were performed based on cirrhosis status, vaccine platform, vaccine type, assay of antibody testing and time interval between second vaccination and antibody measurement. Pooled odds ratio (OR) with 95% CI was used to calculate the pooled effect estimate of risk factor for poor antibody responses. Begg's and Egger's tests were performed to assess publication bias, and funnel plots were constructed to visualize asymmetry when the number of available studies for each analysis was  $\geq 10$ .

### 3 | RESULTS

#### 3.1 | Study characteristics

The initial search identified 1701 articles. After the removal of duplicates and other articles that were irrelevant to this study (based on title and abstract), 41 potentially relevant articles remained and their full texts were evaluated. Based on the inclusion criteria, 19 studies<sup>18-36</sup> that included 4191 participants (1624 CLD patients, 1700 LT recipients and 867 healthy controls) were included (Figure 1). Seven studies<sup>18,24,26,31,33,35,36</sup> included CLD patients and 15 studies<sup>19-23,25-34</sup> included LT recipients. Of the 19 studies, 15 studies<sup>19-23,25-34</sup> used mRNA vaccines (BioNTech vaccine: BNT162B2 or Moderna vaccine: mRNA-1273) and 4 studies<sup>18,24,35,36</sup> used inactivated vaccines (Sinovac vaccine: CoronaVac, Sinopharm vaccine: BBIBP-CorV and Sinopharm vaccine: WIBP-CorV). Three studies<sup>31,33,34</sup> used mRNA vaccines and included a small proportion (0.8%–25%) of patients who received adenovirus vector vaccines (Johnson and Johnson vaccine: JNJ-78436735 and AstraZeneca vaccine: AZD1222), but data were not reported separately, so these

studies were included in the analyses of mRNA vaccines. All participants completed two doses of vaccination. The majority of the studies selected a time frame of 2–5 weeks after the second vaccination to assess the immune responses to COVID-19 vaccines. Five studies<sup>18,21,24,31,36</sup> showed a low risk of bias (7–8 points), with 14 studies<sup>19,20,22,23,25–30,32–35</sup> having a moderate bias risk (5–6 points). Characteristics of the included studies are summarized in Table 1.

#### 3.2 | Humoral immune responses after two doses of vaccination in chronic liver disease patients

Seven studies<sup>18,24,26,31,33,35,36</sup> assessed the humoral immune responses after two doses of vaccination in CLD patients. As shown in Figure 2, the overall proportion of all included CLD patients achieving humoral immune responses was 95% (95% CI = 88%–99%) with considerable heterogeneity ( $I^2 = 95.9\%$ ,  $p < .01$ ). Sensitivity analysis showed that the removal of Ai's and Xiang's studies<sup>18,36</sup> reduced the heterogeneity ( $I^2 = 63.7\%$ ,  $p = .03$ ). The corresponding pooled humoral immune response rate was not changed markedly (98%, 95% CI = 96%–99%) (Figure S1). In addition, we compared the humoral immune responses in cirrhosis patients and non-cirrhotic CLD patients. There was no significant difference in the humoral immune response rate between cirrhosis and non-cirrhotic CLD patients (RR = 0.99; 95% CI = 0.96–1.03) without heterogeneity ( $I^2 = 0\%$ ,  $p = .66$ ) (Figure S2).

#### 3.3 | Subgroup analysis

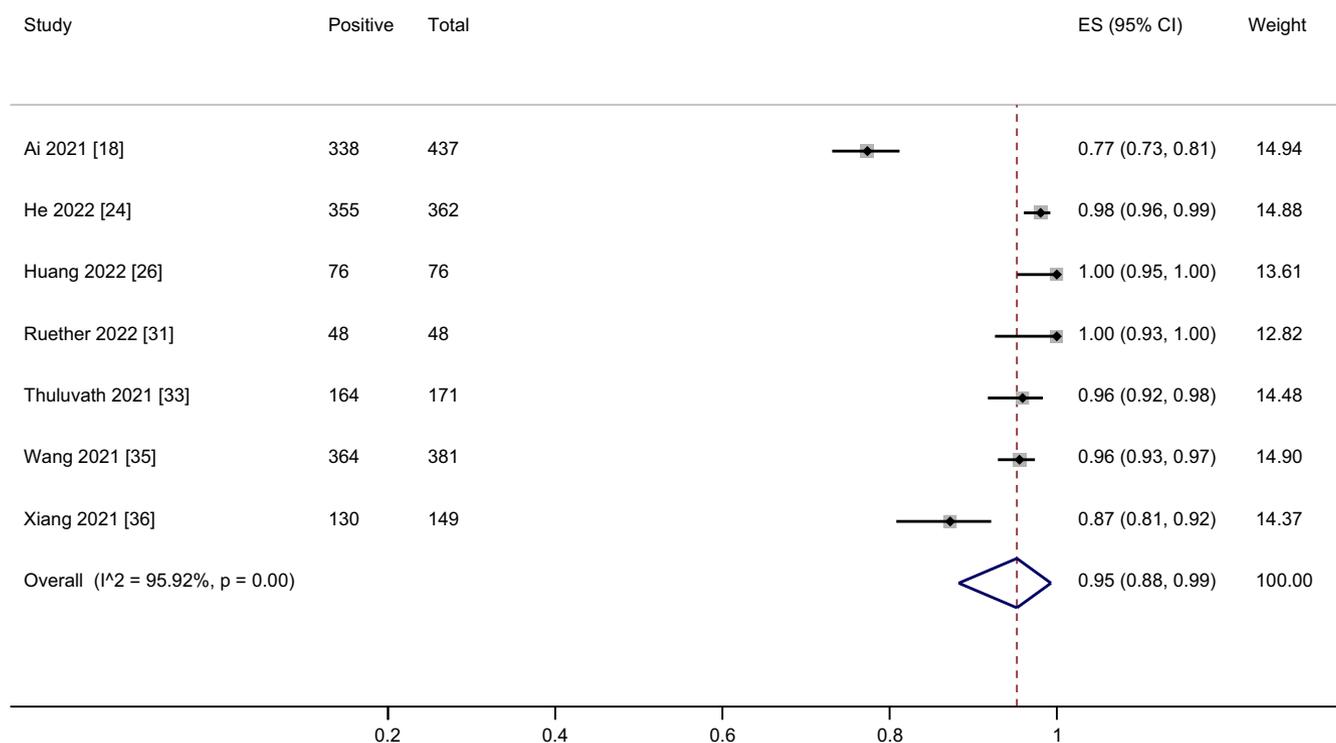
We performed a subgroup analysis based on whether or not patients had cirrhosis. The rates of humoral immune responses were 94% (95% CI = 82%–100%) and 94% (95% CI = 86%–99%) in the cirrhosis and in the non-cirrhotic CLD patients respectively (Figure S3).

We performed a subgroup analysis based on the vaccine platform. The rates of humoral immune responses were 91% (95%

TABLE 2 Potential risk factors for poor antibody responses

Risk factor	Number of included studies	Pooled OR/OR	95% CI	$I^2$
MMF	3 <sup>25,29,31</sup>	3.27	1.45–7.41	65.0%
Diabetes	2 <sup>28,31</sup>	2.75	1.48–5.09	0%
$\geq 2$ immunosuppressants	4 <sup>20,29,31,33</sup>	3.13	1.22–7.99	80.1%
Age	4 <sup>20,25,29,31</sup>	1.08	0.98–1.20	74.9%
Time since transplant	4 <sup>20,25,29,31</sup>	2.54	0.93–6.95	78.5%
eGFR	2 <sup>29,31</sup>	2.53	0.23–27.38	93.5%
Obesity	2 <sup>20,31</sup>	1.86	0.36–9.66	79.2%
Hypertension	1 <sup>31</sup>	2.62	1.28–5.37	NA
High dose prednisone	1 <sup>29</sup>	1.8	1.58–4.61	NA
Time from second vaccination to antibody test	1 <sup>20</sup>	1.01	0.96–1.04	NA
Hypogammaglobulinemia	1 <sup>25</sup>	61	3.70–1004.30	NA

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; MMF, mycophenolate mofetil; NA, not available; OR, odds ratio.



**FIGURE 2** Meta-analysis of the humoral immune responses after two doses of COVID-19 vaccination in CLD patients.

CI = 79%–98%) and 99% (95% CI = 95%–100%) in inactivated vaccines and mRNA vaccines respectively (Figure S4).

We performed a subgroup analysis based on the assay of antibody testing. The rates of humoral immune responses were 88% (95% CI = 73%–97%), 99% (95% CI = 97%–100%), and 97% (95% CI = 95%–99%) in CLIA, ELISA and ECLIA respectively (Figure S5).

We performed a subgroup analysis based on the time interval between second vaccination and antibody measurement. The rates of humoral immune responses were 93% (95% CI = 77%–100%) and 96% (95% CI = 91%–100%) in  $\leq 4$  weeks and  $> 4$  weeks respectively (Figure S6).

### 3.4 | Humoral immune responses after two doses of vaccination in liver transplant recipients

Fifteen studies<sup>19–23,25–34</sup> assessed the humoral immune responses after two doses of vaccination in LT recipients. The overall proportion of patients achieving humoral immune responses was 66% (95% CI = 57%–74%) with considerable heterogeneity ( $I^2 = 92.1\%$ ,  $p < .01$ ) (Figure 3). The funnel plot showed no publication bias (Egger's test  $p = .77$ , Begg's test  $p = .13$ ) (Figure S7). We performed a sensitivity analysis by removing three studies<sup>31,33,34</sup> including adenovirus vector vaccines. The heterogeneity did not decrease after removing the three studies. The corresponding pooled humoral immune response rate hardly changed (62%, 95% CI = 52%–72%) (Figure S8). We found that the heterogeneity was mainly derived

from six studies.<sup>20,22,26–29</sup> The exclusion of these studies effectively removed the heterogeneity ( $I^2 = 0\%$ ,  $p = .57$ ), but the corresponding pooled humoral immune response rate was not changed markedly after the removal of these studies (77%, 95% CI = 74%–79%) (Figure S9). Removing one study at a time also showed that the removal of any individual study had little effect on the pooled rate, indicating that the result was stable.

### 3.5 | Subgroup analysis

We performed a subgroup analysis based on the vaccine type. The rates of humoral immune responses were 64% (95% CI = 41%–84%), 61% (95% CI = 46%–74%), 68% (95% CI = 56%–79%), 74% (95% CI = 66%–81%) and 80% (95% CI = 73%–85%) in mRNA-1273+BNT162B2, BNT162B2, mRNA-1273, mRNA-1273+BNT162B2+AZD1222 and mRNA-1273+BNT162B2+JNJ-78436735 respectively (Figure S10).

We performed a subgroup analysis based on the assay of antibody testing. The rates of humoral immune responses were 79% (95% CI = 75%–82%), 58% (95% CI = 43%–72%) and 63% (95% CI = 47%–77%) in ECLIA, ELISA and CLIA respectively (Figure S11).

We performed a subgroup analysis based on the time interval between second vaccination and antibody measurement. The rates of humoral immune responses were 70% (95% CI = 55%–83%) and 62% (95% CI = 51%–73%) in  $> 4$  weeks and  $\leq 4$  weeks respectively (Figure S12).

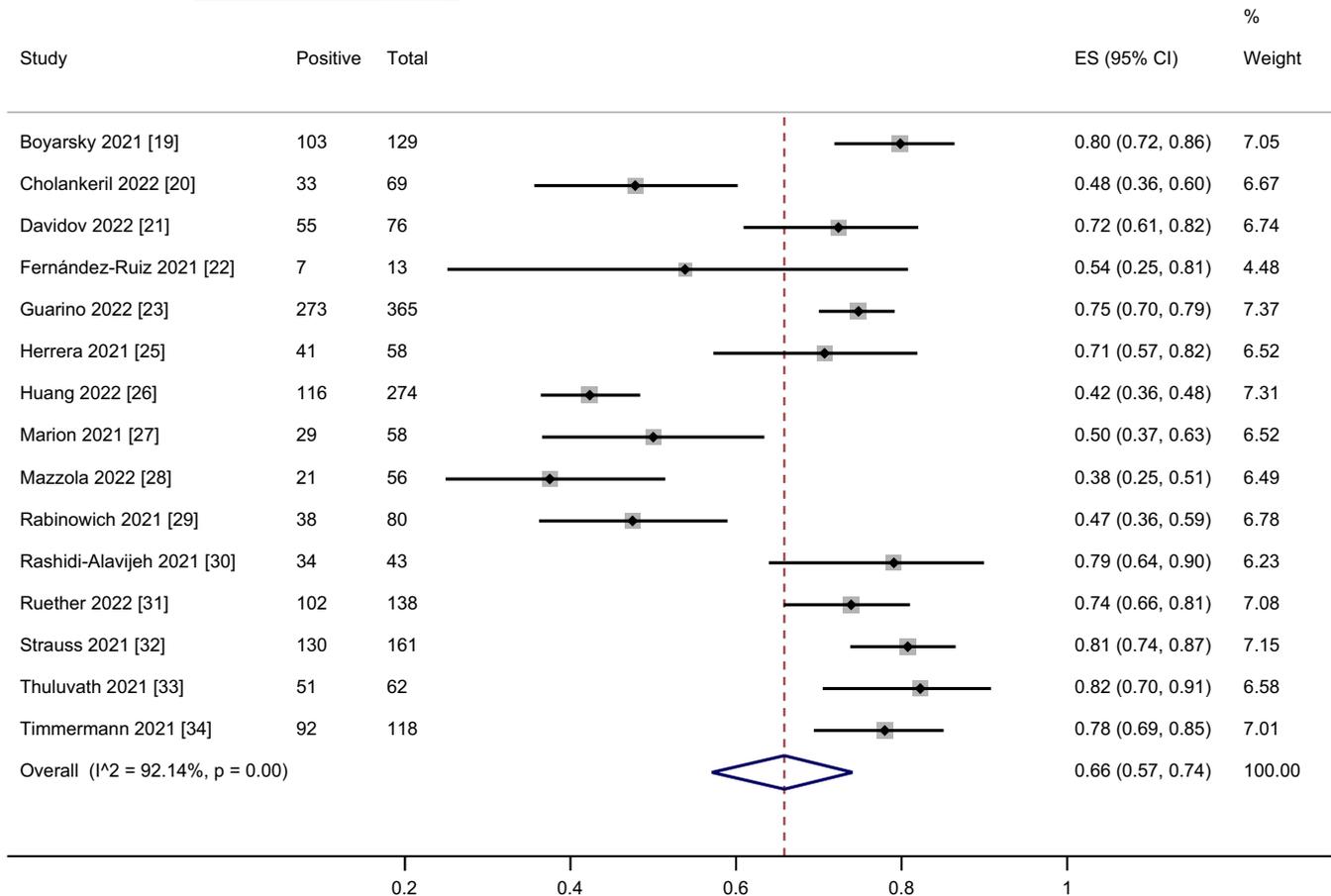


FIGURE 3 Meta-analysis of the humoral immune responses after two doses of COVID-19 vaccination in LT recipients.

### 3.6 | Risk factors for poor antibody responses in liver transplant recipients

Six studies<sup>20,25,28,29,31,33</sup> performed a univariate or multivariate analysis of the risk for negative serology in LT recipients. When more than two studies investigated a risk factor, the pooled OR with 95% CI was used to calculate the pooled effect estimate of risk factor for poor antibody responses. Totally, our results revealed that mycophenolate mofetil (MMF) (OR = 3.27, 95% CI = 1.45–7.41), diabetes (OR = 2.75, 95% CI = 1.48–5.09) and more than two immunosuppressants (OR = 3.13, 95% CI = 1.22–7.99) were risk factors for poor antibody responses in LT recipients. Parameters investigated by univariate or multivariate analysis as potential risk factors for poor antibody responses and results of meta-analysis were summarized in Table 2.

### 3.7 | Comparison of humoral immune responses between patients and healthy controls

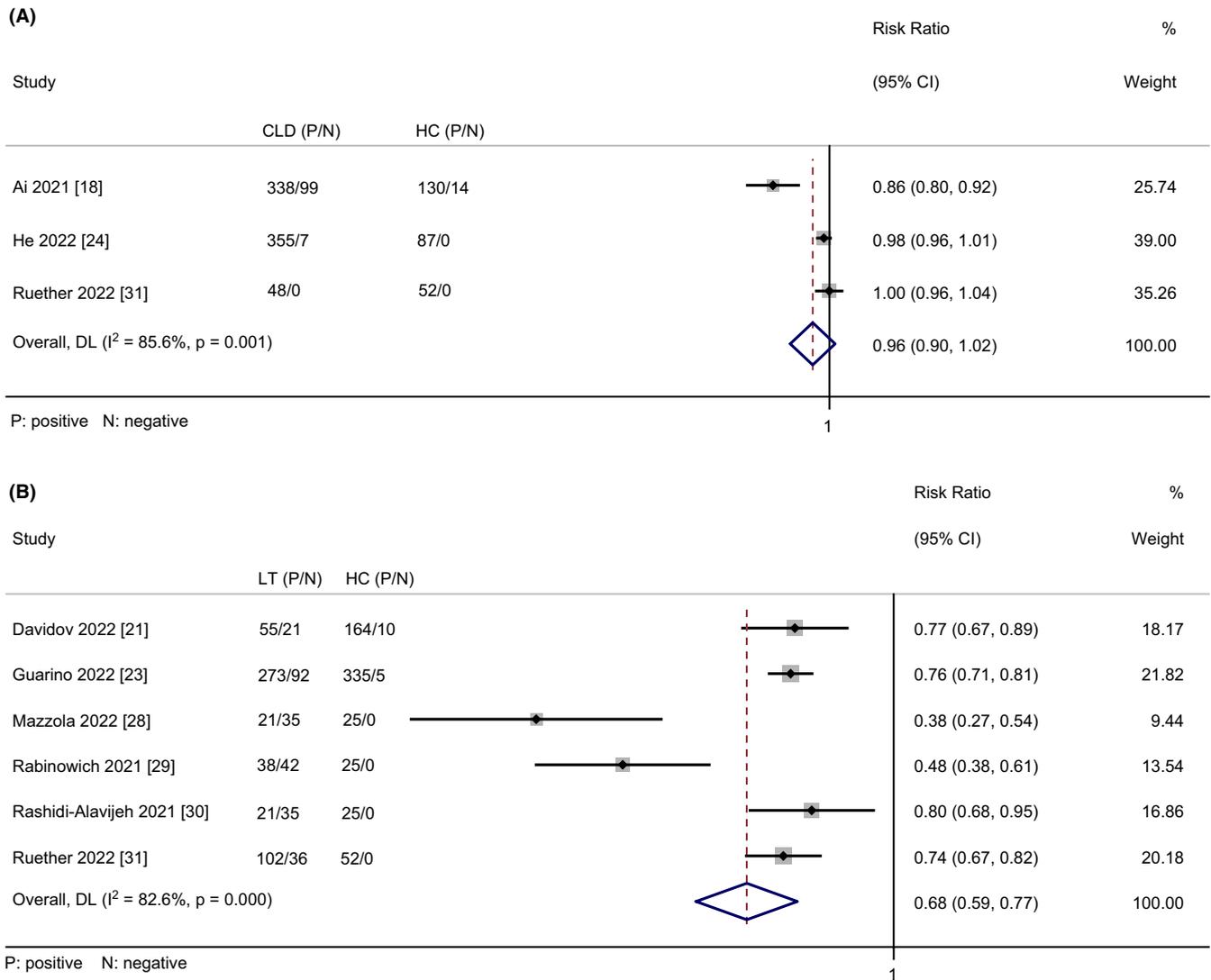
Three studies<sup>18,24,31</sup> assessed the humoral immune responses after two doses of vaccination in CLD patients in comparison with healthy controls. There was no statistically significant difference in the humoral immune response rate between CLD patients and healthy

controls (RR = 0.96, 95% CI = 0.90–1.02) with considerable heterogeneity ( $I^2 = 85.6\%$ ,  $p < .01$ ) (Figure 4A). The meta-analysis result was not changed markedly (RR = 0.99, 95% CI = 0.97–1.01) without heterogeneity ( $I^2 = 0\%$ ,  $p = .53$ ) by removing Ai's study,<sup>18</sup> indicating that the result was stable (Figure S13).

Six studies<sup>21,23,28–31</sup> compared the humoral immune responses after two doses of vaccination between LT recipients and healthy controls. Meta-analysis of the six studies demonstrated that a significantly smaller proportion of LT recipients achieved humoral immune responses compared to healthy controls (RR = 0.68, 95% CI = 0.59–0.77) with considerable heterogeneity ( $I^2 = 82.6\%$ ,  $p < .01$ ) (Figure 4B). The rate of humoral immune response in LT recipients was still lower than healthy controls after removing two studies<sup>28,29</sup> (RR = 0.76, 95% CI = 0.73–0.80) with no heterogeneity ( $I^2 = 0\%$ ,  $p = .90$ ) (Figure S14). Additionally, we found that the RR value was not changed markedly after the removal of any one study, confirming the result's stability.

### 3.8 | Cellular immune responses after two doses of vaccination

Three studies<sup>22,25,31</sup> assessed the cellular immune responses after two doses of vaccination in LT recipients. The overall proportion



**FIGURE 4** (A) Meta-analysis of comparison of the humoral immune responses between CLD patients and healthy controls. (B) Meta-analysis of comparison of the humoral immune responses between LT recipients and healthy controls.

of patients achieving cellular immune responses was 71% (95% CI = 25%–100%) with considerable heterogeneity ( $I^2 = 96.5\%$ ,  $p < .01$ ) (Figure 5). The heterogeneity was effectively decreased after the exclusion of Ruether's study<sup>31</sup> ( $I^2 = 43.6\%$ ,  $p = .18$ ). In addition, the corresponding pooled cellular immune response rate was increased (92%, 95% CI = 83%–98%) (Figure S15). We did not perform the meta-analysis of the cellular immune responses in CLD patients as only Ruether's study reported this result. In Ruether's study, the rates of cellular immune response were 36.6%, 65.4% and 100% in LT recipients, CLD patients and healthy controls respectively.

### 3.9 | Grading the quality of evidence

According to the GRADE approach, the overall quality of evidence was low, as all the data were from observational studies (Table 3).

## 4 | DISCUSSION

We performed this meta-analysis of currently available observational studies to assess the immunogenicity of COVID-19 vaccines in CLD patients and LT recipients. We demonstrated that two doses of COVID-19 vaccination appeared to induce a strong humoral immune response in CLD patients. However, the rate of humoral immune response was low in LT recipients. Moreover, a significantly lower proportion of LT recipients achieved humoral immune responses after two doses of vaccination compared with healthy controls.

Our results indicated that the humoral immune responses to COVID-19 vaccines did not appear to be impaired in CLD patients. These findings are very interesting, which is inconsistent with clinical phenomenon and previous study, where CLD patients especially those with cirrhosis, have reduced humoral immune responses to other vaccines such as HBV vaccines.<sup>37</sup> The included studies have demonstrated that older age, high body mass index,

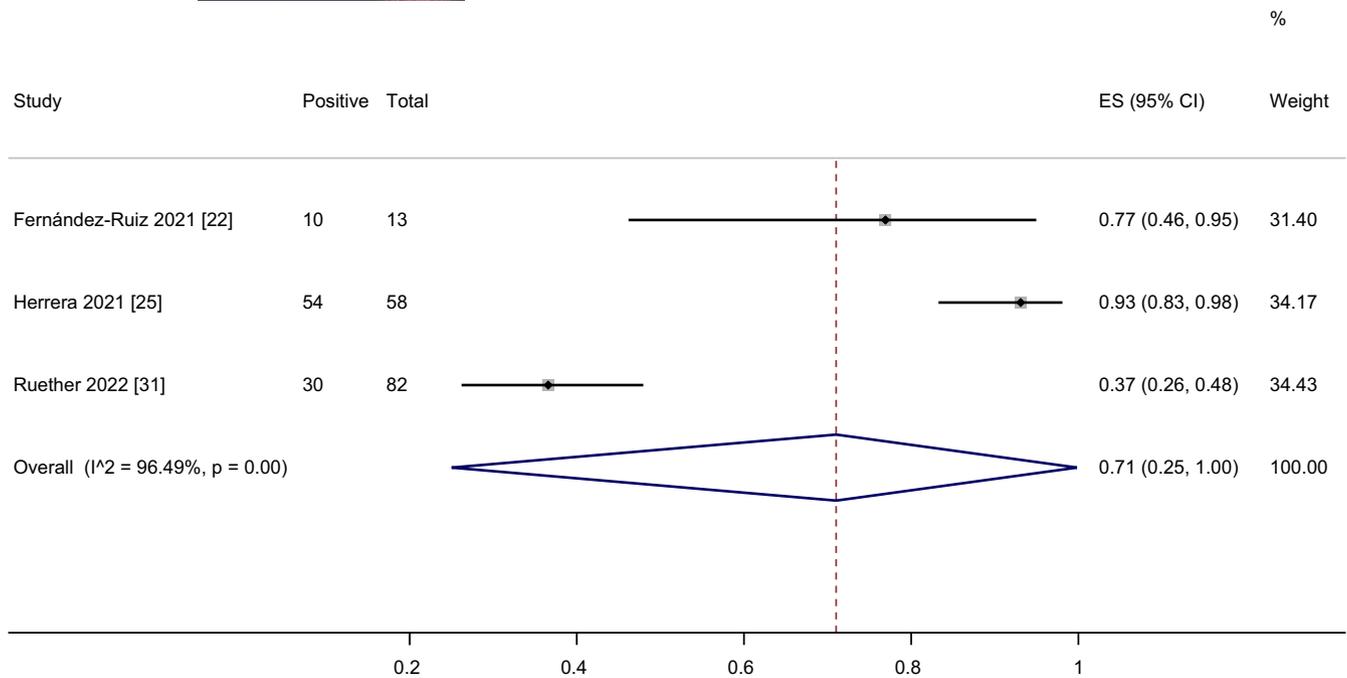


FIGURE 5 Meta-analysis of the cellular immune responses after two doses of COVID-19 vaccination in LT recipients.

renal impairment, diabetes and compensation status in CLD patients are associated with immunosuppressive status, which can contribute to the decreased immune responses to COVID-19 vaccines.<sup>18,33,35</sup> However, in the included studies<sup>18,31,35</sup> most patients were young. Moreover, obesity, diabetes and renal insufficiency were observed only in a small number of patients. These suggest that the majority of CLD patients in the included studies were not severely immunocompromised, which might explain the high seroconversion rate. Another potential reason for the high seroconversion rate may be related to the use of mRNA vaccines. Variability of antibody production among vaccinated populations may be related to the vaccine types, which may lead to different initial immune responses.<sup>38</sup> As the first mRNA vaccines used in humans, the SARS-CoV-2 mRNA vaccines use the synthesis mechanism of host cells to produce SARS-CoV-2 antigen, thereby triggering strong immune responses.<sup>39-41</sup> The previous studies found that compared with other types of vaccines, mRNA vaccines were more likely to cause seroconversion.<sup>42-44</sup> In this study, seven studies<sup>18,24,26,31,33,35,36</sup> explored the humoral immune responses after vaccination in CLD patients. Three<sup>26,31,33</sup> of seven studies used mRNA vaccines and four<sup>18,24,35,36</sup> used inactivated vaccines. Our meta-analysis showed that the rate of seroconversion to mRNA vaccines was higher than in inactivated vaccines (99% vs. 91%).

Patients with cirrhosis are considered more severely immunocompromised than non-cirrhotic CLD patients. However, in the subgroup analysis, we observed similar humoral immune responses in cirrhosis and non-cirrhotic CLD patients, consistent with He's and Thuluvath's studies.<sup>24,33</sup> Thuluvath's study found cirrhosis was not associated with a poor antibody response after COVID-19 vaccination using multivariate analysis.

Regarding the humoral immune response, our meta-analysis results showed that 68% of LT recipients achieved seroconversion after two doses of vaccination. Moreover, we also found that the humoral immune responses were reduced in LT patients compared with healthy controls, which is in line with previous studies.<sup>21,23,28-31</sup> Our results indicated that MMF and more than two immunosuppressants were risk factors related to poor antibody responses. These immunosuppressive regimens can greatly suppress the patient's immune status, resulting in poor antibody responses to vaccines. Many studies<sup>29,31,33</sup> have demonstrated that treatment with MMF or more than two immunosuppressants can decrease the immune responses to COVID-19 vaccines, consistent with the findings in solid organ transplant recipients.<sup>45,46</sup> LT patients who received the MMF show a lower seroconversion rate (45.5%–61%) in comparison with those without the MMF (79%–81%).<sup>30,32</sup> Diabetes is common among transplant recipients, notably as a complication of the transplant immunosuppressive therapy (steroids and calcineurin inhibitors). In the present study, our meta-analysis result showed diabetes is an independent risk factor for poor humoral immune response. This is also consistent with previous studies suggesting that seasonal influenza vaccination uptake remains suboptimal in patients with diabetes probably due to immune dysfunction in patients with diabetes mellitus.<sup>47,48</sup>

It has been found that, despite a lack of seroconversion, the T-cell response may protect an individual against the SARS-CoV-2 infection.<sup>49</sup> Thus, the T-cell response should be examined after vaccination to assist in the determination of vaccine effectiveness. In the present study, only three studies<sup>22,25,31</sup> reported the cellular immune responses to vaccination. The result of meta-analysis showed that the cellular immune responses in LT recipients were still low

**TABLE 3** Grading of recommendations, assessment, development and evaluation (GRADE) criteria for studies included in the meta-analysis assessing the immunogenicity after two doses of COVID-19 vaccines

Outcome	No. of participants	Starting level of evidence	Quality assessment						Reasons to increase level of evidence (large magnitude of effect; dose-response gradient; potential confounding)	Overall quality of evidence
			Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias			
<b>CLD</b>										
Pool rate of HIR	1624	Low	Not serious	Not serious	Serious	Not serious	Not serious	Not serious	Not applicable	Low
HIR (cirrhosis vs. non-cirrhosis CLD)	282 (cirrhosis) 690 (non-cirrhosis CLD)	Low	Not serious	Serious	Serious	Not serious	Not serious	Not serious	Not applicable	Low
HIR (CLD vs. HC)	847 (CLD) 283 (HC)	Low	Not serious	Not serious	Serious	Not serious	Not serious	Not serious	Not applicable	Low
<b>LT</b>										
Pool rate of HIR	1700	Low	Not serious	Serious	Serious	Not serious	Not serious	Not serious	Not applicable	Low
Pool rate of CIR	153	Low	Not serious	Serious	Serious	Not serious	Not serious	Not serious	Not applicable	Low
HIR (LT vs. HC)	758 (LT) 636 (HC)	Low	Not serious	Serious	Serious	Not serious	Not serious	Not serious	Not applicable	Low

Abbreviations: CIR, cellular immune response; CLD, chronic liver disease; HC, healthy controls; HIR, humoral immune response; LT, liver transplantation.

with considerable heterogeneity. After removing Rueher's study,<sup>31</sup> the rate of cellular immune response was increased significantly to 92% without heterogeneity, which indicated the instability of this result. We found clinically heterogeneous participants and different immunosuppressive regimens could be the main source of heterogeneity. Although some studies suggest a decrease in cellular immune response after vaccination in immunocompromised patients, more studies are needed to confirm this conclusion in CLD patients and LT recipients.

The present study has some limitations. Firstly, most included studies only evaluated humoral responses to COVID-19 vaccines, and data on the cellular immune responses to COVID-19 vaccines are still lacking. Secondly, it is important to emphasize that the included studies are observational and have potential sources of bias, such as selection bias or confounding, that cannot be adjusted by meta-analysis.

In conclusion, the present study demonstrated that COVID-19 vaccination elicited strong humoral responses in CLD patients but poor humoral immune responses in LT recipients. The findings indicate that CLD patients and LT recipients should complete the full vaccine schedule without delay and support the administration of a third dose of vaccine to LT recipients. With both the appearance of novel variants of the virus and waning antibody responses, further studies assessing the immunogenicity and effectiveness of different types of vaccines and updated living meta-analyses are warranted.

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## CONFLICT OF INTEREST

The authors do not have any disclosures to report.

## ORCID

De Luo  <https://orcid.org/0000-0002-2295-1822>

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#### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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