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Antibody Response Induced by Two Doses of ChAdOx1 nCoV-19, mRNA-1273, or BNT162b2 in Liver Transplant Recipients

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ABSTRACT

Coronavirus disease 2019 (COVID-19) vaccination in immunocompromised, especially transplant recipients, may induce a weaker immune response. But there are limited data on the immune response after COVID-19 vaccination in liver transplant (LT) recipients, especially on the comparison of Ab responses after different vaccine platforms between mRNA and adenoviral vector vaccines. Thus, we conducted a prospective study on LT recipients who received two doses of the ChAdOx1 nCoV-19 (ChAdOx1), mRNA-1273, or BNT162b2 vaccines compared with healthy healthcare workers (HCWs). SARS-CoV-2 S1-specific IgG Ab titers were measured using ELISA. Overall, 89 LT recipients (ChAdOx1, n=16 [18%]) or mRNA vaccines (mRNA-1273 vaccine, n=23 [26%]; BNT162b2 vaccine, n=50 [56%]) received 3 different vaccines. Of them, 16 (18%) had a positive Ab response after one dose of COVID-19 vaccine and 62 (73%) after 2 doses. However, the median Ab titer after two doses of mRNA vaccines was significantly higher (44.6 IU/ml) than after two doses of ChAdOx1 (19.2 IU/ml, p=0.04). The longer time interval from transplantation was significantly associated with high Ab titers after two doses of vaccine (p=0.003). However, mycophenolic acid use was not associated with Ab titers (p=0.53). In conclusion, about 3-quarters of LT recipients had a positive Ab response after 2 doses of vaccine, and the mRNA vaccines induced higher Ab responses than the ChAdOx1 vaccine.

Keywords: IgG antibody; COVID-19; ChAdOx1 nCoV-19; Liver transplantation; mRNA-1273; BNT162b2

INTRODUCTION

Since the World Health Organization declared the pandemic of coronavirus disease 2019 (COVID-19) on March 11, 2020, more than 500 million individuals worldwide have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), of whom more than 6 million (1%) died (1). After the initial rollout of the COVID-19 vaccine on 8 December 2020, two platforms of COVID-19 vaccines have been widely used. One is an adenoviral-vector vaccine such as ChAdOx1 nCoV-19 (AstraZeneca, Cambridge, UK) and Ad26.COV2.S (Johnson

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Conflict of Interest
The authors declare no potential conflicts of interest.

Abbreviations
ABOi, ABO incompatible; CI, confidential interval; COVID-19, coronavirus disease 2019; GFR, glomerular filtration rate; HCC, hepatocellular carcinoma; HCW, healthcare worker; IQR, interquartile range; KT, kidney transplantation; LT, liver transplant; PE, plasma exchange; Ref, reference value; RTX, rituximab; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Tfh, follicular Th cells; TTS, thrombocytopenia syndrome.

Author Contributions
Conceptualization: Kim SH, Song GW, Lee SG; Data curation: Lim SY, Yoon YI; Formal analysis: Lim SY, Yoon YI; Investigation: Kim JY, Tak E; Methodology: Lim SY, Kim JY, Tak E; Software: Lim SY; Validation: Kim JY, Tak E; Writing - original draft: Lim SY, Yoon YI, Kim JY, Tak E; Writing - review & editing: Lim SY, Kim SH, Song KW, Lee SG.

& Johnson-Janssen, Titusville, NJ, USA), and the other is an mRNA vaccine such as BNT162b2 (Pfizer-BioNTech, Gaithersburg, MD, USA) and mRNA-1273 (Moderna, Cambridge, MA, USA). Although there are some differences in terms of immunogenicity depending on the type of vaccines, primary series COVID-19 vaccination has provided the protection against COVID-19–related hospitalization and death as well as against symptomatic COVID-19 (2,3). However, since the emergence of the Delta variant (B.1.617.2) or Omicron variant (B.1.1.529) and waning of vaccine-induced immunity have significantly decreased the vaccine effectiveness, COVID-19 vaccine boosters have been recommended because booster dose can further enhance or restore protection (4).

While the immunocompromised status increases the risk of severe COVID-19 illness and deaths, COVID-19 vaccination may not be as strong as in immunocompetent individuals. Recent studies that revealed low seropositive rates after COVID-19 mRNA vaccines in kidney transplantation (KT) recipients are in line with this concern (5-8). But there are limited data about the immune response after COVID-19 vaccination in liver transplant (LT) recipients. Also, seropositivity after 2 doses of COVID-19 vaccination in LT recipients is inconsistent between studies, varying from 47.5% (9) to 82.3% (10). In addition, data regarding the comparison of Ab responses for mRNA and adenoviral vector vaccines in LT recipients are more limited (11). Thus, we aimed to investigate the Ab response and the weak Ab response predictors after COVID-19 mRNA vaccines (BNT162b2 or mRNA-1273) and the adenoviral vector vaccine (ChAdOx1 nCoV-19) in LT recipients.

MATERIAL AND METHODS

Study participants and collection of specimens

This study was performed at the Asan Medical Center, a tertiary care hospital in Seoul, South Korea. Healthcare workers (HCWs) who have no COVID-19 infection history and confirmed by PCR, were enrolled in this study. Three types of vaccine, ChAdOx1, mRNA-1273, and BNT162b2, were administered to the participants of HCWs and LT recipients according to a nationwide vaccination program against COVID-19 in South Korea. The BNT162b2 vaccine was allotted to HCWs who are at high-risk as they are in direct contact with COVID-19 patients, otherwise, the ChAdOx1 vaccine was administered, between March and October 2021, according to the policy of the Korean government. In addition, mRNA-1273 vaccine was given instead of ChAdOx1 to individuals under 30 because of the thrombosis with thrombocytopenia syndrome (TTS) issue, as recommended by the Korean government. LT recipients were enrolled between June and October 2021. All participants underwent blood sampling before vaccination, 3 weeks after the first dose of vaccine, and 2 weeks after the second dose of vaccine for SARS-CoV-2 S1-specific IgG Ab testing. Vaccines were administered to the participants according to the vaccine availability in South Korea during the study enrollment period, therefore, the interval between the doses was varied. The interval between the first and second dose was 8, 4, and 3 weeks respectively in healthy healthcare workers as per the manufacturer's recommendations, but was scheduled to be 8, 5 and 6 weeks in LT recipients due to vaccine availability in South Korea during the study enrollment period. Serum FK506 trough level was obtained just before the next dose.

All patients provided written informed consent. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of the Asan Medical Center (IRB No. 2021-0746 and 2021-0170).

Measurement of the Ab response

SARS-CoV-2 S1-specific IgG Ab titers were measured using an in-house developed ELISA qualified with reference pooled sera from the International Vaccine Institute (Seoul, Korea). S1-specific IgG Ab titers are presented in international units per milliliter. To determine the cutoff values for the ELISA, the mean and SD of the negative control plasma were measured, and cutoff values were defined as mean plus 3-fold the SD value. The cutoff value was 10 IU/ml for IgG, as described in our previous study (12).

Protocol for preoperative preparation and immunosuppression

For ABO incompatible (ABOi) LT recipients, a desensitization protocol for overcoming the ABO blood group barrier included rituximab (RTX) administration and plasma exchange (PE). All patients received a single intravenous dose of RTX (300–375 mg/m^2 body surface area) around 3 weeks before liver transplantation. Fresh frozen plasma in the AB+ blood type was used for PE, with the frequency and timing of PE dependent upon the hemagglutinin titer and the goal of an Ab titer of ≤1:8 prior to liver transplantation. Intravenous methylprednisolone (10 mg/kg body weight) was administered just prior to reperfusion. All patients in this study used the same maintenance immunosuppressive regimen including tacrolimus, mycophenolate mofetil (500 mg twice daily), and steroids. Steroids were gradually tapered off and stopped within 3 months after liver transplantation.

Statistical analysis

The χ^2 test or Fisher exact test was used for analysis of categorical variables. The Student's t-test or Mann-Whitney U-test was used for analysis of the continuous variables according to the normality of the data. Logistic and linear regression models were fitted to determine the factors influencing the seropositivity and Ab titer after vaccination. A 2-tailed p-value of <0.05 was considered statistically significant in all analyses. R version 4.1.1 (R Project for Statistical Computing, Vienna, Austria) and GraphPad Prism version 8.0 (GraphPad Software, San Diego, CA, USA) were used for the analyses and graph plotting of the results.

RESULTS

Participant characteristics

The total participants were 223: 134 HCWs and 89 LT recipients who enrolled in this study. LT recipients who received the adenoviral vector vaccine (ChAdOx1 nCoV-19, n=16 [18%]) or mRNA vaccines (mRNA-1273 vaccine, n=23 [26%]; BNT162b2 vaccine, n=50 [56%]) were enrolled in this study. Of the 89 participants, 85 were followed up for blood sampling after the second dose of vaccines. The median interval time between the first and second dose of vaccine in LT recipients was 58 days (interquartile range [IQR], 56–77) for ChAdOx1, 37 days (IQR, 30–42) for mRNA-1273, and 42 days (IQR, 32–42) for BNT162b2. The median time interval between the second dose vaccine and blood sampling for the measuring of Ab levels was 19 days (IQR, 14–28). The mean (±SD) age of the participants was 53.4 (±10.0) years, and 36% of participants were female. The median time from transplantation to vaccination was about 25.4 months (IQR, 8.8–87.0) overall. The number of participants with a history of rejection treatment within 1 year was only one in each vaccine group. The most common reason for LT was liver cirrhosis for any reason (44.9%), followed by hepatocellular carcinoma (43.8%). Almost all participants (94.4%) took a calcineurin inhibitor as the backbone of immunosuppressant maintenance, and about half of the participants (56.2%) took antimetabolite (all mycophenolic acid). Demographic and clinical characteristics of LT recipients according to the vaccination type are summarized in **Table 1**.

Table 1. Demographic and clinical characteristics of liver transplant recipients according to vaccination type

Characteristics	ChAdOx1 (n=16)	mRNA-1273 (n=23)	BNT162b2 (n=50)	p-value
Age (yr), median (range)	63 (60–67)	54 (32–63)	50 (20–75)	<0.001
Age ≥60 years	14 (87.5)	2 (8.7)	5 (10.0)	<0.001
Male	10 (62.5)	15 (65.2)	32 (64.0)	0.99
Years from first transplantation, mean (range)	4.4 (0.25–13)	3.7 (0.22–22)	4.7 (0.12–20)	0.73
GFR				0.006
1	0 (0.0)	5 (21.7)	18 (36.0)	
2	10 (62.5)	13 (56.5)	24 (48.0)	
3a	2 (12.5)	5 (21.7)	6 (12.0)	
3b	4 (25.0)	0 (0.0)	2 (4.0)	
Etiology of transplantation				0.04
Liver cirrhosis	4 (25.0)	6 (26.1)	30 (60.0)	
Fulminant hepatic failure	1 (6.2)	4 (17.4)	4 (8.0)	
Hepatocellular carcinoma	11 (68.8)	13 (56.5)	15 (30.0)	
Hepatoblastoma	0 (0.0)	0 (0.0)	1 (2.0)	
ABOi transplantation	8 (50.0)	8 (34.8)	23 (46.0)	0.58
Rejection treatment history within 1 yr	1 (6.2)	1 (4.3)	1 (2.0)	0.69
Immunosuppressants within 1 mon				
Tacrolimus	15 (93.8)	23 (100.0)	46 (92.0)	0.46
Everolimus	4 (25.0)	4 (17.4)	5 (10.0)	0.30
Mycophenolic acid	7 (43.8)	14 (60.9)	29 (58.0)	0.53
Steroid	2 (12.5)	2 (8.7)	3 (6.0)	0.70
Mean dose (mg, mPD dose)	4.5	8.0	9.7	
Number of immunosuppressants				0.59
1	5 (31.2)	4 (17.4)	17 (34.0)	
2	10 (62.5)	18 (78.3)	32 (64.0)	
3	1 (6.2)	1 (4.3)	1 (2.0)	
Interval between 1st and 2nd vaccination days, mean (range)	58 (56–77)	37 (30–42)	42 (32–42)	<0.001

Data represent number (%) unless indicated otherwise.
mPD, methylprednisolone.

Additionally, the baseline characteristics of 134 HCWs who received the adenoviral vector vaccine (ChAdOx1 nCoV-19, n=84 [63%]) or mRNA vaccines (mRNA-1273 vaccine, n=16 [12%]; BNT162b2 vaccine, n=34 [25%]) enrolled in this study are summarized in **Table 2**. A significant difference in the Ab titer after either the first or second dose of the vaccine was observed between healthy volunteers and LT recipients for all three vaccine types (p<0.001, **Fig. 1**).

LT Ab responses after COVID-19 vaccines

Overall, 16 (18%) participants had a positive Ab response after one dose of the COVID-19 vaccine and 62 (73%) after 2 doses. Seropositivity was similar between the two vaccine platforms (9/16 [56%] vs. 53/69 [77%], p=0.18; **Supplementary Table 1**). Moreover, no significant difference in seropositivity was observed between the three different vaccines after two doses of vaccine (9/16 [56%], 36/48 [75%], and 17/21 [81%] for ChAdOx1 nCoV-19,

Table 2. Baseline characteristics of healthy healthcare workers according to vaccination type

Characteristics	ChAdOx1 (n=84)	mRNA-1273 (n=16)	BNT162b2 (n=34)	p-value
Age (yr), median (range)	36.0 (21–64)	26.5 (24–53)	32.0 (23–64)	<0.001
Male	19 (22.6)	5 (31.2)	12 (35.3)	0.34
Age range (yr)				0.001
20–29	28 (33.3)	15 (93.8)	16 (47.1)	
30–39	32 (38.1)	0 (0.0)	13 (38.2)	
40–49	17 (20.2)	0 (0.0)	4 (11.8)	
50–59	6 (7.1)	0 (0.0)	1 (2.9)	
60–69	1 (1.2)	1 (6.2)	0 (0.0)	
Interval between 1st and 2nd vaccination days, mean (range)	84 (66–91)	21 (20–22)	28 (27–30)	0.001

Data represent number (%) unless indicated otherwise.

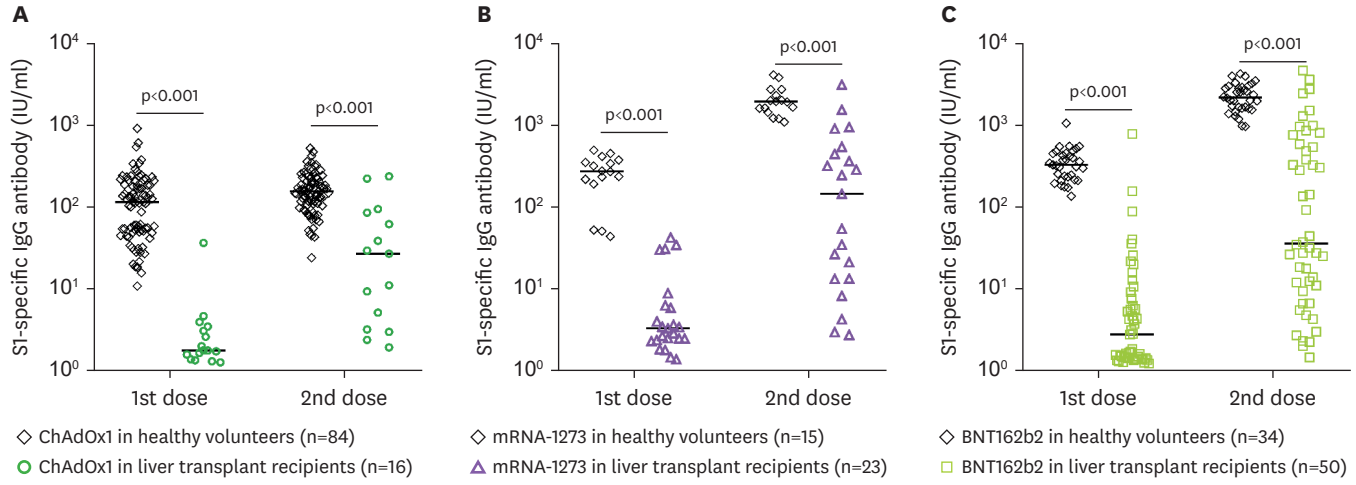

Figure 1. Comparison of S1-specific IgG Ab titers after the first and second dose of COVID-19 vaccine between healthy volunteers and liver transplant recipients. (A) ChAdOx1. (B) mRNA-1273. (C) BNT162b2. Ab titer after either the first or second dose of vaccine was significantly higher in healthy volunteers compared with liver transplant recipients in all three vaccine types.

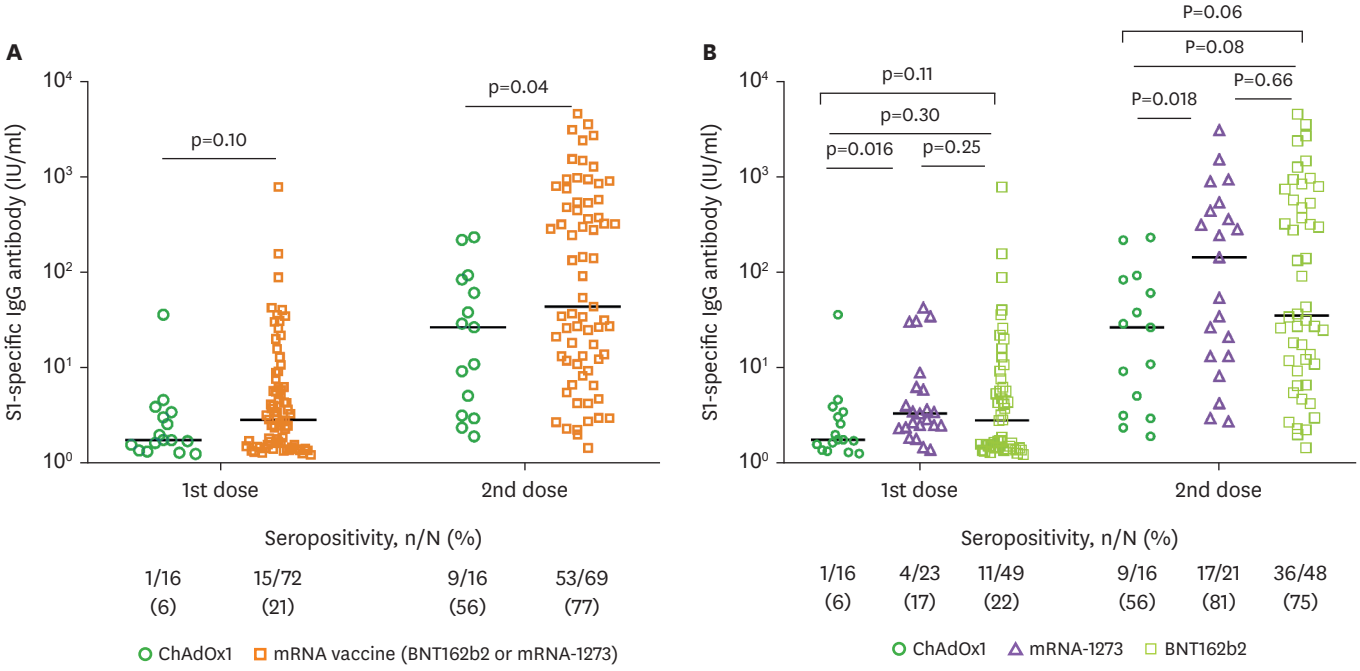

Figure 2. S1-specific IgG Ab titer after the first and second dose of COVID-19 vaccine in liver transplant recipients. (A) Different vaccine platforms. (B) Three vaccine types. Ab titer between ChAdOx1 and mRNA-1273 showed significant differences both after the first and second dose.

BNT162b2, and mRNA-1273 vaccines, respectively, p=0.22; **Supplementary Table 1**). However, the median Ab titer after 2 doses of mRNA vaccine was significantly higher (44.6 IU/ml) than that after two doses of the ChAdOx1 vaccine (19.2 IU/ml, p=0.04; **Fig. 2A**). In addition, the Ab level in the mRNA-1273 group was significantly higher (147 IU/ml) than that in the ChAdOx1 group (19.2 IU/ml, p=0.018; **Fig. 2B**).

Weak Ab response predictors

The risk factors to predict seropositivity after COVID-19 vaccination (**Table 3**) were evaluated. A longer time interval of more than 1 year from LT and decreased kidney function were

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Table 3. Predictors of seropositivity in liver transplant recipients after the second dose of COVID-19 vaccine

Predictors	Univariable analysis			Multivariable analysis*		
	Odds ratios	95% CI	p-value	Odds ratios	95% CI	p-value
Age ≥60 yr	0.55	0.19–1.69	0.28	2.39	0.23–25.04	0.47
Male	0.74	0.25–2.02	0.57	0.92	0.26–3.32	0.90
GFR						
1	Ref	Ref		Ref	Ref	
2	1.06	0.29–3.49	0.93	1.10	0.27–4.60	0.89
3a	0.59	0.12–2.93	0.51	0.36	0.05–2.41	0.29
3b	0.07	0.003–0.63	**0.034**	0.08	0.00–1.67	0.10
Vaccine						
ChAdOx1	Ref	Ref	Ref	Ref	Ref	Ref
mRNA-1273	3.31	0.79–15.68	0.11	3.91	0.27–55.81	0.31
BNT162b2	2.33	0.70–7.70	0.16	2.36	0.21–26.43	0.49
HCC	0.84	0.32–2.22	0.72			
ABOi	0.94	0.36–2.51	0.90			
FK506 trough level (ng/ml)						
Non-user	Ref	Ref	Ref			
Level <8	0.75	0.04–5.49	0.80			
Level ≥8	0.25	0.01–2.75	0.29			
Mycophenolic acid user	0.78	0.29–2.05	0.62			
Everlolimus user	0.53	0.16–1.96	0.32			
Steroid user	0.92	0.18–6.77	0.93			
Number of immunosuppressants†						
1	Ref	Ref	Ref	Ref	Ref	Ref
2	0.69	0.20–2.06	0.53	0.91	0.25–3.35	0.89
3	0.13	0.005–1.64	0.13	0.60	0.03–13.44	0.74
Years from transplantation						
<1						
≥1	6.43	2.33–19.10	**<0.001**	6.68	1.93–23.1	**0.003**

Bold-faced p-values are considered statistically significant.
*Hosmer–Lemeshow goodness-of-fit test for multivariable analysis: p=0.99.
†The number of immunosuppressants has been included instead of individual immunosuppressants as risk factors in multivariable analysis considering p-values in univariate analysis.

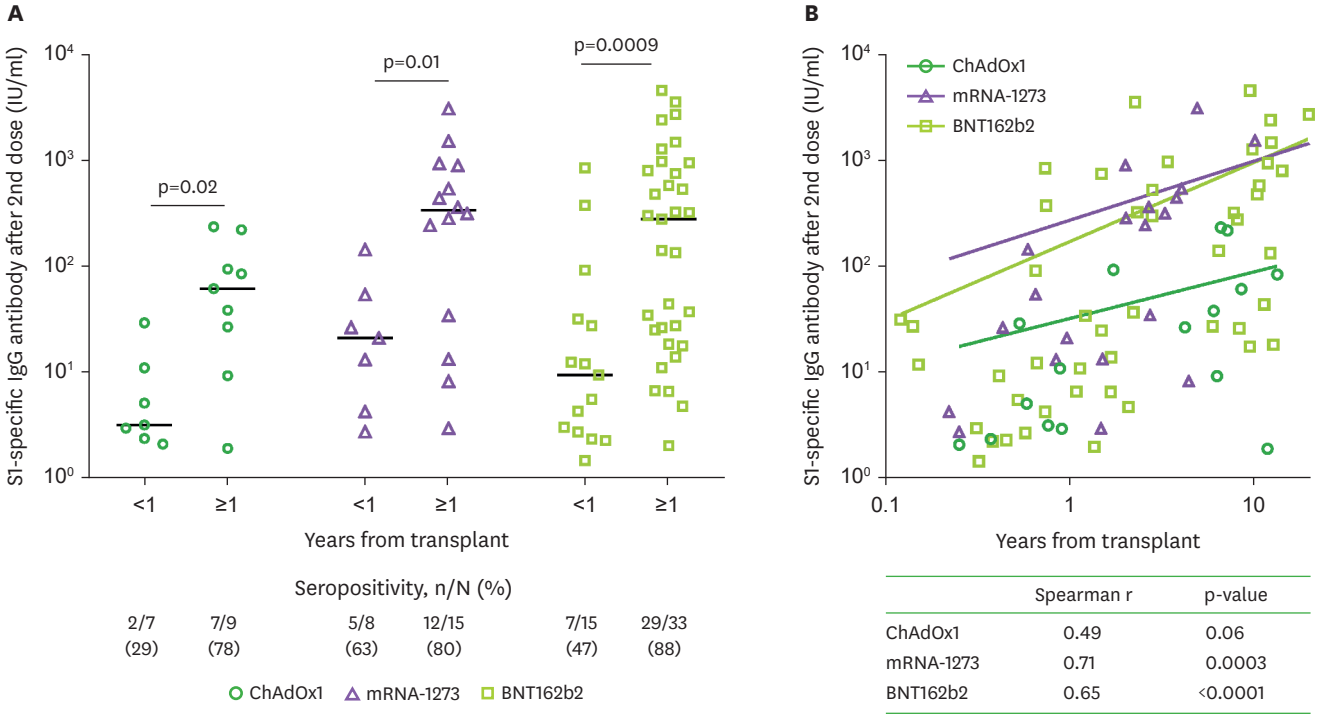
significantly associated with seropositivity after the second dose of vaccine dose in the univariate analysis (p<0.001 and p=0.034, respectively) (**Table 3**). In the multivariable analysis using logistic regression, a longer time interval of more than 1 year from LT (odds ratio, 6.68; p=0.003) was significantly associated with seropositivity after the second dose of vaccine (**Table 3**). Risk factors for predicting a high Ab titer are shown in **Table 3**. A longer time interval after transplantation was significantly associated with a high Ab titer in multivariable analysis (p=0.003). The seropositivity and Ab titers according to the years from transplantation are shown in **Fig. 3**. The longer the time since LT, the higher the Ab titer (**Fig. 3B**), and this correlation was particularly prominent for the mRNA vaccines (mRNA-1273, p=0.0003; BNT162b2, p<0.0001; **Fig. 3B**). Antimetabolite use was not significantly associated with either seropositivity or Ab titers (**Tables 3** and **4**, **Fig. 4**). Moreover, no significant difference was noted in seropositivity and Ab titer according to the age and sex distribution in the multivariable analysis (**Tables 3** and **4**).

The median time from RTX injection to vaccination was 27.5 months (IQR, 7.0–72.9) in ABOi LT recipients. A subgroup analysis of ABOi LT recipients (n=36) revealed that a significant correlation between the time interval from liver transplantation to vaccination and Ab titer (p<0.0001; **Fig. 5**). Furthermore, a longer time interval of more than 1 year from transplantation was significantly associated with seropositivity in the ABOi subgroup analysis (**Table 5**).

Table 4. Predictors of Ab titer in liver transplant recipients after the second dose of COVID-19 vaccine

Predictors	Univariable analysis		Multivariable analysis*	
	Standardized β	p-value	Standardized β	p-value
Age	−0.18	0.10	−0.14	0.27
Male	−0.25	**0.021**	−0.19	0.09
Vaccine				
ChAdOx1	Ref	Ref	Ref	Ref
mRNA-1273	0.20	0.17	0.19	0.20
BNT162b2	0.28	0.06	0.19	0.27
HCC	0.020	0.86	0.14	0.26
ABOi	0.068	0.54	0.10	0.36
FK506 trough level (ng/ml)	−0.11	0.33	0.05	0.73
Mycophenolic acid user	0.075	0.50	0.09	0.53
Everlolimus user	−0.16	0.15	−0.03	0.81
Steroid user	−0.12	0.30	−0.005	0.94
Years from transplantation	0.40	**0.0002**	0.43	**0.003**
More than 1 year from transplantation	0.30	**0.005**	0.26	**0.06**

Bold-faced p-values are considered statistically significant.
*Adjusted R^2 = 0.17, F-statistic p=0.01.



	Spearman r	p-value
ChAdOx1	0.49	0.06
mRNA-1273	0.71	0.0003
BNT162b2	0.65	<0.0001

Figure 3. S1-specific IgG Ab titers in liver transplant recipients according to the time interval since liver transplantation. (A) S1-specific IgG Ab titer according to vaccine type. (B) Correlation between years from transplantation and S1-specific IgG Ab. A longer time interval after transplantation was significantly associated with a high Ab titer.

DISCUSSION

In this LT recipient cohort study, we found that about 3-quarters of LT recipients who received two doses of mRNA vaccines had seropositive Ab responses, while those who had one dose of mRNA vaccine, or two doses of adenoviral vector vaccine (ChAdOx1) showed a suboptimal Ab response. We also demonstrated that a longer time interval from LT to vaccination is significantly associated with seropositivity and a high Ab titer after two doses of COVID-19 vaccine. However, antimetabolites, such as mycophenolic acid, or higher serum FK506

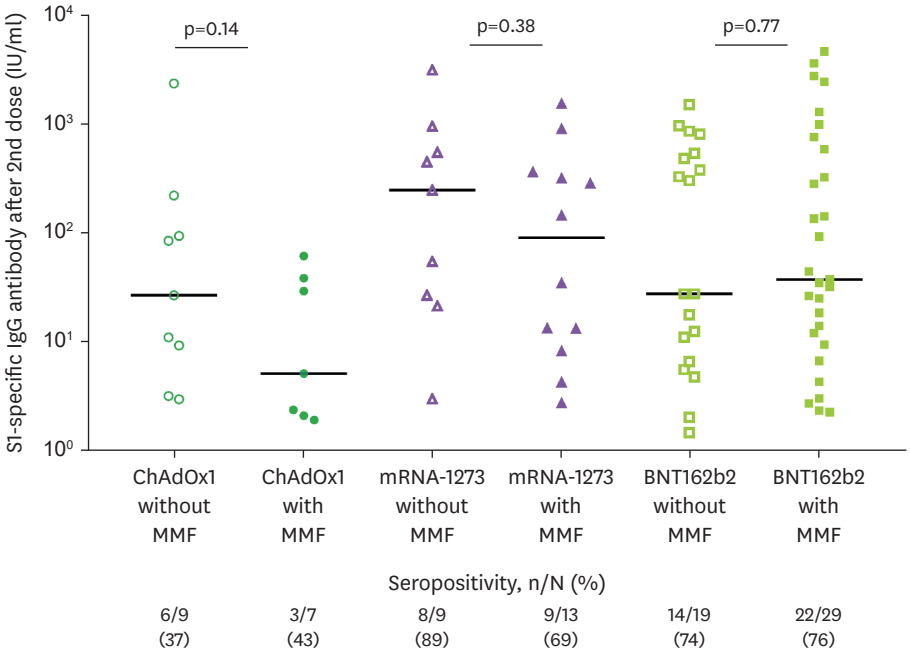
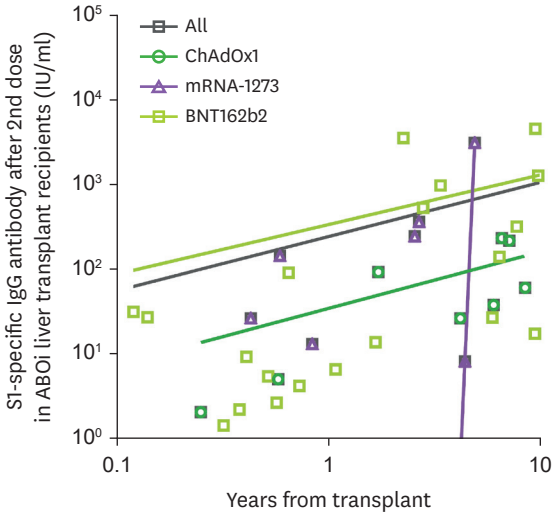


Figure 4. S1-specific IgG Ab titer according to antimetabolite use in liver transplant recipients. Antimetabolite use was not significantly associated with either seropositivity or Ab titers.



	Spearman r	p-value
ChAdOx1	0.71	0.06
mRNA-1273	0.36	0.44
BNT162b2	0.66	0.001
All	0.63	<0.0001

Figure 5. Correlation between the time interval from transplantation to vaccination and S1-specific IgG Ab after the second dose in ABOi liver transplant recipients. The time interval from liver transplantation to vaccination and Ab titer showed a significant correlation.

trough levels were not associated with seropositivity or Ab titer after COVID-19 vaccination. These findings may provide important insights into the immune response for vaccination policies after different platforms of COVID-19 vaccines in transplant recipients.

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Table 5. Subgroup analysis for predictors of seropositivity after the second dose of COVID-19 vaccine in ABO incompatible liver transplant recipients*

Predictors	Univariable analysis			Multivariable analysis†		
	Odds ratios	95% CI	p-value	Odds ratios	95% CI	p-value
Age ≥60 yr	1.47	0.28–11.4	0.67	29.09	0.52–32,200.09	0.18
Male	0.47	0.06–2.40	0.40	1.59	0.04–91.41	0.80
GFR						
1	Ref	Ref	Ref	Ref	Ref	Ref
2	1.42	0.24–7.42	0.68	0.53	0.03–8.68	0.65
3a and 3b	1.50	0.12–37.9	0.76	0.02	0.00–12.36	0.25
Vaccine						
ChAdOx1	Ref	Ref	Ref	Ref	Ref	Ref
mRNA-1273	2.00	0.15–50.2	0.61	29.02	0.20–10,012.41	0.20
BNT162b2	0.67	0.08–3.84	0.67	3.29	0.04–320.55	0.58
HCC	0.91	0.19–3.99	0.90	0.27	0.01–3.15	0.32
FK506 trough level (ng/ml)						
Level <8	Ref	Ref	Ref	Ref	Ref	Ref
Level ≥8	0.13	0.015–0.79	**0.033**	0.09	0.00–3.14	0.28
Mycophenolic acid use	0.34	0.045–1.70	0.22	0.09	0.00–1.66	0.14
Steroid use	0.75	0.064–17.30	0.82	7.98	0.11–2,348.80	0.38
Time from transplantation						
<6 mon	Ref	Ref	Ref			
≥6 mon	5.11	0.90–32.7	0.07			
Time from transplantation						
<1 yr	Ref	Ref	Ref	Ref	Ref	Ref
≥1 yr	13.33	2.55–106.4	**0.005**	22.36	1.62–938.62	**0.04**

Bold-faced p-values are considered statistically significant.
*Only two liver transplant recipients received COVID-19 vaccines less than 3 months from transplantation.
†Hosmer–Lemeshow goodness-of-fit test for multivariable analysis: p=0.16.

There are three important findings of our study. First, the degree of Ab response of LT recipients in this study was higher than that of kidney transplant recipients, which was reported as only 4%–48% seropositivity in previous studies (13). The finding of unexpectedly high seropositivity after COVID-19 vaccination in LT recipients compared to kidney transplant recipients was in accordance with the findings of a recent study showing Ab seropositivity as 88.9% and 57.1% in LT and kidney transplant recipients, respectively (14). The close correlation between chronic kidney disease and immune deficiency, including the depletion of Ag-presenting dendritic cells and naïve and central memory T cells, might partially explain the weaker Ab response in kidney transplant recipients compared with that in LT recipients (15). Similarly, decreased kidney function was associated with seropositivity (p=0.034) in our study despite not in the multivariable analysis (**Table 3**). Moreover, a relatively longer use of steroids and highly maintained serum FK506 level in kidney transplant recipients compared with those in LT recipients may be a reason despite center variability. Further studies are needed on vaccine effectiveness based on immune responses after COVID-19 vaccination between different solid organ transplant recipients.

Second, antimetabolite, the traditional predictor of a weaker Ab response, was not significantly associated with seropositivity or Ab titer after vaccination in this study. As antimetabolites suppress follicular Th cells (Tfh) (16), which are essential for B-cell proliferation in germinal center, seropositivity after vaccination in solid organ transplant recipients with antimetabolites was reported for about half of those without antimetabolites (17). In fact, not only antimetabolites but also other immunosuppressants, such as calcineurin inhibitor or mTOR inhibitor, have been hypothesized to inhibit the activation of B cells via Tfh suppression in several studies (18,19), and the degree of immunosuppression affecting the Ab response would not be solely dependent on the use of antimetabolites. Interestingly, we found that ABOi liver transplantations, in which all LT recipients receive RTX therapy, were

not a significant factor associated with Ab seropositivity or titer. This may be partially due to a gradual decrease of the RTX effect on B cells in most of our patients because only two LT recipients received a COVID-19 vaccine less than 3 months from liver transplantation. Despite this, the Ab titer was correlated with years since ABOi liver transplantation.

Third, this study reported the Ab response after ChAdOx1 vaccination in LT recipients, which has been reported only recently by one other study (9) that included only a small number of participants (n=6, 4.3%). In our study, the seropositivity induced by ChAdOx1 was comparable with that induced by mRNA vaccines, whereas the Ab titer by ChAdOx1 was significantly lower than that by mRNA vaccines. Ad26.COV2.S similar to ChAdOx1 in that it is an adenoviral vector vaccine, have also shown comparable seropositivity with mRNA vaccines in a previous study, including in both LT recipients and patients with chronic liver diseases (10). However, a higher proportion of suboptimal Ab levels has been observed compared with mRNA vaccines despite the absence of an Ab titer.

Our study had some limitations. First, the time interval between first and second dose of vaccine was different between healthy healthcare workers and LT recipients due to vaccine availability at study enrollment, which might have affected the Ab titer difference between 2 cohorts. Second, relatively small sample size and different participants between vaccines would limit further interpretation of our results. Third, a different distribution of ages according to vaccination type might have affected the Ab titers especially in ChAdOx1 vaccine recipients with older age and lower Ab titer compared with other types of vaccine recipients

Despite these limitations, this study demonstrated a considerable Ab response after two mRNA vaccine doses (mRNA-1273 or BNT162b2) in LT recipients, but only about half of LT recipients with the ChAdOx1 nCoV-19 vaccine showed seropositivity. We also found that a longer time interval from liver transplantation was a predictor for seropositivity and a higher Ab titer.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1

Demographic and clinical characteristic of liver transplant recipients according to seropositivity after two doses of the COVID-19 vaccine

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