

# Antibody Response to Severe Acute Respiratory Syndrome-Coronavirus-2 Messenger RNA Vaccines in Liver Transplant Recipients

## TO THE EDITOR:

Prior studies have demonstrated a decreased humoral response in solid organ transplant recipients (SOTRs) to severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) messenger RNA (mRNA) vaccination (17% antibody response after dose 1 [D1], 54% after dose 2 [D2]) compared with the general population (100%).

*Abbreviations: aIRR, adjusted incident rate ratio; BMI, body mass index; CI, confidence interval; D1, dose 1; D2, dose 2; IgG, immunoglobulin G; IQR, interquartile range; LT, liver transplantation; mRNA, messenger RNA; RBD, receptor binding domain; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2; SOTRs, solid organ transplant recipients; S1, subunit 1.*

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However, these studies were dominated by kidney transplant recipients and included only a small percentage of liver transplantation (LT) recipients (19.6%).<sup>(1-4)</sup> Because LT recipients often receive milder induction and maintenance immunosuppression, they may have a more robust humoral response. To investigate this, we studied SARS-CoV-2 antibody development in a cohort of LT recipients who completed a 2-dose mRNA vaccine series of either mRNA-1273 (Moderna, Cambridge, MA) or BNT162b2 (Pfizer-BioNTech, New York, NY).

## Patients and Methods

Inclusion criteria were post-LT patients with no reported prior positive SARS-CoV-2 polymerase chain reaction result. Participants were excluded if they were younger than 18 years old. Participants were recruited via convenience sampling through social media or transplant center advertisements and if they completed a 2-dose mRNA vaccine course between January 7, 2021, and March 26, 2021 and were followed through April 7, 2021. Data on demographics, body mass index (BMI), prior COVID-19 diagnosis, hospitalization, transplant information, medications, other immune conditions, and allergies were collected. The study had institutional review board approval, and informed consent was obtained. The blood sampling protocol used 2 SARS-CoV-2 spike protein immunoassays (EUROIMMUN [Lubek, Germany] to the subunit 1 [S1] domain and Roche Elecsys [Indianapolis, IN] to the receptor binding domain [RBD] of the SARS-CoV-2 spike protein) and has been described elsewhere.<sup>(1)</sup> We have shown in prior work that the distribution of vaccine responses did not differ when using the anti-S1 or anti-RBD assay.<sup>(4)</sup> The post-D1 assay was performed as close to D2 as possible, and the post-D2 assay was collected as close to 28 days as possible. Of note, the Roche assay is artificially truncated at >250 U/mL.

Participants were divided into the following 3 categories: priming dose responders (developed antibodies after both D1 and D2), booster responders (antibodies only after D2), and nonresponders (no antibodies after both doses). The proportion of patients who developed a positive antibody response was assessed with exact binomial 95% confidence intervals (CIs), and associations between variables were assessed using modified Poisson regression with a robust variance estimator. All 2-sided and  $\alpha$ -level 0.05 testing was performed using Stata 16.0 (StataCorp, College Station, TX).

## Results and Discussion

Of 225 participants meeting the inclusion criteria, 201 provided blood specimens after D1. Of these, 161 provided specimens after D2, 26 of which were previously reported in an all-organ summary of antibody responses.<sup>(4)</sup> In the full cohort of 161 participants, 53% received the BNT162b2 vaccine and 47% received the mRNA-1273 vaccine (Table 1). Antibody was detectable in 34% (95% CI, 27%-42%) of participants at a median of 21 days (interquartile range [IQR], 19-25 days) after D1, and in 81% (95% CI, 74%-87%) at a median of 30 days (IQR, 28-31 days) after D2 (Fig. 1); 34% were priming dose responders (D1+/D2+), 47% were booster responders (D1-/D2+), and 19% were nonresponders (Table 2). The median semiquantitative SARS-CoV-antispikes antibody immunoassay after D2 was >250 U/mL (IQR, >250 U/mL) on Roche Elecsys testing for priming dose responders, 81.9 U/mL (IQR, 12.4-250 U/mL) for booster responders, and 0 (IQR, 0-0) for nonresponders. A similar trend was seen for those tested with the EUROIMMUN immunoassays (Table 3). Crossover between immunoassays was minimal (7/161). No participants reported a laboratory-confirmed diagnosis of COVID-19 following vaccination by the end of follow-up.

**TABLE 1. Demographic and Clinical Characteristics of LT Recipients Who Completed a SARS-CoV-2 mRNA Vaccine Series**

Participant Characteristics	Total, n = 161
Age, years, median (IQR)	64 (48-69)
Sex, % female	57
Non-White, %	8
Hispanic ethnicity, %	3
BMI, kg/m <sup>2</sup> , median (IQR)	26.0 (23.0-30.5)
Years since transplant, median (IQR)	6.9 (2.9-15.0)
Maintenance immunosuppression, %*	
Tacrolimus	81
Mycophenolate	35
Corticosteroids	22
Sirolimus	11
Cyclosporine	8
Azathioprine	6
Everolimus	3
Vaccine type (manufacturer), %	
BNT162b2 (Pfizer-BioNTech)	53
mRNA-1273 (Moderna)	47

\*Not mutually exclusive.

Of 66 LT recipients on an antimetabolite, 18% were priming dose responders, 42% were booster responders, and 39% were nonresponders (Table 2). Among the 95 participants not on an antimetabolite, 45% were priming dose responders, 50% booster responders, and 5% nonresponders. Patients on antimetabolites were much less likely to develop an antibody response to D1 (adjusted incident rate ratio [aIRR], 0.51; 95% CI, 0.28-0.91;  $P = 0.02$ ) or D2 (aIRR, 0.67; 95% CI, 0.55-0.81;  $P < 0.001$ ). Participants  $\geq 6$  years from LT were more likely to be priming dose responders ( $P < 0.001$ ). The mRNA-1273 vaccine recipients were more likely to develop an antibody response to D1 (aIRR, 2.07; 95% CI, 1.32-3.25;  $P = 0.001$ ) and D2 (aIRR, 1.25; 95% CI, 1.09-1.43;  $P = 0.001$ ).

Our findings of a robust immune response of 81% are in contrast to an Israeli cohort of 80 LT recipients who had received 2 doses of the BNT162b2 vaccine and demonstrated an antibody response of only 47.5%.<sup>(5)</sup> This difference may be attributed to a different assay or other population factors such as age or antimetabolite use. Our study augments these findings to a larger sample size and patients who received the mRNA-1273 vaccine as well.

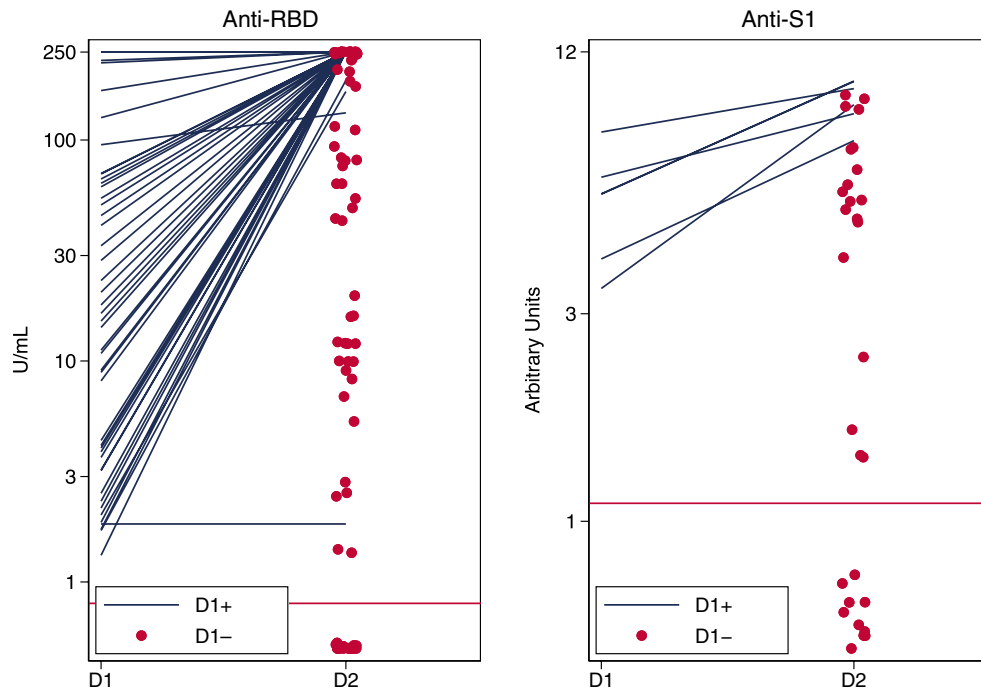
Differences in antibody response between the mRNA vaccine types may be related to dosing, timing,

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**FIG. 1.** D1 and D2 semiquantitative SARS-CoV-2 anti-spike antibody immunoassay results of LT recipients by assay type. The blood sampling protocol used 2 SARS-CoV-2 spike protein immunoassays (anti-RBD and anti-S1) and has been described elsewhere.<sup>(1)</sup> Individual priming dose responders (D1+) are represented by blue lines connecting immunoassay results following D1 and D2. Individual booster responders and nonresponders (D1-) are represented by red points indicating immunoassay results following D2. Of 161 participants, 7 were tested using an anti-RBD assay after D1 and an anti-S1 assay after D2; these individuals are excluded from this figure. Antibody-positive cutoffs (determined by the manufacturer and identified in the figure by horizontal red lines) were  $\geq 0.80$  U/mL for the anti-RBD immunoassay (Roche Elecsys) and  $\geq 1.1$  arbitrary units for the anti-S1 immunoassay (EUROIMMUN).

or drug delivery formulations. The mRNA-1273 vaccine series is 2 100-mg doses separated by 28 days, and the BNT162b2 vaccine series is 2 30-mg doses 21 days apart.<sup>(2)</sup> The greater antibody response to the higher dosed mRNA-1273 vaccine might suggest a dose-response relationship. Differences between the effects of different vaccine dosing may be less apparent in the general population because both are so highly immunogenic in immunocompetent people, but an immunocompromised population may “unmask” these potential differences.

Limitations include selection bias resulting from convenience sampling, which contributed to sociodemographic homogeneity. Because race has not been found to be associated with antibody response, the difference in target population representation likely does not largely affect external validity. There was no immunocompetent comparator group; this makes direct comparisons difficult, but the robust 100% response rate seen in the general population studies is

a notable benchmark.<sup>(2)</sup> Future immunologic response investigations could include comorbidities and immunosuppression doses and drug levels, which were not collected in our study, as well as outcomes of interest such as B cell/T cell responses, SARS-CoV-2 infection, hospitalizations, and mortality. We used 2 serological assays to assess antibody response, but this was to enable us to study as many LT recipients as possible. As explained previously (see the Patients and Methods section), there is very high correlation between anti-S1 and anti-RBD assays, so the use of 2 assays likely did not lead to substantial measurement error. Despite these limitations, this nationwide sample of patients during a rapidly evolving clinical climate provides the transplantation community and primary care providers with immunogenicity data using readily available commercial assays for this unique population.

In conclusion, LT recipients who received 2 doses of SARS-CoV-2 mRNA vaccines have a much more robust antibody response compared with other

**TABLE 2. Demographic and Clinical Characteristics of LT Recipients, Stratified by Antibody Response to a 2-Dose Course of SARS-CoV-2 mRNA Vaccine, and Associations With Developing an Antibody Response**

Participant Characteristics	Vaccine Response, n (%)						Dose 1 aIRR* (95% CI)	P Value	Dose 2 aIRR* (95% CI)	P Value
	Priming Dose Responders, 55 (34)	Booster Responders, 75 (47)	Nonresponders, 31 (19)							
Age group, years										
18-39	13 (52)	10 (40)	2 (8)	0.44	0.93 (0.75-1.15)	0.50	0.98 (0.90-1.07)	0.65		
40-59	16 (38)	19 (45)	7 (17)							
≥60	26 (28)	46 (49)	22 (23)							
Sex										
Male	23 (32)	33 (47)	14 (20)	0.98	0.90 (0.62-1.29)	0.56	1.01 (0.88-1.17)	0.86		
Female	32 (35)	42 (46)	17 (19)							
Race										
White	48 (33)	72 (49)	27 (18)	0.18						
Non-White	7 (50)	3 (21)	4 (29)							
Time since transplant, years										
<3	5 (11)	26 (59)	13 (30)	<0.001	1.64 (1.30-2.07) <sup>†</sup>	<0.001	1.05 (0.99-1.11) <sup>‡</sup>	0.09		
3-6	5 (16)	18 (58)	8 (26)							
7-11	14 (42)	13 (39)	6 (18)							
≥12	31 (58)	18 (34)	4 (8)							
Immunosuppression										
Includes antimetabolite <sup>‡</sup>	12 (18)	28 (42)	26 (39)	<0.001	0.51 (0.28-0.91)	0.02	0.67 (0.55-0.81)	<0.001		
No antimetabolite	43 (45)	47 (50)	5 (5)							
Vaccine type										
mRNA-1273	37 (49)	31 (41)	8 (11)	<0.001	2.07 (1.32-3.25)	0.001	1.25 (1.09-1.43)	0.001		
BNT16b2	18 (21)	44 (52)	23 (27)							

NOTE: Priming dose responders developed positive results after both D1 and D2. Booster responders developed positive results only after D2. Nonresponders maintained negative results after D1 and D2; n = 161.

\*Model adjusted for age, sex, time since transplant, antimetabolite maintenance immunosuppression, and vaccine type. Comparison of mRNA-1273 and BNT16b2 was further adjusted for number of days between vaccination and antibody testing.

<sup>†</sup>Comparison of 6 or more years since transplant versus less than 6 years since transplant.

<sup>‡</sup>Antimetabolite maintenance immunosuppressive regimens included mycophenolate mofetil, mycophenolic acid, and azathioprine.

**TABLE 3. Median Semiquantitative SARS-CoV-2 Antispike Antibody Immunoassay Results of LT Recipients by Antibody Response**

Type of Responder	D1		D2	
	Roche Elecsys	EUROIMMUN	Roche Elecsys	EUROIMMUN
	U/mL (IQR), n = 126	Arbitrary Unit (IQR), n = 35	U/mL (IQR), n = 119	Arbitrary Unit (IQR), n = 42
Priming dose responders	17.4 (3.4-63.2)	5.2 (3.5-5.7)	250 (250-250)	8.9 (8.2-9.8)
Booster responders	0 (0-0)	0.1 (0.1-0.6)	81.9 (12.4-250)	5.6 (4.4-8.1)
Nonresponders	0 (0-0)	0.1 (0.02-0.2)	0 (0-0)	0.1 (0.1-0.2)

NOTE: Anti-RBD immunoassay (Roche Elecsys) results are reported as a concentration of IgG against the target protein with a measurement range of 0.4 to 250 U/mL; results  $\geq 250$  U/mL are reported as 250 U/mL. Anti-S1 immunoassay (EUROIMMUN) results are reported as an arbitrary unit (a sample-to-control ratio of optical density). Antibody-positive cutoffs (determined by the manufacturer) were  $\geq 0.80$  U/mL for the former and  $\geq 1.1$  AU for the latter. Priming dose responders developed positive results after both D1 and D2. Booster responders developed positive results only after D2. Nonresponders maintained negative results after D1 and D2.

SOTRs. Those vaccinated within 6 years from transplant, on antimetabolite immunosuppression, or vaccinated with BNT162b2 are more likely to have a diminished response. LT recipients may have different clinical factors contributing to a more robust response, compared to other SOTR, and important considerations for antimetabolite treatment before vaccination may be necessary. Therefore, guidelines should be tailored in this population.

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## REFERENCES

- 1) Boyarsky BJ, Werbel WA, Avery RK, Tobian AAR, Massie AB, Segev DL, Garonzik-Wang JM. Immunogenicity of a single dose of SARS-CoV-2 messenger RNA vaccine in solid organ transplant recipients. *JAMA* 2021;325:1784-1786.
- 2) Walsh EE, Frenck RW, Falsey AR, Kitchin N, Absalon J, Gurtman A, et al. Safety and immunogenicity of two RNA-based Covid-19 vaccine candidates. *N Engl J Med* 2020;17: 2439-2450.
- 3) Boyarsky BJ, Ou MT, Greenberg RS, Teles AT, Werbel WA, Avery RK, et al. Safety of the first dose of SARS-CoV-2 vaccination in solid organ transplant recipients. *Transplantation* 2021;105: e56-e57.
- 4) 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.
- 5) 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.