Immunogenicity and Adverse Effects of the 2-Dose BNT162b2 Messenger RNA Vaccine Among Liver Transplantation Recipients

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The BNT162b2 messenger RNA (mRNA) vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been shown to be safe and effective in immunocompetent patients. The safety and efficacy of this vaccine in liver transplantation (LT) recipients is still under evaluation. The objective of this study was to assess the safety and efficacy of the BNT162b2 vaccine among transplant recipients. The immune responses of 76 LT recipients receiving 2 doses of the vaccine were compared with those of 174 age-matched immunocompetent controls. Postvaccination immunoglobulin G (IgG) antibodies against the receptor-binding domain (RBD) of SARS-CoV-2 and neutralizing antibodies (NA) to the BNT162b2 mRNA vaccine were determined at least 14 days after the second dose of the vaccine. IgG antibody titers ≥ 1.1 were defined as positive antibodies. Adverse effects were monitored during the study period. Following administration of the second dose, transplant recipients showed reduced immune responses compared with controls (72% versus 94.2%; $P < 0.001$). At a median time of 38 days after the second vaccination, the geometric mean of RBD IgG and NA titers were 2.1 (95% confidence interval [CI], 1.6-2.6) and 150 (95% CI, 96-234) among transplant recipients and 4.6 (95% CI, 4.1-5.1) and 429 (95% CI, 350-528) in the control group, respectively ($P < 0.001$). Antibody responses were lower in transplant recipients who were receiving combined immunosuppression therapy and in those with impaired renal function. Among the LT recipients with negative antibody responses, 1 became infected with SARS-CoV-2, but no recipients with positive antibody responses became infected. Overall, most (n = 39 [51%]) adverse effects self-reported by transplant recipients were mild and occurred more often in women than in men. Compared with patients who were immunocompetent, LT recipients had lower immune responses. The durability of immune responses to the BNT162b2 vaccine among LT recipients requires further investigation.

Coronavirus disease 2019 (COVID-19) is associated with considerable morbidity and mortality. Solid organ transplantation (SOT) recipients are at risk of

Abbreviations: AE, adverse event; ALD, alcohol-related liver disease; ALP, alkaline phosphatase; ALT, alanine aminotransferase; BMI, body mass index; CF, cystic fibrosis; CI, confidence interval; CNI, calcineurin inhibitor; COVID-19, coronavirus disease 2019; IgG, immunoglobulin G; IQR, interquartile range; LT, liver transplantation; MMF, mycophenolate mofetil; mRNA, messenger RNA; mTOR, mammalian target of rapamycin; NAs, neutralizing

severe outcomes as a result of their lifelong immunosuppression and metabolic complications after transplantation.[1]

The COVID-19 vaccination campaign was initiated in Israel on December 19, 2020, with the Pfizer-BioNTech BNT162b2 messenger RNA (mRNA) vaccine being the only vaccine administered countrywide. A randomized clinical trial of the 2-dose Pfizer-BioNTech vaccine reported 95% effectiveness in preventing COVID-19.[2] A recent real-world study conducted in Israel on the vaccine reported 94% effectiveness in preventing symptomatic COVID-19.[3]

TABLE 1. Comparison of Demographic Characteristics and Immunologic Response to Vaccination Between Study Group and Control Group

Variable	Study Group, n = 76	Control Group, n = 174	P Value
Age, years, mean ± SD	59 ± 15	59 ± 13	0.89
Male, n (%)	43 (56.6)	86 (49.4)	0.3
Time from second dose of the vaccine, days, mean ± SD	38 ± 24	36 ± 22	0.46
Positive IgG-RBD, n (%)	55 (72.4)	164 (94.3)	<0.001
SARS-CoV-2 NAs, mean (95% CI)	150 (96-234)	429 (350-528)	<0.001
SARS-CoV-2 IgG titers, mean (95% CI)	2.1 (1.6-2.6)	4.6 (4.1-5.1)	<0.001

Yet, there are still negligible data regarding the effectiveness and safety of the vaccine among SOT recipients because they were excluded from the registration trials. Recently, low effectiveness of the BNT162b2 mRNA COVID-19 vaccine in this patient population was reported.[4-6] However, apparently liver transplantation (LT) recipients had a better immune response than other SOT recipients to mRNA vaccines,[7] and vaccination of LT recipients is recommended by the international professional societies.[8,9]

To better characterize the efficacy and safety of the Pfizer-BioNTech BNT162b2 mRNA vaccine among LT recipients, this work prospectively assessed the immune response and adverse effects of LT recipients receiving 2 doses of the vaccine.

Patients and Methods

The study was conducted at the Sheba Medical Center between January 2021 and May 2021. The study population included 76 adult (aged >18 years) LT recipients routinely followed at the Liver Diseases Center

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as well as a control group of 174 immunocompetent Sheba health care workers (Table 1). Of a total of 95 LT recipients who agreed to receive the 2 BioNTech BNT162b2 vaccine doses before May 2021, 76 agreed to participate in study (most of them preferred follow-up visits via telemedicine to avoid contact with medical staff and facilities).

The control group participants were matched accordingly to age, time between administration of the second vaccine dose, and the time between the collection of blood samples for serology (immunoglobulin G [IgG] antibodies against the receptor-binding domain [RBD] of severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]).

Patients who had recovered from SARS-CoV-2 or had active infection at the time of the vaccination or up to 7 days after the second vaccine dose were excluded. All participants received 2 intramuscular 30-μg doses of the diluted Pfizer-BioNTech BNT162b2 vaccine administered at a 21-day interval. Blood samples were collected from the LT patients following a routine visit to the Liver Diseases Center at least 10 days after the second injection. Blood samples were collected from participants in the control group at routine intervals of 4 weeks throughout the 120 days, beginning at least 2 weeks after the second vaccine. The study was approved by the Sheba Medical Center local institutional review board. All participants signed a written informed consent.

Information regarding vaccine adverse effects was reported by all participants after each dose of the vaccination. Adverse effects were monitored throughout the 30 days and were categorized as local or systemic adverse effects.

Clinical and laboratory data were extracted from electronic patient records. The demographic data collected for each patient included age, sex, indication for LT, time since transplantation, and immunosuppressive medications, including dosage. Blood

tacrolimus or everolimus trough levels were determined, and routine blood tests were performed between the time the second vaccine was administered and before the serology test. Renal function was calculated using the chronic kidney disease epidemiology collaboration creatinine equation. Chronic kidney disease was defined as estimated glomerular filtration rate $<60\,\text{mL/minute/1.73}\,\text{m}^2$ for a duration of >3 months.[10]

SEROLOGY ASSAYS

The presence of IgG antibodies against the RBD of SARS-CoV-2 in the blood samples of all participants was tested with an enzyme-linked immunosorbent assay.[11] Sera not capable of reducing viral replication by 50% at a 1:8 dilution or below were considered nonneutralizing. All samples that were positive for RBD-IgG were also tested for neutralizing antibodies (NAs). A SARS-CoV-2 pseudovirus (ps-SARS-2) neutralization assay was performed using a propagation-competent vesicular stomatitis virus spike similar to the spike previously published, which was kindly provided by Gert Zimmer, University of Bern, Bern, Switzerland.[12]

STATISTICAL ANALYSIS

Continuous variables are presented as median (interquartile range [IQR]). Categorical variables are expressed as count (percentage). Antibody titers were log-transformed prior to the statistical analysis. Geometric mean concentrations of SARS-CoV-2 IgG and NAs were calculated for both groups and presented as geometric mean titers and 95% confidence intervals (CIs).

The control group was matched to the study group according to age and time interval of blood sample collection after the second vaccine dose. Patients were stratified according to time of blood sample collection after the second vaccine dose.

IgG antibody titers ≥1.1 sample-to-cutoff ratio were defined as a positive antibody test and below 1.1 sample-to-cutoff ratio as a negative test.[11,13,14] Patients were then grouped by level of IgG antibodies. The categorical variables were compared by using chi-squared analysis and Fisher's exact test. Continuous measurements were compared by Student t test or Mann-Whitney U test according to their distribution.

To evaluate predictors of reduced immune response, patients were divided according to their immunosuppressive therapy: calcineurin inhibitor (CNI) monotherapy versus combined immunosuppressive therapy. The 1 patient who received everolimus monotherapy was excluded from the statistical analysis.

A logistic regression analysis model was used to explore the factors associated with the vaccine-induced antibody response. Covariates for the multivariate models were selected using clinical judgment and variables that significantly differed between the groups. $P < 0.05$ was considered a statistically significant difference. All tests were 2-sided. Statistical analysis was performed with IBM SPSS Statistics (version 25; IBM Corp., Armonk, NY). Scatter plots of the analyzed data were produced using GraphPad Prism version 9.2.0 for Windows (GraphPad Inc., San Diego, CA).

Results

EFFICACY OF THE BNT162B2 MRNA VACCINE

Baseline demographics and clinical and laboratory characteristics of the LT recipients are presented in Table 2. The median age of the LT recipients was 64 years (IQR, 49-69 years; range, 22-83 years); 56.6% were men. Median time since LT was 7 years (IQR, 4-16 years). Comorbidities were frequent, with hypertension (48.6%), diabetes mellitus (42%), chronic kidney disease (35.2%), and dyslipidemia (48.6%) being the most common. Mean time ± standard deviation (SD) between second vaccine dose and blood sampling for detection of IgG antibodies against the RBD of SARS-CoV-2 and NA was 38 ± 24 days; 66% of samples were collected 21 days after vaccination.

CNI was administered as the principal immunosuppressive agent to 75 patients (68 tacrolimus and 7 cyclosporine). CNI monotherapy was given to 40 patients (53%); 31 patients (41%) were receiving double immunosuppression (combination of CNI and mycophenolate mofetil [MMF], 12 patients; CNI and everolimus, 10 patients; CNI and prednisone, 9 patients). Triple immunosuppression was being given to only 4 (5.3%) patients (combination of CNI, MMF, and prednisone). Of the patients, 1 was receiving sirolimus monotherapy.

TABLE 2. Baseline Demographics and Clinical and Laboratory Characteristics of Patients With Versus Without Immunologic Response to Vaccination

Variable	Total Cohort, n = 76	Antibody Negative,* n = 21 (28%)	Antibody Positive,* n = 55 (72%)	P Value
Age, years	64 (49-69)	68 (61-71)	60 (46-69)	0.046
Male	43 (56.6)	10 (47.6)	33 (60)	0.3
Indications for LT				0.13
Hepatitis C virus	19 (25.3)	7 (33.3)	12 (21.8)	
NASH	13 (17.3)	5 (23.8)	8 (14.5)	
Hepatitis B virus	7 (9.3)	0	7 (12.7)	
PSC	11 (14.7)	0	11 (20)	
PBC	3 (4.0)	1 (4.8)	2 (3.6)	
Others†	23 (30.3)	8 (38.1)	15 (27.3)	
Transplant age, years	51 (38-63)	58 (51-64)	47 (29-62)	0.02
Time since LT, years	7 (4-16)	8 (3-11)	12 (4-17)	0.084
Double organ transplant, kidney and liver	5 (6.6)	4 (19)	1 (1.8)	0.01
Diabetes mellitus	31 (42)	10 (50)	21 (38.9)	0.4
Hypertension	36 (48.6)	13 (65)	23 (42.6)	0.09
Dyslipidemia	36 (48.6)	13 (65)	23 (42.6)	0.09
Chronic kidney disease	25 (35.2)	14 (73.7)	11 (21.2)	<0.001
BMI, kg/m^2	25 (22-28)	25 (23-28)	25 (22-28)	0.85
White blood cells, K/μL	6.0 (4.5-7.1)	5.4 (4.1-6.6)	6.2 (4.73-7.34)	0.16
Hemoglobin, g/dL	13.3 (11.9-14.2)	11.5 (10-13.9)	13.5 (12.4-14.5)	0.006
Platelets, K/μL	157 (127-195)	155 (127-195)	159 (127- 196)	0.8
Creatinine, mg/dL	1.0 (0.9-1.3)	1.37 (1.0-1.6)	0.97 (0.8-1.2)	<0.001
ALT, IU/L	20 (15-29)	16 (14-22)	22 (17-34)	0.015
ALP, IU/L	100 (74-130)	99 (66-140)	100 (76-130)	0.72
Bilirubin, mg/dL	0.6 (0.5-0.8)	0.5 (0.4-0.6)	0.7 (0.5-1.0)	0.001
Albumin, g/dL	4.2 (3.9-4.3)	4.1 (4.0-4.3)	4.2 (3.9-4.3)	0.93
Hemoglobin A1c, %	6.1 (5.4-6.9)	6.4 (5.8-7.0)	6 (5.4-6.9)	0.515
Cholesterol, mg/dL	182 (149-204)	179 (121-211)	182 (149-204)	0.89
Triglycerides, mg/dL	135 (106-196)	137 (113-192)	134 (105-207)	0.97
Tacrolimus dose, mg	3 (2-4)	3 (1.5-4.1)	3 (2-4)	0.9
Tacrolimus trough level, μg/L	5 (4.2-6)	4.6 (3.4-5.4)	5.1 (4.3-6.2)	0.09
Prednisone	12 (16)	5 (25)	7 (13)	0.2
Prednisone dose, mg	5 (5-10)	5 (5-8)	6 (5-13)	0.5
MMF	16 (21.3)	10 (47.6)	7 (11.1)	0.001
MMF dose, mg	1000 (500-1000)	1000 (500-1000)	750 (250-1000)	0.4
Everolimus	11 (14.7)	5 (25)	6 (10.9)	0.1
Everolimus dose, mg	2 (2-2.5)	2.3 (2-3)	2 (2-2)	0.3
Everolimus trough level, ng/mL	2.5 (2.2-4.1)	3.45 (2.2-4.8)	2.4 (1.8-3.1)	0.49
Double immunosuppression‡	31 (41)	16 (76)	15 (28)	<0.001
Triple immunosuppression§	4 (5.3)	2 (9.5)	2 (3.7)	0.01
Time from second vaccine to serology collection, days	36 (17-52)	26 (15-41)	39 (17-57)	0.121

NOTE: Data are presented as median (IQR) or n (%). For categorical variables, the chi-square statistic was used. Continuous variables were compared by using a *t* test if normally distributed or by Mann-Whitney U test if non-normally distributed. A *P* value of 0.05 or less was considered statistically significant for all analyses.
*IgG antibody titers ≥1.1 were defined as positive antibody tests and <1.1 as negative antibody tests.
†Other indications to LT: ALD, biliary atresia, CF, fulminant liver failure.
‡Double immunosuppression denotes CNI and MMF (12 patients), CNI and everolimus (10 patients), or CNI and prednisone (9 patients).
§Triple immunosuppression denotes CNI, MMF, and prednisone.

The control group included 174 immunocompetent health care workers, and their demographic characteristics are shown in Table 1.

LT recipients showed a reduced immune response to the BNT162b2 mRNA vaccine compared with age-matched immunocompetent controls (Table 1). A positive antibody response was documented for 55 of the 76 LT recipients (72.4%) compared with 164 of the 174 immunocompetent controls (94.3%; odds ratio [OR], 6.26; 95% CI, 2.8-14.1; $P < 0.0001$), as measured at a median 35 days (IQR, 17-52 days) after the second vaccine dose. The geometric mean titers of the IgG antibodies and NAs in LT recipients were lower compared with the control group (2.1 [95% CI, 1.6-2.6] versus 4.6 [95% CI, 4.1-5.1; $P < 0.0001$] and 150 [95% CI, 96-234] versus 429 [95% CI, 350-528; $P < 0.001$], respectively; Table 1, Fig. 1A,B).

A univariate analysis found that LT recipients who did not develop IgG antibodies were older compared with those who developed antibodies (68 years versus 60 years; $P = 0.046$), were of older age at transplantation (58 years versus 47 years; $P = 0.02$), underwent combined liver and kidney transplantation (19% versus 1.8%; $P = 0.01$), and were more likely to have chronic kidney injury (73.7% versus 21.2%; $P < 0.0001$). Moreover, LT recipients who did not develop IgG antibodies had lower levels of hemoglobin (11.5 g/dL versus 13.5 g/dL; $P = 0.006$),and had higher levels of alanine aminotransferase (ALT; 16 U/L versus 22 U/L; $P = 0.015$) and bilirubin (0.5 mg/dL versus 0.7 mg/dL; $P = 0.001$) compared with those who did develop antibodies. The antibody response was reduced in transplant recipients who were receiving double immunosuppression compared with CNI monotherapy (15 [28%] versus 16 [76%]; $P < 0.0001$) or triple immunosuppression therapy compared with CNI monotherapy (2 [3.7%] versus 2 [9.5%]; $P = 0.01$). Antibody responses were significantly reduced in LT recipients who received immunosuppression therapy that included the combination of CNI and MMF (45% versus 12.7%; $P = 0.01$). Antibody responses were also lower in recipients who were receiving a combination of CNI and everolimus (25% versus 10.9%; $P = 0.1$) and CNI and prednisone compared with CNI monotherapy (25% versus 13%), but the difference was not statistically significant ($P = 0.2$). A multivariate analysis using a linear regression analysis revealed that combined immunosuppression and chronic kidney disease were
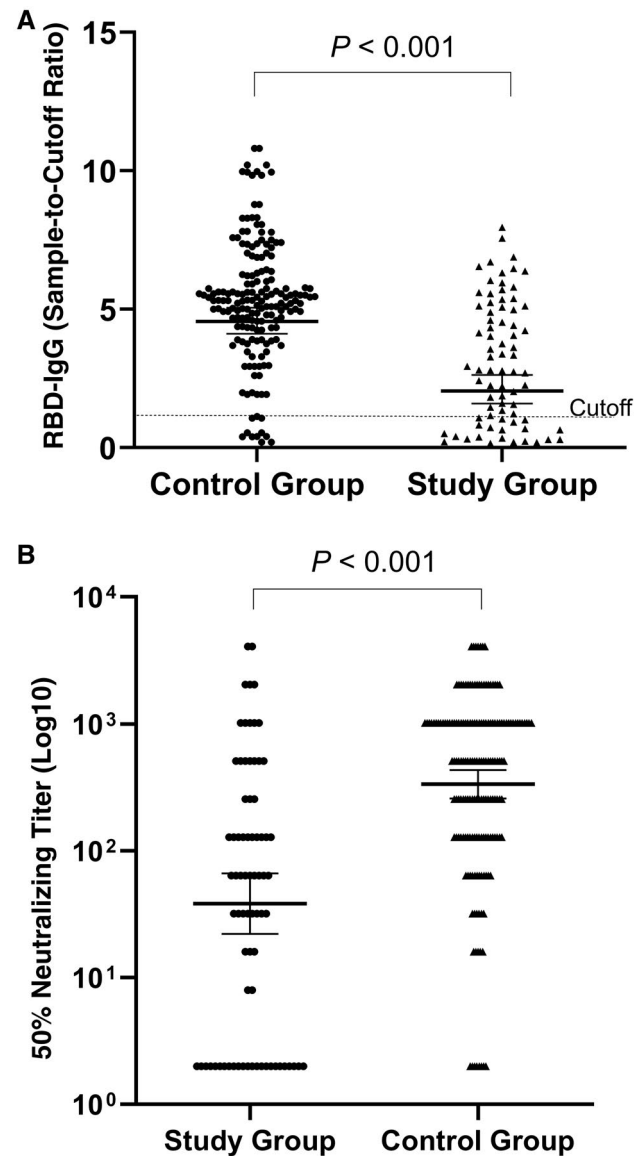

FIG. 1. Comparison of antibody responses in LT recipients versus control immunocompetent patients: (A) titers of SARS-CoV-2 RBD-IgG antibodies and (B) titers of NAs among LT recipients (n = 76) and immunocompetent controls (n = 174) following second doses of the BNT162b2 mRNA vaccine. The dotted line indicates the cutoff level of positive antibodies titers ≥1.1 sample-to-cutoff ratio. Solid lines indicate geometric mean. Each marker represents 1 serum sample.

predictors of low immune response to vaccination (Table 3).

The geometric mean of the SARS-CoV-2 IgG and NA titers was significantly lower in LT recipients who were receiving combined immunosuppression versus CNI monotherapy (1.1 [95% CI, 0.8-1.6] versus 3.5

TABLE 3. Factors Associated With Immunologic Response to Vaccination in Multivariate Regression Analysis

Variable	P Value	Hazard Ratio	95% CI
Age at vaccination, years	0.8	0.9	0.9-1.1
Time from second vaccine to serology collection, days	0.3	1.0	0.99-1.1
Hemoglobin, g/dL	0.9	1.0	0.7-1.4
Chronic kidney disease	0.02	7.1	1.3-37.4
ALT, IU/L	0.049	1.1	1.0-1.2
CNI monotherapy versus combined immunosuppression	0.002	0.1	0.02-0.4

NOTE: A logistic regression analysis model was used to explore the factors associated with immunologic response to vaccination. Covariates for the multivariate models were selected using clinical judgment and variables that significantly differed between the groups. $P < 0.05$ was considered a statistically significant difference.

[95% CI, 2.8-4.4; $P < 0.001$] and 10.35 [95% CI, 5.4-19.8] versus 123 [95% CI, 60-254.6; $P < 0.001$], respectively; Fig. 2A,B).

In the study group, among all the patients with negative antibody responses (IgG antibody titers <1.1 sample-to-cutoff ratio), only 1 patient (1/21) became infected with SARS-CoV-2, whereas in the group with positive antibody responses, no cases of infection were reported (0/55).

Adverse Events

The BNT162b2 mRNA vaccine was well tolerated by all LT recipients. No transplant rejection or allergic reactions at a mean follow-up of 30 days following the second dose were observed. Adverse events (AEs) were reported by 39 (51%) LT recipients (Table 4). The frequency of local AEs following the first and second vaccines was 30.3% and 19.7%. The most common local reaction was pain at the injection site, which was mild in most cases and subsided within 24 hours. Systemic AEs following both doses occurred in 19.7% of patients and included mostly fatigue and headache. Of the patients, 1 developed Bell's palsy after the first dose and fully recovered after treatment with antivirals and steroids.

The immune response did not correlate with the number of adverse effects (27/65 [49%] in patients who were seronegative and 12/21 (57%) in the patients who were seropositive; $P = 0.5$).

Younger LT female patients showed a higher tendency to develop adverse effects (Table 5). Other
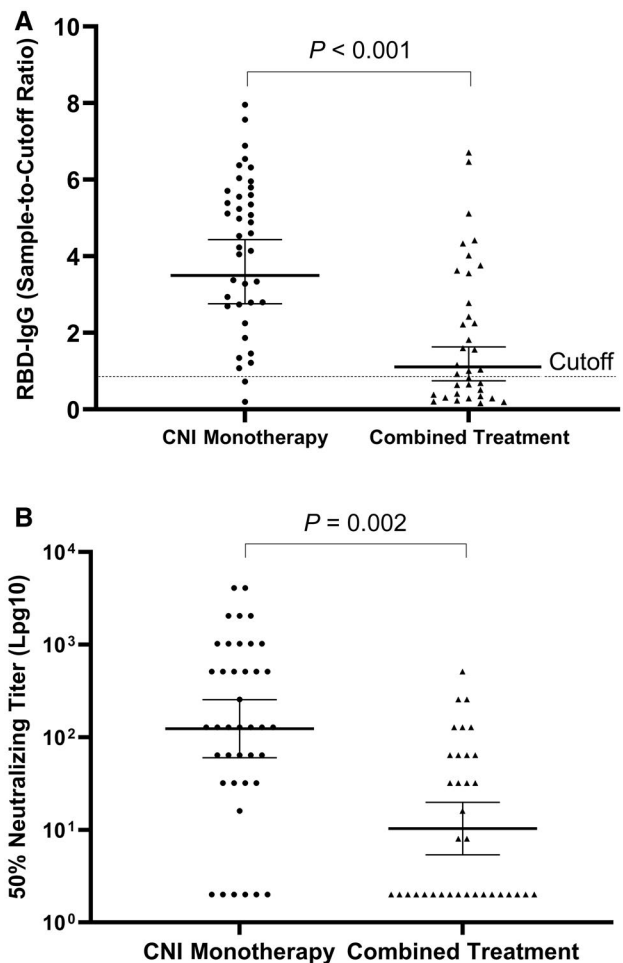

FIG. 2. Comparison of antibody responses according to type of immunosuppression therapy among LT patients: (A) titers of SARS-CoV-2 RBD-IgG antibodies and (B) titers of NAs among combined immunosuppression (combination of CNI, MMF, prednisone) versus CNI monotherapy following second doses of the BNT162b2 mRNA vaccine. The dotted line indicates the cutoff level of positive antibodies titers ≥1.1 sample-to-cutoff ratio. Solid lines indicate geometric mean. Each marker represents 1 serum sample.

clinical and demographic characteristics were not associated with AEs. We found that female sex adjusted to age was significantly associated with AEs following vaccination (relative risk [RR], 2.6; 95% CI, 1.0-6.8; $P = 0.049$; Table 5).

Discussion

The immune response rate to the BNT162b2 mRNA vaccine in our cohort of LT patients was 72% compared with 94.2% in the control immunocompetent

group. In recently published reports, LT recipients appeared to have a better immune response to the SARS-CoV-2 mRNA vaccine compared with other SOT recipients.[4-7,15-17] Specifically, Rabinowich et al.[5] recently reported on a 47.5% immune response to the BNT162b2 mRNA vaccine among LT recipients, whereas lower immune responses were measured among kidney transplant recipients (22%-41%),[4,7,16,18] heart transplant recipients (15%-18%),[6,19] and lung transplant recipients (18%).[15] These findings can be attributed to the reduced immunosuppressive burden in LT compared with other SOT recipients. The lower immune response among the LT recipients reported by Rabinowich et al.[5] compared with our study might be related to the median/mean time after transplantation, which was considerably longer in our cohort, and thus the immunosuppressive burden was lower. In the cohort of LT recipients reported by Rabinowich et al.,[5] the majority of the patients received combined immunosuppression (62.5% received 2 immunosuppressive medications and 21.2% received triple therapy), whereas in our cohort CNI monotherapy was given to 53%. Moreover, we showed improvement in immune response 1 month after the second vaccination (mean time $\pm$ SD 38 $\pm$ 24 days; 66% of samples were collected 21 days after vaccination) among LT recipients treated with combined immunosuppression. Previous work reported an immune response of the

BNT162b2 mRNA vaccine among SOT patients 10 to 21 days after the second dose.[6,16,17]

Rashidi-Alavijeh et al.[17] also reported superior results compared with other SOT recipients, with a 79% response rate following the 2 doses of the BNT162b2 vaccine. The slightly higher response rate in the Rashidi-Alavijeh et al. study[17] compared with our study might be related to the older age of the transplant patients in our cohort (median 64 [IQR, 49-69] versus 57 [IQR, 49-64] years). A higher percentage of transplant recipients in the Rashidi-Alavijeh et al. cohort (55%) received combined immunosuppression of CNI with everolimus compared with our study (14.7%). Moreover, in univariate analysis, although Rashidi-Alavijeh et al. reported a lower immune response rate to the vaccine among recipients treated with the combination of CNI and MMF, they did not provide information regarding the impact of renal failure function on the immune response.

We found that the antibody response was reduced in transplant recipients who were receiving combined immunosuppression compared with CNI monotherapy. CNIs are the principal immunosuppression agents prescribed after LT. Among the available CNIs, tacrolimus is the drug of choice in almost 90% of LT recipients.[20] Because of the known nephrotoxicity that is associated with the administration of CNI, administration at reduced dosages, with or without renal-sparing agents such as sirolimus, everolimus, low-dose steroids, or MMF, is common practice.[20] The effect of mammalian target of rapamycin (mTOR) on the humoral response to mRNA vaccines was reported among kidney transplant recipients[18] with some studies reporting a more favorable humoral response and other that obtained opposing results or no differences in immunosuppressive drugs between kidney transplant recipients tested positive and negative for SARS-CoV-2 IgG.[21] Everolimus and sirolimus were associated with a significant rise in the antigen-specific

TABLE 4. Rate of AEs Among LT Recipients After Vaccination With the BNT162b2 mRNA (n = 76)

Variable	n (%)
Local AE	
Any local AE after first vaccine	23 (30.3)
Any local AE after second vaccine	15 (19.7)
Systemic AE	
Any systemic AE after first vaccine	21 (27.6)
Any systemic AE after second vaccine	15 (19.7)

TABLE 5. Univariate and Multivariate Analyses of Associations Between Clinical and Laboratory Characteristics and Development of Adverse Effects After BNT162b2 mRNA Vaccination

	Adverse Effects		Univariate Analysis		Multivariate Analysis	
Variable	None After Vaccination	Any After Vaccination	P Value	OR (95% CI)	P Value	RR (95% CI)
Age, years, median (IQR)	64 (51-70)	61 (47-69)	0.4		0.42	
Female, n (%)	12 (32.4)	21 (53.8)	0.06	0.4 (0.2-1.01)	0.049	2.62 (1.0-6.83)

IgG antibody level after pneumococcal, tetanus, and influenza vaccines.[21]

We found that renal failure and combined immunosuppression are significant factors associated with reduced antibody response. Patients with chronic renal failure may have attenuated vaccine responses.[22] Reduced immune response to the BNT162b2 mRNA vaccine was also reported in SOT recipients with decreased renal function.[23] This might explain our findings of renal failure and combined immunosuppression as factors associated with reduced antibody response. However, it is difficult to determine which of the 2 is the key factor.

In line with prior reports, the BNT162b2 mRNA vaccine was well tolerated by both immunocompetent and SOT recipients. In the LT cohort, most of the self-reported adverse effects were mild and self-limiting. There were no significant adverse effects, except for 1 patient who developed Bell's palsy after the first dose. Associations between several types of vaccines and Bell's palsy have been studied extensively, and it is thought to be immune-mediated or induced by viral reactivation.[24,25] Renoud et al.[24] analyzed 133,883 cases of adverse drug reactions to the mRNA COVID-19 vaccines reported in the World Health Organization pharmacovigilance database and identified 844 (0.6%) facial paralysis–related events; 749 cases were reported for the Pfizer-BioNTech vaccine, and 95 cases were reported for the Moderna vaccine. The incidence of facial paralysis after the influenza vaccine was 0.7%. However, Ozonoff et al.[25] reported a higher incidence of Bell's palsy after mRNA vaccines than in the general population.

In line with a recent large observational study from the United Kingdom,[26] more adverse effects were reported by women. Menni et al.[26] reported that the overall incidence of adverse effects after vaccination with the Pfizer-BioNTech (BNT162b2) or the Oxford-AstraZeneca vaccine (less than 30% local adverse effects and 25% of systemic adverse effects) was higher in women and in people aged 55 years or younger.

This study has several limitations. First, our study did not include recent LT recipients (mean time ± SD since LT was 11 ± 9 years), which can partially explain the low rate of combined immunosuppression therapy and consequently the higher level of immunologic response to the BNT162b2 mRNA vaccine in this cohort compared with previous reports. Second, it relied on self-reported data, which can introduce information bias, including misclassification. Third, we have no data on AEs in the control group. Fourth, using health care professionals as controls is problematic, particularly to evaluate clinical efficacy. The level of exposure to SARS-CoV-2 after vaccination is expected to be higher in the control group. However, this had little impact in our study, which was not powered to evaluate efficacy. Fifth, the study was conducted in a single medical center and on a relatively small sample size.

The strength of the study is that despite the high percentage of older age of included in our cohort patients in our cohort we found detected a relatively high level of immune response. Furthermore, we found a negative influence of combine immunosuppression (MMF along with mTOR in combination with CNI) on the immune response.

In conclusion, the immune response of LT recipients to the BNT162b2 mRNA vaccine was relatively high (72%) but was lower than those of age-matched immunocompetent controls. Combined immunosuppression and impaired renal function were associated with reduced antibody response to the vaccine. Overall, mild and self-limiting AEs were reported in 51% of the patients after vaccination. Adverse effects were more common in women.

The durability of both the humoral immune response and the cellular immune response to the BNT162b2 mRNA vaccine among LT recipients and the cellular immune response will require further investigation. We suggest that low response among LT recipients calls for further boosts vaccine to achieve good immune response.

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