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Humoral and Cellular Responses to mRNA-1273 and BNT162b2 SARS-CoV-2 Vaccines Administered to Hemodialysis Patients

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Rationale & Objective: Patients with kidney failure who are receiving maintenance dialysis have a higher risk of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and worse clinical outcomes after coronavirus disease 2019 (COVID-19) than the general population. Therefore, immunization against SARS-CoV-2 with effective vaccines is an important component of health-maintenance strategies for these patients. This study evaluated the humoral and cellular responses to messenger RNA (mRNA) SARS-CoV-2 vaccines in this population.

Study Design: Observational prospective multicenter cohort study.

Setting & Participants: 205 patients treated at 3 dialysis units at the Hospital Clínic of Barcelona (Spain) were vaccinated from February 3 to April 4, 2021, and followed until April 23, 2021.

Exposure: Immunization with either the mRNA-1273 (Moderna) or BNT162b2 (Pfizer-BioNTech) SARS-CoV-2 mRNA vaccine.

Outcome: Seroconversion, defined as the detection of IgG antibodies to the receptor-binding domain of the S1 spike antigen of SARS-CoV-2 (anti-S1-RBD IgG), and the identification of activated CD4⁺ T cells 3 weeks after completing vaccination. Anti-S1-RBD IgG

levels were also analyzed as a secondary outcome.

Analytical Approach: Univariate and multivariable logistic and multiple linear regression models were used to evaluate the associations between vaccination and study outcomes.

Results: We found that 97.7% of 175 vaccinated patients who were seronegative at baseline developed a response (humoral, cellular, or both); 95.4% of these patients seroconverted, while 62% of those tested for cellular immunity had a positive response. Greater age and immunosuppressive treatment were associated with lower antibody levels.

Limitations: Mandatory vaccine administration by health authorities. Anti-S1-RBD IgG levels were reported up to 150 U/mL and cellular immune responses were characterized qualitatively. Antibody assay and cellular response assessment may not be comparable to previously published laboratory approaches.

Conclusions: Immunization with mRNA vaccines generated a humoral and cellular immune response in a high proportion of patients with kidney failure receiving maintenance dialysis. These findings as well as the high risk of infection and poor clinical outcomes among these patients make their vaccination a health priority.

Complete author and article information provided before references.

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During the past year, numerous coronavirus disease 2019 (COVID-19) outbreaks have occurred in hemodialysis units because of their patients' high risk for viral exposure, given that they share transport and dressing rooms and they spend, on average, 12 hours a week with their peers and health care professionals.¹⁻³ Moreover, once infected, patients with kidney failure receiving hemodialysis have poor clinical outcomes. They have more hospital admissions, more extended hospital stays, and greater mortality than the general population.^{4,5} In fact, during the disease's first wave in 2020, we found a mortality rate of 34% among hemodialysis patients from our 3 affiliated units,⁶ strikingly higher than the overall 9.7% seen in all admitted patients in our hospital.⁷ These poor outcomes have been attributed to the multiple comorbidities afflicting these patients as well as their increased age, fragility, and immunologically deficient state.^{6,8} Considering the combination of these high-risk

factors, this population must be promptly immunized against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as recommended by several nephrology societies.⁹⁻¹²

There are currently several vaccines available and approved for use in the general population. However, despite the shortage of data on their effectiveness, some authors have suggested using the mRNA vaccines for special populations such as patients with kidney failure receiving hemodialysis.¹³ Two mRNA vaccines have been approved for use: mRNA-1273 (Moderna) and the BNT162b2 (Pfizer-BioNTech). Both consist of lipid-encapsulated nanoparticles that encapsulate mRNA encoding the prefusion-stabilized full-length SARS-CoV-2 spike, which induces T-helper, cytotoxic T-cell, and humoral immune responses.¹⁴ Randomized trials showed 94.1% and 95% efficacy at preventing COVID-19, with complete absence of hospital admissions and deaths among

those vaccinated.^{15,16} Routine data have suggested these vaccines prevent 94% of symptomatic COVID-19 cases, 85% to 87% of hospital admissions, and 92% of severe disease.^{17,18}

Even though the most appropriate method to evaluate a vaccine response is by assessing clinical outcomes (eg, hospital admissions and mortality), there is an urgent demand to immunize kidney failure patients receiving hemodialysis. Furthermore, the immunodeficient state of this population, as demonstrated by their reduced seroconversion in other immunization programs such as that against hepatitis B virus,¹⁹ has generated great concern about the effectiveness of SARS-CoV-2 vaccines to elicit real-life protection from severe COVID-19. Consequently, despite the US Centers for Disease Control and Prevention (CDC) not recommending antibody testing after vaccination to assess individuals' response to immunization (nor are there US Food and Drug Association–authorized tests for this purpose due to the heterogeneity of test results and scarce external validation), many studies have evaluated vaccine response based on capacity to generate an adaptive immune response, whether it be humoral (ie, the formation of antibodies that prevent viral entry into cells) or cellular (ie, the activation of specific T cells that kill infected cells and thus prevent viral replication). A recent report by Irsara et al²⁰ found a good correlation between the level of IgG antibodies to the receptor-binding domain of the S1 spike antigen of SARS-CoV-2 (anti-S1-RBD IgG) measured by the Siemens SARS-CoV-2 IgG (sCOVG) assay and viral neutralization levels, suggesting their potential use as a surrogate for virus neutralization capacity. Therefore, even though rapidly emerging results on both mRNA vaccines' efficacy in the hemodialysis population^{21,22} must be interpreted carefully, there is hope that these cellular and humoral responses can act as indirect signs of COVID-19 protection.

Currently, the literature is lacking in large cohorts that include both the mRNA-1273 and BNT162b2 vaccine in similar proportions. We assessed the humoral and cellular responses to both SARS-CoV-2 mRNA vaccines in maintenance hemodialysis patients while looking for potential predictors of antibody generation and intensity.

Methods

Study Design and Setting

This observational, prospective, multicenter study to evaluate immunogenicity in terms of antibody response and T-cell activation after SARS-CoV-2 mRNA vaccination in hemodialysis patients was carried out in Hospital Clínic of Barcelona and 2 affiliated centers, Centre de Diàlisi i Recerca Aplicada Clínic and Institut Hemodiàlisi Barcelona. The 2 mRNA vaccines approved by the European Medicines Agency, mRNA-1273 (Moderna) and BNT162b2 (Pfizer-BioNTech), were administered in each dialysis facility. Allocation was carried out following the national health authorities'

instructions: mRNA-1273 for in-hospital hemodialysis centers and BNT162b2 for out-of-hospital hemodialysis centers. Vaccination took place from February 3 to April 4, 2021, following the first and second dose interval recommended by the manufacturer of 21 days for the BNT162b2 vaccine and 28 days for the mRNA-1273 vaccine. Follow-up continued until April 23, 2021.

Participants

All prevalent maintenance hemodialysis patients over 18 years old in the 3 dialysis facilities were considered for inclusion. Patients were excluded if they were previously vaccinated in other health care centers, refused vaccination, were admitted to the hospital during the inclusion period, had a history of SARS-CoV-2 infection less than 3 months before the vaccination period finalized, or declined to participate. Participants were classified according to the cellular and humoral responses observed after completing vaccination. Seropositive patients (those who were positive for anti-S1-RBD IgG at baseline) were excluded from the humoral response analysis. Cellular response was only available in a subset of the study participants, as there were logistic impediments that required laboratory samples to be received during the morning.

Humoral Response Assessment

Humoral response was measured in all patients at 3 different time points (baseline, immediately before administering the second dose, and 3 weeks thereafter) with the Siemens Healthineers Atellica IM SARS-CoV-2 IgG (sCOVG) assay, which detects IgG antibodies to the receptor-binding domain of the S1 spike antigen of SARS-CoV-2 (anti-S1-RBD IgG). The sample is considered nonreactive when the result is less than 1 or reactive when greater than or equal to 1, with a maximum measurable level of up to 150 U/mL. According to the manufacturer, this test has 96.41% (95% CI, 92.74%–98.54%) sensitivity and 99.9% (95% CI, 99.63%–99.99%) specificity.

Cellular Response Assessment

Heparinized peripheral blood was collected from study participants to measure CD4⁺ T cell response at 3 weeks after completing vaccination by an intracellular cytokine stimulation assay. For detection of cells expressing CD69 and intracellular interferon γ (IFN- γ), white blood cells from each study participant were stimulated with spike and nucleocapsid SARS-CoV-2 peptide pools (Miltényi Biotec), with a negative (vehicle) and a positive (staphylococcal enterotoxin B superantigen) control. Flow cytometric detection of more than 10 events of CD4⁺ IFN- γ ⁺ CD69⁺, with greater than 2-fold change compared with the unstimulated condition, was considered a positive peptide-specific response.

All assays were performed at 37°C, 5% CO₂, and 95% humidity. Flow cytometric acquisition and analysis of

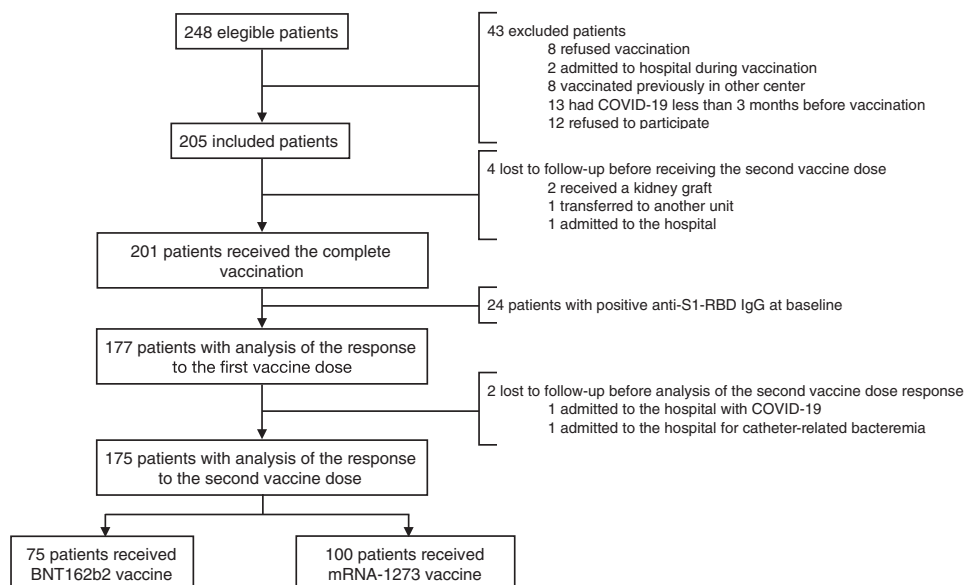


Figure 1. Flow diagram with the number of individuals, eligibility, reasons for nonparticipation or loss to follow-up, and vaccine received, at each stage of the study.

activation-induced markers was performed in an Attune Flow Cytometer (ThermoFisher) after 40,000 CD4⁺ T cells were acquired.

Other Variables

Other studied variables included age, sex, race, CKD etiology, type of dialysis unit, dialysis vintage and dose (Kt/V), body mass index, comorbidities such as type 2 diabetes or previous SARS-CoV-2 infection, the use of immunosuppressive therapy, and the most recent available albumin

and C-reactive protein levels and white and red blood cell counts. These data were collected at baseline from electronic medical records and were considered as potential confounding variables for vaccine response in these analyses.

Outcomes

The primary outcomes evaluated in this study were the qualitative humoral and cellular responses to the mRNA vaccine. Secondary evaluated outcomes were quantitative

Table 1. Demographic and Clinical Characteristics of Study Participants

Variable	Total (N = 175)	Vaccine		P
		mRNA-1273 (n = 100 [57.1%])	BNT162b2 (n = 75 [42.9%])	
Age, y	70.90 ± 14.96	68.20 ± 15.54	74.58 ± 13.32	0.004
Male sex	118 (67.4%)	69 (69%)	49 (65%)	0.6
Race				0.1
White	155 (88.6%)	85 (85%)	70 (93%)	
Non-White	20 (11.4%)	15 (15%)	5 (7%)	
Dialysis unit				<0.001
In-hospital	46 (26.3%)	45 (45%)	1 (1%)	
Out-of-hospital	129 (73.7%)	55 (55%)	74 (99%)	
Dialysis vintage, mo	67.87 ± 102.79	84.12 ± 116.47	48.21 ± 78.58	0.006
Kt/V	1.95 ± 0.41	2.03 ± 0.44	1.85 ± 0.35	0.04
BMI, kg/m ²	25.29 ± 5.39	24.39 ± 4.6	26.34 ± 6.19	0.04
Diabetes	68 (39.1%)	38 (38%)	30 (41%)	0.8
Immunosuppressive therapy	10 (5.7%)	8 (8%)	2 (3%)	0.2
C-reactive protein, mg/L	0.88 ± 1.18	0.75 ± 1.54	1.05 ± 0.24	< 0.001
WBC count, ×10 ⁹ /L	6.7 ± 5.4	6.7 ± 2.2	6.5 ± 8	0.004
Lymphocytes, ×10 ⁹ /L	1.3 ± 0.64	1.4 ± 0.7	1.1 ± 0.5	0.001
Hemoglobin, g/dL	11.34 ± 1.3	11.53 ± 1.32	11.09 ± 1.23	0.02
Albumin, g/dL	4.06 ± 2.55	3.93 ± 0.41	4.24 ± 3.9	0.01

Values for continuous variables given as mean ± standard deviation; for categorical variables, as count (percentage). Abbreviations: BMI, body mass index; WBC, white blood cell.

anti-S1-RBD IgG levels among the patients who were seronegative at baseline. A comparison between them and the remaining patients who were seropositive was also performed.

Statistical Methods

Quantitative variables are reported with mean and standard deviation, while presence or absence of response is reported with absolute and relative frequencies. Univariate analysis was used to estimate the associations between vaccination and outcomes. Differences in demographic and clinical variables (sex, race, type of dialysis unit, diabetes, immunosuppressive therapy) and humoral and cellular responses between responder and nonresponder groups were analyzed with the χ^2 test or Fisher exact test when one or more expected values were less than 5 or the data were very unequally distributed among the table's cells. The normal distribution of the quantitative variables was tested with the Shapiro-Wilk test and Q-Q plots.

Comparison of quantitative variables between 2 groups were made with the Mann-Whitney U test when non-normal (age, dialysis vintage, Kt/V, body mass index, C-reactive protein, white blood cells, lymphocytes, and albumin) or the independent t test when normally distributed (hemoglobin). The comparison of anti-S1-RBD IgG levels between groups was made by the independent-samples median test as we performed a semiquantitative test with a maximum detection limit of 150 U/mL. For analyses involving more than 2 groups, the Kruskal-Wallis H test or analysis of variance (ANOVA) were performed if variables were non-normal or normally distributed, respectively. A 2-sided $P < 0.05$ was considered statistically significant.

Variables that were associated with the chosen outcome ($P < 0.05$) were also entered into the multivariable logistic and multiple linear regression models. Odds ratio, mean or median differences, or exponentiated β -coefficient are presented as effect measures of each studied variable, accordingly. Analyses were performed with IBM SPSS Statistics version 26, and graphics were prepared with GraphPad Prism version 8 (GraphPad Software).

Ethical Considerations and Disclosures

All patients gave their written informed consent to participate in this study, which was approved by the institute's committee on human research. The study was conducted following the World Medical Association Declaration of Helsinki, national and local laws, and good clinical practice standards.

Results

Participants

Two hundred and five patients were included in the study. Humoral response was assessed in 175 patients who received both doses, and cellular response was measured in

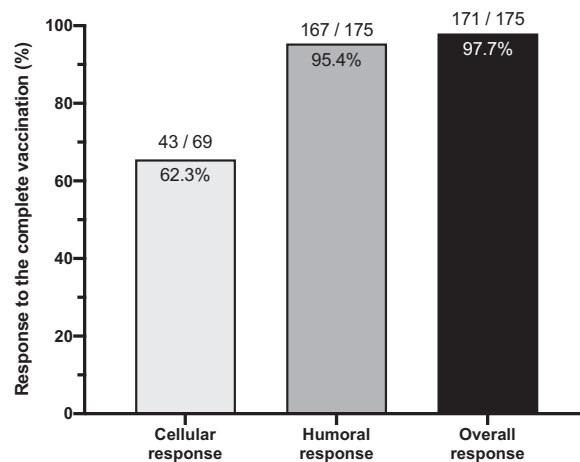


Figure 2. Cellular, humoral and overall responses after completing vaccination.

69 (39.4%). The number of seropositive individuals at baseline, the vaccine received, and reasons for loss to follow-up observation at each stage of the study are described in Figure 1. The patients' demographics and clinical characteristics, both overall and grouped by mRNA vaccine received, are detailed in Table 1.

Global Humoral and Cellular Response

Overall, and irrespective of vaccine type, we found that 97.7% of the 175 patients assessed developed a response (humoral, cellular, or both). Of these 175 patients, 95.4% seroconverted, and 62% of those tested (43 of 69) developed a cellular immune response (Fig 2).

Humoral Response

Of the 175 seronegative patients at baseline who received both doses of either the BNT162b2 or mRNA-1273 vaccine, 167 (95.4%) developed a humoral response: 69 of 75 (92%) with BNT162b2 and 98 of 100 (98%) with mRNA-1273. The use of immunosuppressive treatment ($P < 0.001$), longer dialysis vintage ($P = 0.03$), lower hemoglobin ($P = 0.04$) and albumin ($P < 0.001$) concentrations, and lower white blood cell ($P = 0.04$) and lymphocyte ($P = 0.004$) counts were predictors of no response in univariate analysis; whereas immunosuppressive treatment ($P = 0.001$) and lower albumin ($P = 0.003$) maintained statistical significance in the multivariable analysis (Table 2). This model was statistically significant by the Hosmer and Lemeshow test ($\chi^2 = 15.9$, $P = 0.04$), explained 56.7% (Nagelkerke R^2), and correctly classified 98.8% of cases.

Anti-S1-RBD IgG levels generated are shown in Figure 3A. Lower levels of anti-S1-RBD IgG were correlated with higher age ($P < 0.001$) (Fig 3B), type of dialysis unit ($P = 0.02$), diabetes ($P = 0.04$), immunosuppressive therapy ($P < 0.01$), lower albumin level ($P = 0.04$), and lower lymphocyte count ($P = 0.04$). In the multiple linear

Table 2. Demographic and Clinical Characteristics Comparisons Between Humoral Nonresponders and Responders to SARS-CoV-2 mRNA Vaccination

Variable	Responder ^a		Univariate Analysis			Multivariable Analysis	
	No (n = 8 [4.6%])	Yes (n = 167 [95.4%])	OR or RR (95% CI) ^b	Median or Mean Difference	P	OR (95% CI) ^b	P
Age, y	72.88 ± 17.91	70.81 ± 14.86		-0.96 (-1.88 to -0.40) ^c	0.6		
Male sex	7 (88%)	111 (66.5%)	3.33 (0.42 to 33.3)		0.3 ^d		
Race			0.95 (0.91 to 0.98) ^e		0.6 ^d		
White (reference)	8 (100%)	147 (88%)					
Non-White	0 (0)	20 (12%)					
Dialysis unit			1.1 (0.2 to 5.5)		0.9 ^d		
Out-of-hospital (reference)	6 (75%)	123 (73.7%)					
In-hospital	2 (25%)	44 (26.3%)					
Dialysis vintage, mo	79.50 ± 52.73	67.31 ± 104.65		31 (3 to 59) ^c	0.03	1.00 (0.99 to 1.03)	0.3
Kt/V	1.80 ± 0.33	1.96 ± 0.41		-0.1 (-0.4 to 0.1) ^c	0.5		
BMI, kg/m ²	22.59 ± 4.69	25.42 ± 5.40		-2.7 (-5.9 to 0.5) ^c	0.1		
Diabetes	2 (25%)	66 (39.8%)	0.53 (0.10 to 2.5)		0.5 ^d		
Immunosuppressive therapy	4 (50%)	6 (3.6%)	25 (5 to 143)		< 0.001 ^d	57.6 (4.85 to 684)	0.001
C-reactive protein, mg/L	1.02 ± 0.25	0.87 ± 1.21		0.2 (-0.7 to 1) ^c	0.2		
WBC count, ×10 ⁹ /L	4,948.75 ± 994.94	6,738.68 ± 5,546.57		-1,255 (-2,430 to -40) ^c	0.04	1 (0.99 to 1)	0.9
Lymphocytes, ×10 ⁹ /L	750 ± 484.03	1,282.42 ± 635.43		-500 (-800 to -200) ^c	0.004	1 (0.99 to 1)	0.2
Hemoglobin, g/dL	10.43 ± 1.48	11.38 ± 1.28		-0.85 (-2 to 0.1) ^f	0.04	1.1 (0.54 to 2.34)	0.7
Albumin, g/dL	3.19 ± 0.62	4.1 ± 2.6		-0.6 (-1 to -0.3) ^c	< 0.001	22.9 (2.96 to 176.4)	0.003

Humoral response defined by anti-S1-RBD IgG level. Abbreviations: BMI, body mass index; OR, odds ratio; RR, relative risk; WBC, white blood cell.

^aValues for continuous variables given as mean ± standard deviation; for categorical variables, as count (percentage).

^bORs are for the association of each variable with being a nonresponder. For continuous variables, the OR is per 1-unit lower value.

^cMedian (95% CI).

^dP values were calculated using Fisher exact tests due to 1 or more cells with expected values less than 5.

^eRelative risk.

^fMean (95% CI)

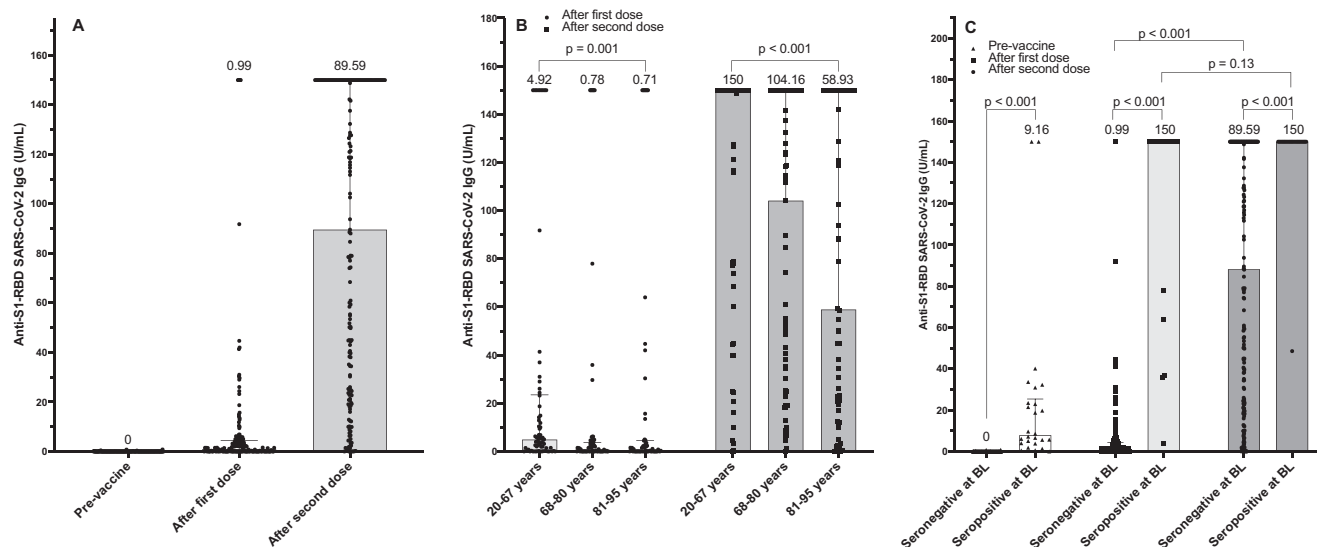


Figure 3. Anti-S1-RBD IgG (A) with each vaccine type after the first and second doses, (B) by age groups after the first and second dose of both mRNA vaccines, and (C) comparing those seronegative and seropositive at baseline (BL). Data represented as median and interquartile range.

regression model, age ($\beta = -0.25$, $P = 0.001$), type of dialysis unit ($\beta = 0.2$, $P = 0.01$), and immunosuppressive treatment ($\beta = -3.6$, $P < 0.001$) maintained statistical significance. This model was statistically significant ($P < 0.001$) but had a low predictive capacity of 17.1% (adjusted R^2) of the cases.

Eight of these 175 patients did not generate anti-S1-RBD IgG antibodies (Table 3). Four of these 8 nonresponders were on immunosuppressive therapy (3 patients were treated with tacrolimus, of whom 2 were liver transplant recipients; 1 had a failed kidney graft who continued to take immunosuppressors to avoid HLA sensitization; and 1 was treated with eculizumab as a treatment for atypical hemolytic uremic syndrome). Of the remaining 4, 3 were elderly, and 1 had no other apparent risk factor besides having type 2 diabetes.

Regardless of vaccine received, every patient who was seropositive at baseline developed antibody levels that were significantly higher than those who were seronegative at baseline ($P < 0.001$), with all but one reaching levels over 150 IU/mL (Fig 3C). These baseline-seropositive patients also had a higher response with 1 vaccine dose than did the baseline-seronegative patients after 2 doses (133.95 ± 37.4 vs 86.2 ± 59.83 U/mL, $P < 0.001$).

Cellular Response

T cells specifically activated by either SARS-CoV-2 nucleocapsid or spike proteins were detected in 46 of the 69 (62%) evaluated patients. Type of dialysis unit significantly correlated with a positive cellular response ($P = 0.03$). No other associations were found between any of the analyzed potential response predictors (Table 4); thus, multivariable

analysis was not performed. Twenty-three patients mounted a humoral but not a cellular response, while 4 did the opposite (Table 3). There was no statistically significant correlation between both immune responses ($P = 0.8$) or between positive cellular response and higher levels of anti-S1-RBD IgG ($P = 0.3$).

Clinical Efficacy

Three patients who had received both vaccine doses became infected with SARS-CoV-2. One developed severe COVID-19 that required hospital admission. He received the BNT162b2 vaccine and did not mount a humoral response after the first dose (data regarding cellular or humoral responses after the second dose were not available due to loss to follow-up). The other 2 patients had asymptomatic SARS-CoV-2 infections that were detected by a monthly nasopharyngeal reverse transcriptase-polymerase chain reaction screening program. Both had developed a humoral response after the first mRNA-1273 vaccine dose (anti-S1-RBD IgG levels of 2.25 and 14.16 U/mL, respectively), and both had anti-S1-RBD IgG levels > 150 U/mL after the second dose.

Discussion

The key outcomes that the nephrology community and patients are seeking to improve with SARS-CoV-2 immunization programs are COVID-19 mortality and intensive care unit and hospital admissions. Whether mRNA vaccines can significantly improve these “hard” outcomes in patients with kidney failure receiving hemodialysis is yet to be determined. However, given concern regarding the vaccine’s efficacy in this population, and until the

Table 3. Clinical Characteristics of Patients Without Humoral Response to SARS-CoV-2 mRNA Vaccination

Pt No.	Sex	Age	Vaccine	Cause of Kidney Failure	Dialysis Vintage, mo	BMI, kg/m ²	Immunosuppressor Treatment	Comorbidities	Lymphocytes, x10 ⁹ /L	Albumin, g/dL	Vaccine Cellular Response
1	M	92	BNT162b2	IgAN	69	26	No	No	600	3.0	Negative
2	M	88	BNT162b2	CNI toxicity	53	22	Tacrolimus	Cancer	1,100	3.6	Positive
3	M	65	BNT162b2	DKD	34	32	No	Diabetes	700	2.1	Positive
4	M	70	BNT162b2	FSGS	24	21	Tacrolimus	No	500	3.7	Positive
5	F	83	BNT162b2	Unknown	94	23	No	Diabetes	1,800	3.4	Positive
6	M	89	BNT162b2	Unknown	62	22	No	No	500	3.3	Negative
7	M	54	mRNA-1273	Unknown	111	17	Tacrolimus and mycophenolic acid	Cancer, liver transplant	300	3.9	Negative
8	M	43	mRNA-1273	HUS	189	18	Ecilizumab	No	500	2.5	Negative

Abbreviations: BMI, body mass index; CNI, calcineurin inhibitor; DKD, diabetic kidney disease; FSGS, focal and segmental glomerulosclerosis; HUS, hemolytic uremic syndrome; IgAN, IgA nephropathy; Pt, patient.

forementioned clinical outcomes are studied, one available approach is to evaluate how these vaccines elicit immunity to SARS-CoV-2 by examining seroconversion, T-cell activation, and anti-S1-RBD IgG levels.¹⁴

Under this premise, our multicenter cohort immunization program study of 205 hemodialysis patients with mRNA vaccines was successful. Of the 175 seronegative patients at baseline who received both vaccine doses, 97.7% developed a response (humoral, cellular, or both), and 95.4% seroconverted. By contrast, only 62% of those tested developed cellular immunity.

Currently, there are scarce data on the cellular response to commercially available mRNA vaccines among maintenance hemodialysis patients. There is only 1 general population report where half of the baseline seronegative patients generated T-cell responses after a single dose of the BNT162b2 vaccine.²³ The only available data after complete vaccination comes from 3 studies. In comparison with them, our results show percentages of T-cell activation that are closer to the general population (88.2%)²⁴ than to those in kidney transplant recipients (5.13% to 35%).^{25,26} Even so, this is an inadequate response, which is consistent with the response reported after hepatitis B virus vaccination of maintenance hemodialysis patients.²⁷ No correlations were found between cellular and humoral responses, nor with other studied predictors like age or immunosuppressive therapy, except for the type of dialysis unit, in keeping with other published reports.²³

Regarding the humoral response, we found that 95.4% generated anti-S1-RBD IgG in response to either mRNA-1273 or BNT162b2, resembling results reported in the vaccine clinical trials.^{28,29} Emerging data on the humoral response of other hemodialysis cohorts have shown similar seroconversion results ranging from 82% to 96%. All but the Frantzen et al³⁰ study (244 patients) had a smaller number of participants than ours.^{21,22,31-34} Moreover, to our knowledge ours is the largest hemodialysis cohort to have evaluated the immune response to the mRNA-1273 vaccine.²² The strongest predictors of humoral vaccine response and antibody levels seen in our results are concordant with those reported across other publications such as age, immunosuppressive treatment, and previous SARS-CoV-2 infection.^{22,35,36}

A correlation between seroconversion, its intensity, and patient age was seen in our findings, as also observed in other previously reported results on SARS-CoV-2 mRNA vaccines.^{28,31,37} This was expected, given that age has been previously associated with an impaired ability to mount a robust humoral or cellular immune response.³⁸ However, when comparing age-matched patients receiving maintenance hemodialysis with the general population, what stands out is that the former have a slower pace of seroconversion.³¹ This may be related to the widely described impaired immune response of maintenance hemodialysis patients found in other immunization programs,^{19,27,39} though it seems not to be relevant when evaluating seroconversion after completing the vaccination scheme in the

Table 4. Demographic and Clinical Characteristics Comparisons Between Cellular Nonresponders and Responders to SARS-CoV-2 mRNA Vaccination

Variable	Total (N = 69) ^a	Cellular Response ^a		Univariate Analysis		
		No (n = 26 [38%])	Yes (n = 43 (62%))	OR ^b	Mean or Median Difference	P
Age, y	68.57 ± 14.69	69.12 ± 16.01	68.23 ± 14.02		1 (−0.6 to 9) ^c	0.6
Male sex	49 (67%)	19 (73%)	29 (67%)	1.3 (0.4 to 3.8)		0.6
Race				1.6 (0.3 to 8.8)		0.6
White (reference)	62 (90%)	24 (92%)	38 (88%)			
Non-White	7 (10%)	2 (8%)	5 (12%)			
Dialysis unit				0.3 (0.1 to 0.9)		0.03
Out-of-hospital (reference)	28 (41%)	6 (23%)	22 (51%)			
In-hospital	41 (59%)	20 (77%)	21 (49%)			
Dialysis vintage, mo	101.75 ± 139.24	100.77 ± 122.44	102.35 ± 149.89		10 (−12 to 32) ^d	0.4
Kt/V	2.04 ± 0.47	2.11 ± 0.48	2.00 ± 0.46		0.13 (−0.11 to 0.29) ^d	0.4
BMI, kg/m ²	24.53 ± 4.91	23.34 ± 4.50	25.25 ± 5.06		−1.9 (−4.3 to 0.5) ^c	0.2
Diabetes	25 (36%)	7 (27%)	18 (42%)	0.5 (0.2 to 1.5)		0.2
Immunosuppressive therapy	6 (9%)	2 (8%)	4 (9%)	0.8 (0.1 to 4.8)		0.8
CRP, mg/L	0.76 ± 1.35	0.91 ± 1.59	0.67 ± 1.18		0 (0 to 0.44) ^d	0.3
WBC count, ×10 ⁹ /L	6,880.01 ± 2,439.82	7,211.96 ± 2,376.25	6,679.3 ± 2,483.4		485.5 (−500 to 1,580) ^d	0.3
Lymphocytes, ×10 ⁹ /L	1,428.99 ± 830.86	1,400 ± 914.33	1,446.51 ± 786.9		−100 (−400 to 200) ^d	0.6
Hemoglobin, g/dL	11.46 ± 1.31	11.45 ± 1.45	11.47 ± 1.23		−0.02 (−0.7 to 0.6) ^c	0.9
Albumin, g/dL	3.85 ± 0.47	3.81 ± 0.49	3.88 ± 0.46		−0.1 (−0.2 to 0.1) ^d	0.7
Humoral response	62 (90%)	23 (89%)	39 (91%)	0.8 (0.2-3.8)		0.8
Anti-S1-RBD IgG level	97.81 ± 58.61	91.07 ± 59.30	101.89 ± 58.51		0 (−33.14 to 0) ^d	0.3

Abbreviations: BMI, body mass index; CRP, C-reactive protein; OR, odds ratio; WBC, white blood cell.

^aValues for continuous variables given as mean ± standard deviation; for categorical variables, as count (percentage).

^bOR (95% CI) for the association of each variable with being a nonresponder.

^cMean (95% CI).

^dMedian (95% CI).

peritoneal dialysis population.⁴⁰ Patients will continue to be monitored for the presence of anti-S1-RBD IgG in serum in subsequent months, given that the duration of the vaccine response in patients with CKD-related immune deficiency is unknown and that they may serorevert faster than the general population.

In accordance with the data observed in studies that evaluated the vaccine response in kidney transplant recipients^{25,41-44} we found that the use of immunosuppressive therapy is a predictor of weak response in comparison to nonimmunosuppressed participants, with fewer seroconverted patients and significantly lower anti-S1-RBD IgG levels in those who do generate a humoral response. Eleven participants in our study were on immunosuppressive treatment: 4 did not develop a humoral response to the complete vaccination, and 5 did respond but mounted low anti-S1-RBD IgG levels. In addition, every patient on corticosteroid treatment seroconverted, while none on tacrolimus did. This weakened anti-S1-RBD IgG production could be secondary to the tacrolimus inhibition of T-helper cell differentiation, resulting in a reduced B-cell activation.⁴⁵ For these reasons, some authors have proposed that the administration of a third dose may be beneficial in patients taking immunosuppressive medication.⁴¹

Our results confirm that seropositive patients at baseline produce a more intense humoral response,^{23,31,46} reaching anti-S1-RBD IgG levels with the first dose as high as seronegative patients achieve after the second dose. However, the findings regarding antibody levels must be interpreted carefully: even though there is evidence of a correlation between anti-S1-RBD IgG levels and viral neutralization,²⁰ their amount cannot be reliably correlated with higher protection because real-world information on prevention of severe COVID-19 after vaccination in hemodialysis patients is lacking. In this regard, the 2 patients from our cohort infected with SARS-CoV-2 after completing vaccination remained asymptomatic throughout the duration of the infection.

Important limitations of our study include that our microbiology laboratory was only able to report anti-S1-RBD IgG levels up to 150 U/mL and to provide a qualitative assessment of cellular response, limiting the complete analysis of the immune response's intensity. Moreover, we found substantial heterogeneity of antibody measurement assays, making it difficult to compare the antibody levels and cellular responses measured in our study. In addition, the multivariable analysis of predictors of humoral response may have been unstable as a result of the very small number of patients who did not have a serological response. These points hamper the generalizability of our results.

In conclusion, even though real-life clinical protection from COVID-19 in this population is yet to be seen, we found that immunization programs were effective in

generating an overall immune response in patients with kidney failure receiving hemodialysis. These findings, together with the high risk of infection and poorer outcomes among these patients, makes their vaccination a health priority, with special attention to patients on immunosuppressive treatment and of older age. Further studies are needed to evaluate the maintenance of these immune responses and the potential need for booster doses.

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