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Studies are urgently needed to characterize immunogenicity, efficacy, and safety of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccines in kidney transplant (KT) recipients, excluded from major clinical trials. Complex ELISPOT and other cellular response techniques have been applied, but simpler tools are needed. An easy-to-use real-world monitoring of SARS-CoV-2 IgG antibodies against the Spike protein and QuantiFERON® SARS-CoV-2 IFNγ release assay (IGRA) were performed at baseline and 28 days after the second dose in KT recipients and controls (dialysis patients and healthy ones). All healthy controls and >95% dialysis controls became positive for anti-S IgG antibodies, while only 63.3% of KT patients seroconverted with a very low antibody level. A positive IGRA was documented in 96.9% of controls, 89.3% peritoneal dialysis, 77.6% hemodialysis, 61.3% of KT patients transplanted more than 1 year ago and only 36% of those transplanted within the previous 12 months. Overall, 100% of healthy controls, 95.4% of dialysis patients and 78.8% KT recipients developed any immune response (humoral and/or cellular) against SARS-CoV-2. KT patients showed low rates of immune responses to mRNA Coronavirus infectious disease 2019 vaccines, especially those with recent transplantations. Simple humoral and cellular monitoring is advisable, so that repeated doses may be scheduled according to the results.
1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for coronavirus infectious disease 2019 (COVID-19), which has caused the worst pandemic in the last decades. COVID-19 cases can be asymptomatic or mild in around 80% of individuals, especially in young adults and children. However, patients over 60 years old and with comorbidities are at higher risk of severe and fatal COVID-19. Several studies indicate that chronic kidney disease (CKD) is the most common comorbidity in severe COVID-19. Furthermore, patients on renal replacement therapy, on dialysis or with a kidney transplant (KT), have shown the highest morbidity and mortality.

A functional immune system is essential to overcome SARS-CoV-2 infection. In the acute phase, activation of CD4 and CD8 T cells is observed in most infected patients. CD4 T cells conduct T helper 1 (Th1) responses, expressing cytokines like interferon gamma (IFNγ) that contribute to viral clearance. CD8 T cells directly destroy infected cells through cytotoxicity. Regarding humoral response, SARS-CoV-2 antigen-specific antibodies are detected in the first weeks since symptoms onset, reaching peak levels in the third week. Neutralizing antibodies, which bind to the Spike (S) protein, prevent interaction with the cellular receptor ACE2 and also generated, granting immune protection against SARS-CoV-2 by disabling viral entry. Antibody durability has not yet been uniformly established, although some studies suggest that levels decrease just after reaching a peak. Despite this, as antibody levels that ensure protection have not been determined, this decrease may not imply loss of immunity against reinfections. Two studies have shown persistence of antibody and cellular responses 6 months after COVID-19 in over 100 adult hemodialysis (HD) patients. Transplant recipients can also show robust although delayed humoral and cellular responses after infection.

Since the beginning of the pandemic, governments of states affected by COVID-19 have implemented sanitary measures to limit virus propagation and reduce high morbidity and mortality rates. The most suitable way to achieve these objectives is generating herd immunity with vaccines. Vaccines must induce antibody production and T cell activation to prevent infection and spread to others. Cellular immunity stimulated by mRNA-1273 is characterized by activation of S-specific CD4 T cells with Th1 profile, while BNT162b2 additionally induces a considerable CD8 T cell response, and both induce antibodies against the S protein. Due to the increased risk of severe and fatal COVID-19 in KT patients, they have been prioritized for COVID-19 vaccination. Because the response to several vaccines is recognized to be poorer in these patients, it is imperative to assess the proportion of responders, the quality of the response as well as the best time for vaccination across the lifetime of the CKD patient with simple and reliable immune response tools. In 104 heart and liver transplant recipients, 64% developed antibodies and 79% T cell responses measured with ELISPOT against the S protein 1 month after completing mRNA-1273 vaccination. Although ELISPOT responses have been documented in transplant recipients, the technique is time-consuming and cumbersome. Thus, we designed a cohort study to assess and compare antibody and cellular responses in KT patients, using simple tools, 28 days after the administration of two doses of Moderna mRNA-1273 or Pfizer BNT162b2 SARS-CoV-2 mRNA vaccines.

2 | MATERIALS AND METHODS

2.1 | Population, endpoints, and vaccines

An observational prospective cohort study was conducted in the Nephrology department of Hospital del Mar and two HD centers in Barcelona, Spain, including 251 individuals without known COVID-19 who were going to receive mRNA vaccines. Exclusion criteria were history of severe adverse reaction associated with a vaccine, previous known COVID-19 infection, active malignancy, inherited immune deficiency, pregnancy and a condition that would contraindicate intramuscular injection. At the hospital, all individuals, including all KT recipients received two 100 µg doses of the mRNA-1273 vaccine (Moderna) separated by 28 days, and in the HD centers, controls and dialysis patients received two doses of 30 µg BNT162b2, Comirnaty® (Pfizer/BioNTech) 21 days apart. The primary endpoint was the antibody-based immune response on day 28 after the second vaccination, to classify individuals as responders or non-responders defined with thresholds prior to data analyses. T cell COVID-19 specific response and safety were secondary endpoints.

The study was approved by the Internal Review Board at Hospital del Mar (2021/9726/I) and adheres to the Declaration of Istanbul. Before receiving the first dose, all participants signed informed consent.

2.2 | SARS-CoV-2 Spike serological assay

SARS-CoV-2 IgG antibodies against Spike were assessed using LIAISON® SARS-CoV-2 TrimericS IgG kit (DiaSorin Inc.). Serum samples obtained before vaccination with positive serology served as exclusion criterion. Following 28 days (±3 days) from the last vaccine dose, humoral response was assessed again. Antibody levels are expressed in arbitrary units per milliliter (AU/ml) and considered
positive if values reached ≥13.0 AU/ml, in accordance with the man-
ufacturer’s guidelines. Serum samples that exceeded assay measur-
ing range (>800 AU/ml) were diluted with LIAISON® TrimericS IgG
Diluent Accessory (Diasoin Inc.) by a 1:20 factor and tested again.

2.3 | IFNγ release assay

Cellular immune response in vaccinated patients was evaluated
using QuantiFERON® SARS-CoV-2 IFNγ release assay (IGRA). At
baseline and 28 days (±3 days) after the second dose, whole blood
samples were collected into the four tubes of QuantiFERON® SARS-
CoV-2 Blood Collection Tubes (QIAGEN). Two (Antigens tubes) were
coated with a combination of SARS-CoV-2 Spike antigens to stimu-
late T lymphocytes: tube 1 contains CD4+ epitopes derived from
the S1 subunit (Receptor Binding Domain) of the S protein while tube
2 contains CD4+ and CD8+ epitopes from the S1 and S2 subunits
of the S protein. The other two tubes, Nil and Mitogen, were used
to adjust the background and as a positive control, respectively.
Samples were incubated for 16–24 h at 37 ± 1°C, followed by cen-
trifugation at 2000–3000 g for 15 min. Finally, IFNγ levels in plasma
were quantified using QuantiFERON® ELISA (QIAGEN), according
to the manufacturer’s instructions. Samples are considered positive
for T cell response when exceeding the cut-off value in one or both
Antigen tubes.

2.4 | Safety assessment

Patients were called by telephone and answered a standardized
questionnaire 7 days after receiving both the first and second dose
of the mRNA vaccine. This questionnaire, created from previous data,27,28 included solicited local (pain, redness and swelling at in-
jection site) and systemic (fever, fatigue, headache, chills, vomits,
diarrhea, myalgia, and arthralgia) adverse events (AE) and their se-
verity. Patients were also followed through electronic chart records
28 days after the second dose to detect unsolicited adverse re-
actions, serious AE or medically attended side effects.

2.5 | Statistical analysis

Categorical variables were analyzed with chi-squared or Fisher’s
exact tests and expressed as counts and percentages. Continuous
variables were first tested for normal distribution using Kolmogorov–
Smirnov test. If normally distributed, continuous data were analyzed
using t-test or ANOVA and expressed as mean values ± standard
deviation; if not, Mann–Whitney or Kruskal–Wallis test were used
and values were expressed as the median and interquartile range
(IQR). Univariate and multivariate logistic regression analyses was
performed to identify factors associated with seroconversion and
low or absent humoral response. Spearman test was used to explore
correlations between continuous variables. A receiver operating
characteristic (ROC) analysis was employed to obtain cut-off values
for IGRA. p < .05 were considered significant. Statistical analysis
was performed using IBM SPSS Statistics 25 (SPSS Inc.).

3 | RESULTS

3.1 | Population

A total of 251 individuals were recruited, and 209 were finally in-
cluded. Excluded cases were: 25 positives for SARS-CoV-2 anti-S
IgG or IGRA at baseline, 6 did not receive the second dose and 11
could not be contacted or rejected second sample extraction. The
definitive group included 90 KT recipients, 87 dialysis controls, and
32 healthy controls. Two doses of Moderna were administered to 90
KT recipients, 48 dialysis controls and 11 healthy ones vaccinated
at Hospital del Mar, and Pfizer vaccine was administered to 39 HD
and 21 controls vaccinated at HD centers. Baseline characteristics
are shown in Table 1. Characteristics of KT recipients transplanted
within the previous year or later are depicted in Table 2.

3.2 | Humoral response and factors associated
with response

Four weeks after completing vaccination, all healthy controls elicited
detectable humoral responses, as did almost all peritoneal dialysis
(PD) (96.6%) and HD controls (94.8%) (Figure 1). Only 57 out of 90
KT (63.3%) seroconverted.

Factors associated with lack of seroconversion in KT recipients
in univariate analysis were darbepoetin need for anemia manage-
ment, a KT performed during the previous 6 months, high serum
creatinine or low estimated glomerular filtration rate (eGFR). At mul-
tivariate analysis, only KT <6 months showed marginal association
with a negative antibody response to vaccination according to the
manufacturer cut-off point (p = .05) (Table 3).

Establishing good response in the 25th percentile of antibody
production, risk factors for not reaching this cut-off in the univari-
ate analysis were darbepoetin treatment, recent KT, and low eGFR.
In the multivariate analysis, a recent KT was the only significant
factor associated with a lack of substantial production of antibod-
ies (Table 4). Every month of posttransplant period increased by
1% the possibilities of achieving the 25th percentile of antibody
production.

Including only seropositive patients, median (IQR) antibody lev-
els were 412 (165–704) AU/ml (Table 5). As expected, healthy con-
trols generated the highest amount of antibodies (734 [532–1149]
AU/ml), while PD and HD controls achieved 559 (216–908) AU/ml
and 378 (195–664) AU/ml, respectively. KT elicited significantly
lower median antibody levels: 139 (43–440) AU/ml. In this case, time
since transplantation was again an important factor as patients with
a KT <1 year barely generated antibodies in contrast to KT >1 year
(p = .017).
| TABLE 1 Baseline characteristics of patients and controls |
|-----------------------------------------------------------|
| **Sociodemographics**                                     |
| Age (years, mean ± SD)                                    | 52.7 ± 10.7 | 67.0 ± 13.9 | 67.0 ± 13.9 | 59.7 ± 12.5 | .001 |
| Sex (female, n [%])                                       | 27 (84.4)   | 19 (32.8)   | 7 (24.1)    | 35 (38.9)   | .329 |
| Body mass index (kg/m², mean ± SD)                        | 25.0 ± 4.3  | 27.5 ± 6.1  | 29.2 ± 5.5  | 27.7 ± 5.9  | .396 |
| Time on RRT, months (median [IQR])                        | —           | 27 (10–49)  | 12 (2–24)   | 42 (9–99)   | .001 |
| Administered vaccine, n (%)                               | mRNA-1273 (Moderna) 11 (34.4) | 19 (32.8) | 29 (100) | 90 (100) | <.001 |
| BNT162b2 (Pfizer)                                         | 21 (65.6)   | 39 (67.2)   | —           | —           | —    |
| **Other vaccines in the last 12 months**                  |
| No, n (%)                                                 | 19 (59.4)   | 23 (39.7)   | 13 (44.8)   | 59 (65.6)   | .012 |
| Influenza vaccine, n (%)                                  | 13 (40.6)   | 31 (53.4)   | 16 (55.2)   | 28 (31.1)   | —    |
| Others, n (%)                                             | —           | 4 (6.9)     | 3 (3.3)     | —           | —    |
| Time since last vaccine, months (median [IQR])            | 4 (3–4)     | 3 (3–4)     | 3 (2.3–3)   | 3 (3–4)     | .319 |
| Darbepoetin treatment, n (%)                              | —           | 43 (74.1)   | 20 (69.0)   | 10 (11.1)   | <.001 |
| Vitamin D supplementation, n (%)                          | —           | 37 (63.8)   | 21 (72.4)   | 18 (20.0)   | <.001 |
| **Comorbidities**                                         |
| Arterial hypertension, n (%)                              | 6 (18.8)    | 56 (96.6)   | 29 (100)    | 88 (97.8)   | .594 |
| Diabetes mellitus, n (%)                                  | 1 (3.1)     | 36 (62.1)   | 17 (58.6)   | 37 (41.1)   | .030 |
| Cardiovascular disease, n (%)                             | 1 (3.1)     | 24 (41.4)   | 15 (51.7)   | 32 (35.6)   | .295 |
| Pulmonary disease, n (%)                                  | 0 (0)       | 24 (41.4)   | 12 (41.4)   | 18 (20.0)   | .008 |
| Underlying diabetic kidney disease, n (%)                 | —           | 22 (37.9)   | 4 (13.8)    | 10 (11.1)   | .002 |
| **Blood tests**                                           |
| White blood cells, ×10³ U/µl (mean ± SD)                  | 7.82 ± 2.28 | 6.91 ± 1.90 | 8.24 ± 2.71 | 8.20 ± 2.57 | .005 |
| T lymphocytes, ×10³ U/µl (mean ± SD)                      | 2.29 ± 0.81 | 1.45 ± 0.57 | 1.29 ± 0.65 | 2.17 ± 1.06 | <.001 |
| Creatinine, mg/dl (mean ± SD)                             | 0.70 ± 0.15 | —           | —           | 1.63 ± 0.75 | <.001 |
| eGFR, ml/min per 1.73 m² (mean ± SD)                      | 98.1 ± 14.6 | —           | —           | 49.9 ± 22.9 | <.001 |
| C-reactive protein, mg/dl (mean ± SD)                     | 0.31 ± 0.53 | 2.21 ± 3.30 | 1.35 ± 2.96 | 0.61 ± 1.06 | .001 |
| Albumin, g/dl (mean ± SD)                                 | 4.56 ± 0.25 | 3.83 ± 0.36 | 3.47 ± 0.43 | 4.29 ± 0.50 | <.001 |
| **Maintenance immunosuppression in kidney transplant recipients** |
| Prednisone, n (%)                                          | —           | —           | —           | 82 (91.1)   | —    |
| Mycophenolic acid derivatives, n (%)                      | —           | —           | —           | 49 (54.4)   | —    |
| Dose, mg/kg/day (mean ± SD)                               | —           | —           | —           | 8.06 ± 2.90 | —    |
| Tacrolimus, n (%)                                          | —           | —           | —           | 82 (91.1)   | —    |
| Dose, mg/kg/day (mean ± SD)                               | —           | —           | —           | 0.048 ± 0.034 | —    |
| Blood levels, ng/ml (mean ± SD)                           | 6.12 ± 2.06 | —           | —           | —           | —    |
| Cyclosporin A, n (%)                                       | —           | —           | —           | 3 (3.3)     | —    |
| Dose, mg/kg/day (mean ± SD)                               | —           | —           | —           | 1.19 ± 0.32 | —    |
| Blood levels, ng/ml (mean ± SD)                           | —           | —           | —           | 217.3 ± 139.3 | —    |
| Everolimus, n (%)                                          | —           | —           | —           | 22 (24.4)   | —    |
| Dose, mg/kg/day (mean ± SD)                               | —           | —           | —           | 0.037 ± 0.02 | —    |
| Blood levels, ng/ml (mean ± SD)                           | —           | —           | —           | 4.36 ± 1.25 | —    |

Bold values indicate statistically significant p values (p < .05).

Abbreviations: eGFR, estimated glomerular filtration rate; IQR, interquartile range; RRT, renal replacement therapy; SD, standard deviation.
| Sociodemographics                                | KT <1 year (n = 26) | KT >1 year (n = 64) | p-value |
|-------------------------------------------------|---------------------|---------------------|---------|
| Age (years, mean ± SD)                          | 56.5 ± 12.7         | 60.9 ± 12.3         | .132    |
| Sex (female, n [%])                             | 12 (46.2)           | 23 (35.9)           | .368    |
| Body mass index (kg/m², mean ± SD)              | 28.7 ± 7.45         | 27.3 ± 5.15         | .309    |
| Darbepoetin treatment, n (%)                    | 4 (15.4)            | 6 (9.4)             | .411    |
| Vitamin D supplementation, n (%)                | 4 (15.4)            | 14 (21.9)           | .485    |

| Blood tests                                      |                     |                     |         |
|-------------------------------------------------|---------------------|---------------------|---------|
| White blood cells, ×10³ U/µl (mean ± SD)         | 7.23 ± 2.33         | 8.60 ± 2.58         | .021    |
| T lymphocytes, ×10³ U/µl (mean ± SD)             | 1.95 ± 0.85         | 2.26 ± 1.12         | .202    |
| Creatinine, mg/dl (mean ± SD)                    | 1.75 ± 0.71         | 1.58 ± 0.76         | .338    |
| eGFR, ml/min per 1.73 m² (mean ± SD)             | 45.1 ± 19.5         | 51.9 ± 24.0         | .202    |
| C-reactive protein, mg/dl (mean ± SD)            | 0.72 ± 1.40         | 0.56 ± 0.88         | .524    |
| Albumin, g/dl (mean ± SD)                        | 4.22 ± 0.36         | 4.32 ± 0.55         | .374    |

| Comorbidities                                    |                     |                     |         |
|-------------------------------------------------|---------------------|---------------------|---------|
| Arterial hypertension, n (%)                    | 26 (100)            | 62 (96.9)           | .362    |
| Diabetes mellitus, n (%)                        | 10 (38.5)           | 27 (42.2)           | .745    |
| Cardiovascular disease, n (%)                   | 9 (34.6)            | 23 (35.9)           | .905    |
| Pulmonary disease, n (%)                        | 5 (19.2)            | 13 (20.3)           | .907    |
| Underlying diabetic kidney disease, n (%)       | 4 (15.4)            | 6 (9.4)             | .728    |

| Induction therapy                                |                     |                     |         |
|-------------------------------------------------|---------------------|---------------------|---------|
| No, n (%)                                        | 0 (0)               | 1 (1.6)             | .64     |
| Anti-IL2R, n (%)                                 | 23 (88.5)           | 52 (81.3)           |         |
| Antithymocyte globulin, n (%)                    | 3 (11.5)            | 11 (17.2)           |         |

| Maintenance immunosuppression                    |                     |                     |         |
|-------------------------------------------------|---------------------|---------------------|---------|
| Prednisone, n (%)                                | 26 (100)            | 56 (87.5)           | .059    |
| Mycophenolic acid derivatives, n (%)             | 14 (53.8)           | 35 (54.7)           | .942    |
| Dose, mg/kg/day (mean ± SD)                      | 9.07 ± 3.65         | 7.65 ± 2.49         | .122    |
| Tacrolimus, n (%)                                | 25 (96.2)           | 57 (89.1)           | .469    |
| Dose, mg/kg/day (mean ± SD)                      | 0.063 ± 0.041       | 0.041 ± 0.028       | .018    |
| Blood levels, ng/ml (mean ± SD)                  | 6.55 ± 2.58         | 5.93 ± 1.77         | .214    |
| Cyclosporin A, n (%)                             | 0 (0)               | 3 (4.7)             | –       |
| Dose, mg/kg/day (mean ± SD)                      | –                   | 1.19 ± 0.32         | –       |
| Blood levels, ng/ml (mean ± SD)                  | –                   | 217.3 ± 139.3       | –       |
| mTOR inhibitors (everolimus, n [%])              | 7 (36.9)            | 15 (23.4)           | .727    |
| Dose, mg/kg/day (mean ± SD)                      | 0.048 ± 0.020       | 0.03 ± 0.019        | .098    |
| Blood levels, ng/ml (mean ± SD)                  | 4.49 ± 1.35         | 4.30 ± 1.24         | .757    |

| Biopsy proven acute rejection*                   |                     |                     |         |
|-------------------------------------------------|---------------------|---------------------|---------|
| Cellular acute rejection, n (%)                 | 1 (3.8)             | –                   | –       |
| Treated with methylprednisolone bolus therapy 250 mg x 3 | – | – | – |

| SARS-CoV–2 immune response                      |                     |                     |         |
|-------------------------------------------------|---------------------|---------------------|---------|
| Seropositivity, n [%]                            | 13 (50)             | 44 (68.8)           | .094    |
| Antibody levels, AU/ml (median [IQR])            | 12.0 (1.85–30.2)    | 80.4 (5.09–316.8)   | .003    |
| T cell response, n [%]                           | 9 (36.0)            | 38 (61.3)           | .032    |

*Bold values indicate statistically significant p values (p < .05).  
Abbreviations: eGFR, estimated glomerular filtration rate; IQR, interquartile range; KT, kidney transplant; SD, standard deviation.  
*Twelve months before the vaccine.
Regarding the type of vaccine, individuals of the healthy control group immunized with Moderna elicited higher antibody levels than with Pfizer. Conversely, no significant differences were observed in HD controls (Table 5).

Antibody levels negatively correlated with increasing age in HD controls (Spearman $\rho = -0.28$ [95% confidence interval, CI $-0.504$ to $-0.021$], $p = .035$) and KT recipients $> 1$ year (Spearman $\rho = -0.404$ [-0.592 to $-0.174$], $p = .001$). Additionally, eGFR and time after KT positively correlated with the amount of antibodies (Spearman $\rho = 0.355$ [0.157–0.525], $p = .001$ and Spearman $\rho = 0.34$ [0.141–0.513], $p = .001$), while a higher dose of mycophenolate correlated with lower antibody response (Spearman $\rho = -0.295$ [-0.475 to $-0.091$], $p = .042$) (Figure 2).

### 3.3 Cellular response and concordance with humoral response

A ROC analysis was used to obtain cut-off values for IFN$\gamma$-response detection with IGRA. Data from the healthy control group were used, considering pre-vaccination results as negative and post-vaccination as positive. The resulting cut-off was 0.015 IU/ml for each antigen tube [area under the curve (AUC) 0.92 [95% CI 0.85–0.99], $p < .001$ and AUC 0.976 [95% CI 0.93–1.00], $p < .001$], with a sensitivity and specificity of 84.4% and 90.6% for antigen tube 1 and 96.9% and 90.6% for antigen tube 2, respectively (Figure 3).

Like seropositive rates, 96.9% of healthy controls showed a positive IGRA test. With this cut-off value, 89.3% PD and 77.6% HD controls generated reactive T cells 28 days after vaccination, respectively. Within the KT group, only 36% of KT $< 1$-year patients developed cellular responses and 61.3% of KT $> 1$ year did (Figure 4).

No significant differences in cellular response in dialysis and healthy controls were observed between vaccines; no comparison could be established in KT as they were all vaccinated with Moderna (Table 5). Factors associated with IGRA response are described in Table 6.

Roughly two thirds (65.9%) of IGRA(+) individuals were also positive for anti-S IgG, while only 11.2% were negative for assays. However, 47 patients (22.9%) had discordant results: 34 were IgG(+)/IGRA(–) and 13 IgG(–)/IGRA(+) All healthy controls and most dialysis controls (96.6% PD, 94.8% HD) developed any response (humoral and/or cellular) against SARS-CoV-2 after vaccination. This percentage was only 77.8% in KT patients.

Antibody levels of IGRA(+) individuals (n = 148) were significantly higher than IGRA(–) (n = 57) (451 [158–725] vs. 24 [1.8–180], $p < .001$). This tendency prevailed within the different groups of patients, especially in HD ($p = .001$) and KT ($p = .007$) (Figure 5).

### 3.4 Safety

COVID-19 mRNA vaccines were safe and well tolerated in renal patients, showing mild AE without serious reactions (Figure 6). Pain (76.6%) and swelling (8.1%) were the most prevalent local AE after the first dose, and fatigue (23%) and headache (8.8%) were the most frequent systemic reactions.

No cases of COVID-19 infection, acute rejection, Guillain-Barré syndrome, anaphylactic reactions, or enhanced respiratory disease were observed. No participant had any serious AE requiring emergency hospitalization.

A similar pattern was observed after the second dose, with pain (67.8%) and swelling (16.8%) being the main local solicited AE and fatigue (29.3%) and headache (15.9%) the systemic reactions. The second dose was significantly worse tolerated in terms of swelling ($p = .021$), fever ($p = .002$), headache ($p = .007$), and myalgia ($p = .024$), whereas the incidence of pain was lower ($p = .006$). Again, no serious AE was detected.

Compared to Pfizer, those that received Moderna vaccine presented more pain after both doses (first: 84.6% vs. 56.6%, $p < .001$; second: 74.7% vs. 53.3%, $p = .012$) and arthralgia (first: 6.7% vs. 1.7%, $p = .036$; second: 11.7% vs. 0%, $p = .022$), whereas swelling (11.4% vs 0%, $p = .024$), fatigue (10.7% vs 3.3%, $p = .035$) and myalgia (6.7% vs. 1.7%, $p = .036$) were more prevalent only after the first dose.
We performed subgroup analyses comparing patients and controls. Data are shown in Figure 6.

4 | DISCUSSION

Clinical trials of both mRNA vaccines disregarded the immune response that CKD or immunosuppressed patients could generate. Therefore we attempted to shed light in this topic. To the best of our knowledge, this is one of the first studies that evaluates cellular immunogenicity of mRNA COVID-19 vaccines with an IGRA in a KT cohort. Additionally, we also provided data on humoral response and safety in KT and compared them with healthy controls and dialysis controls. Our analysis evidences a robust and timely humoral and cellular response to mRNA COVID-19 vaccines in healthy controls and CKD patients on HD or PD 28 days after full vaccination. Contrarily, the response of KT

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### TABLE 3 Factors associated with a negative antibody response after vaccination in KT recipients

| Univariate                          | Multivariate                      |
|------------------------------------|-----------------------------------|
|                                    | OR      | 95% CI    | p-value | OR      | 95% CI    | p-value |
| Sociodemographics                  |         |           |         |         |           |         |
| Age (years)                        | 1.035   | 0.99–1.07 | .06     | 1.03    | 0.98–1.074 | .16     |
| Sex (ref: female)                  | 0.53    | 0.22–1.27 | .15     |         |           |         |
| Body mass index (kg/m²)            | 1.034   | 0.96–1.11 | .36     |         |           |         |
| Seasonal vaccine (ref: no)         | 0.85    | 0.33–2.22 | .75     |         |           |         |
| Darbepoetin treatment (ref: no)    | 8.80    | 1.74–44.46 | .009   | 6.02    | 0.89–34.35 | .17     |
| Vitamin D supplementation (ref: no)| 1.50   | 0.52–4.92 | .44     |         |           |         |
| Comorbidities                      |         |           |         |         |           |         |
| Hypertension²                      | —       | —         | —       |         |           |         |
| Diabetes mellitus                  | 1.08    | 0.45–2.59 | .84     |         |           |         |
| Cardiovascular disease             | 1.05    | 0.43–2.58 | .90     |         |           |         |
| Pulmonary disease                  | 1.50    | 0.52–4.29 | .44     |         |           |         |
| Underlying diabetic nephropathy    | 2.53    | 0.50–12.70 | .25    |         |           |         |
| Blood tests                        |         |           |         |         |           |         |
| White blood cells (x10³ U/µl)      | 0.83    | 0.69–1.013 | .12    |         |           |         |
| T lymphocytes (x10³ U/µl)          | 0.68    | 0.42–1.10 | .11     |         |           |         |
| C-reactive protein (mg/dl)         | 1.19    | 0.77–1.82 | .41     |         |           |         |
| Albumin (g/dl)                     | 0.77    | 0.30–2.00 | .60     |         |           |         |
| Transplantation characteristics    |         |           |         |         |           |         |
| Time after transplantation (months)| 0.99    | 0.98–1.01 | .10     |         |           |         |
| Transplantation >1 year            | 0.45    | 0.17–1.15 | .09     | 0.42    | 0.14–1.12 | .11     |
| Transplantation >6 months          | 0.37    | 0.12–1.12 | .07     | 0.29    | 0.08–1.01 | .05     |
| Serum creatinine (mg/dl)b          | 2.17    | 1.12–4.22 | .02     | 1.60    | 0.75–3.40 | .22     |
| eGFR (ml/min per 1.73 m²)b         | 0.97    | 0.95–0.99 | .02     | 0.98    | 0.96–1.01 | .30     |
| Immunosuppression treatment        |         |           |         |         |           |         |
| Prednisone²                        | —       | —         | —       |         |           |         |
| Mycophenolic acid                  | 1.48    | 0.62–3.54 | .37     |         |           |         |
| Tacrolimus or cyclosporin A        | 2.56    | 0.27–23.94 | .41    |         |           |         |
| Tacrolimus dose (mg/kg/day)        | 0.013   | 0.01–22.28 | .38    |         |           |         |
| Tacrolimus blood levels (ng/ml)    | 1.97    | 0.92–1.03 | .45     |         |           |         |
| Everolimus                         | 1.98    | 0.36–2.66 | .97     |         |           |         |
| Everolimus dose (mg/kg/day)        | 0.11    | 0.01–3.99 | .45     |         |           |         |
| Everolimus blood levels (ng/ml)    | 1.65    | 0.74–3.66 | .21     |         |           |         |

Bold values indicate statistically significant p values (p < .05).
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; KT, kidney transplant; OD, odds ratio.
²Impossible calculation, as patients without prednisone and a negative response were = 0.
²Different models, using either serum creatinine or eGFR.
TABLE 4 Factors associated with insufficient humoral response to vaccine in KT recipients, defined as not reaching the 25th percentile of antibody levels

| Factors                                      | Univariate     | Multivariate   |
|----------------------------------------------|----------------|----------------|
|                                              | OR  | 95% CI  | p-value | OR  | 95% CI  | p-value |
| Sociodemographics                            |     |         |         |     |         |         |
| Age (years)                                  | 1.030 | 0.99–1.06 | .08    | 1.01 | 0.97–1.05 | .38 |
| Sex (ref: female)                            | 0.49  | 0.20–1.17 | .10    |      |         |         |
| Body mass index (kg/m²)                      | 1.078 | 1.00–1.16 | .05    | 1.06 | 0.97–1.16 | .15 |
| Seasonal vaccine (ref: no)                   | 0.63  | 0.25–1.56 | .32    |      |         |         |
| Darbepoetin treatment (ref: no)              | 9.94  | 1.20–82.21 | .03    | 5.96 | 0.59–54.41 | .13 |
| Vitamin D supplementation (ref: no)          | 2.90  | 0.93–8.99 | .07    | 2.90 | 0.81–10.43 | .10 |
| Comorbidities                                |     |         |         |     |         |         |
| Hypertension                                 | 1.09  | 0.06–18.06 | .94    |      |         |         |
| Diabetes mellitus                            | 1.13  | 0.48–2.62 | .77    |      |         |         |
| Cardiovascular disease                       | 1.87  | 0.36–2.06 | .75    |      |         |         |
| Pulmonary disease                            | 1.57  | 0.57–4.51 | .40    |      |         |         |
| Underlying diabetic nephropathy              | 1.57  | 0.15–2.18 | .41    |      |         |         |
| Blood tests                                  |     |         |         |     |         |         |
| White blood cells (x10³ U/µl)                | 0.87  | 0.73–1.034 | .11    |      |         |         |
| T lymphocytes (x10³ U/µl)                    | 0.74  | 0.48–1.12 | .16    |      |         |         |
| C-reactive protein (mg/dl)                   | 1.012 | 0.66–1.54 | .95    |      |         |         |
| Albumin (g/dl)                               | 0.75  | 0.31–1.81 | .53    |      |         |         |
| Transplantation characteristics              |     |         |         |     |         |         |
| Time after transplantation (months)          | 0.99  | 0.983–0.998 | .009   | 0.99 | 0.98–0.99 | .012 |
| Transplantation > 1 year                     | 0.21  | 0.07–0.61 | .004   | 0.16 | 0.50–0.57 | .004 |
| Transplantation > 6 months                   | 0.11  | 0.24–0.54 | .006   | 0.60 | 0.01–0.33 | .001 |
| Serum creatinine (mg/dl)                     | 1.94  | 0.98–3.85 | .05    | 1.45 | 0.64–3.28 | .37 |
| eGFR (ml/min per 1.73 m²)                    | 0.97  | 0.95–0.99 | .01    | 0.98 | 0.95–1.005 | .12 |
| Immunosuppression treatment                  |     |         |         |     |         |         |
| Prednisone                                   | —    | —        | —      |      |         |         |
| Mycophenolic acid                            | 1.07  | 0.46–2.47 | .86    |      |         |         |
| Tacrolimus or cyclosporin A                  | 5.11  | 0.54–47.73 | .15    |      |         |         |
| Tacrolimus dose (mg/kg/day)                  | 0.037 | 0.001–8.35 | .24    |      |         |         |
| Tacrolimus blood levels (ng/ml)              | 1.96  | 0.93–1.02 | .32    |      |         |         |
| Everolimus                                    | 1.13  | 0.43–2.96 | .80    |      |         |         |
| Everolimus dose (mg/kg/day)                  | 0.47  | 0.01–3.32 | .97    |      |         |         |
| Everolimus blood levels (ng/ml)              | 1.44  | 0.68–3.04 | .33    |      |         |         |

Bold values indicate statistically significant p values (p < .05).

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; KT, kidney transplant; OR, odds ratio.

*aDifferent multivariate models maintain the three different variables within the model, all significant: months after transplant (continuous variable), KT of more than a year or KT of more than 6 months.
*bNot significant either including serum creatinine or eGFR.

cImpossible to calculate, as patients negative without prednisone were = 0.

recipients is less frequent and significantly less intense, especially in those transplanted within the previous year.

Almost all HD and PD controls generated antibodies against SARS-CoV-2 S protein, but antibody levels were significantly lower than in our healthy controls. Seroconversion rates in this study resemble those described in other ones.31–34

KT recipients had discouraging antibody levels after vaccination, indicating a poor response to mRNA vaccines. They are in a more
TABLE 5 Humoral and cellular responses between Moderna and Pfizer vaccines

| Humoral response | Antibody levels (median [IQR]) | Seropositivity n (%) | n | Positive IGRA | p-value |
|------------------|--------------------------------|----------------------|---|---------------|---------|
|                  | N(N Pfizer) | Moderna | Pfizer |  | | |
| Group            |           |        |        | All | | |
| All              | 205 (60)  | 148 (72.2) | 47 (54.0) | — | — | — |
| KT <1 year       | 26        | 139 (63.4–440) | 25.7 (23–167) | — | — | — |
| Healthy controls | 64        | 221 (166–494) | — | — | — | — |
| Dialysis controls | 32 (12.1) | 774 (63-1349) | 1570 (793–1742) | — | — | — |
| HD controls      | 44 (6.8)  | 387 (189–664) | 470 (218–744) | — | — | — |
| PD controls      | 28 (6.6)  | 55 (9.8) | 559 (216–908) | — | — | — |

Note: Median antibody levels in AU/mL of responders in each group with two different vaccines. Differences between HD and PD were significant. Differences between HD and KT were significant when considering only individuals vaccinated with Moderna. Differences were similar when considering only individuals vaccinated with Pfizer. Bold values indicate statistically significant differences (p < 0.05 in each case). Differences between KT <1 year and KT >1 year were also significant (p = 0.017). Differences were significant (p < 0.05) in each group.

Abbreviations: HD, hemodialysis; IGRA, interferon gamma release assay; IQR, interquartile range; KT, kidney transplant; PD, peritoneal dialysis.

Concerning situation as their antibody levels slightly exceeded the cut-off to be considered positive. Two different studies reported seropositive rates of 22% and 37.5% after BNT162b2 vaccination, lower than in the present study using kits from the same manufacturer (DiaSorin) with similar cut-off values. However, their post-vaccination analysis was conducted earlier, 10–14 days after the second dose, so there may not have been enough time to develop a detectable response in some patients. At 28 days after booster dose, Benotmane et al. observed with an Abbott kit that 46% of 205 KT recipients vaccinated with mRNA-1273 elicited antibody levels >50 AU/ml. Surprisingly, the Berlin group detected lower anti-BNT162b2 responses in naive dialysis and KT recipients (70.5% and 0%) 3 to 4 weeks after vaccination with ELISA and cut-offs based on optical density ratios. Technical design, sensitivity and established cut-off values of the different kits may explain the disparity of seropositive rates seen in KT recipients. However, studies involving patients on dialysis report similar rates even when using different kits.

KT with worse kidney graft function were less likely to seroconvert in univariate analysis, as reported previously. However, multivariate analyses showed that the association was not significant. Older age has been associated with lower antibody levels in dialysis patients and this correlation was seen in our HD and KT patients, but again the multivariate adjustment diluted the effect. A short time since transplantation became the only detectable risk factor for a negative response to vaccination, and a lower production of antibodies, as seen in transplant recipients. This finding suggests that the capacity to produce antibodies is impaired early after KT, probably related to the amount of immunosuppression administered, independently of recipient age. It is worth noting, however, that immunosuppressive drug class, dose and levels were not associated to a negative response.

T cell responses showed trends like humoral responses across all groups. Lower T cell responses were observed in the KT patients than in healthy and dialysis controls, especially in those who had received the kidney graft <1 year before vaccination. A previous smaller study reported that 57.8% of KT recipients elicited SARS-CoV-2 cell-mediated immunity in contrast to all their HD patients using an ELISPOT assay. We employed a new and simple kit that assesses T cell immunity through IGRA, looking for a simpler tool for monitoring. Using this assay, Stumpf et al. described similar positive rates in their KT and dialysis patients (30% and 78%). In contrast to ELISPOT or intracellular cytokine staining, QuantiFERON®-TB has proved to increase sensitivity even in immunocompromised patients. This format has been used in tuberculosis detection for over a decade. Several societies recommend their use, and the latest generation of QuantiFERON®-TB has proved to increase sensitivity even in immunocompromised patients. In addition, tuberculosis and cytomegalovirus QuantiFERON® assays have shown a good correlation with ELISPOT in renal patients. Interestingly, the most relevant factor associated with a good IGRA response was...
**FIGURE 2** Correlations of serum antibody levels and several variables: (A) age in HD patients (Spearman $\rho = -0.28$ [95% CI $-0.504$ to $-0.021$], $p = .035$), (B) time after KT in KT recipients (Spearman $\rho = 0.34$ [95% CI $0.141$ to $0.513$], $p = .001$), (C) eGFR in KT recipients (Spearman $\rho = 0.355$ [95% CI $0.157$ to $0.525$], $p = .001$), (D) mycophenolate dose in KT recipients (Spearman $\rho = -0.295$ [95% CI $-0.475$ to $-0.091$], $p = .042$), and (E) age in KT recipients with more than 1 year of a functioning graft (Spearman $\rho = -0.404$ [95% CI $-0.592$ to $-0.174$], $p = .001$). CI, confidence interval; HD, hemodialysis; KT, kidney transplant.

**FIGURE 3** ROC analysis to identify the cut-off for positive IGRA using results of healthy controls before (considered negative) and after vaccination (considered positive). IGRA, interferon gamma release assay; ROC, receiver operating characteristic.
the number of peripheral blood T lymphocytes. Cut-off values for IFNγ detection with this ELISA kit have not yet been established, however we obtained one through ROC analysis similarly to other studies involving COVID-19 convalescent patients.40,46 Once standardization is achieved, QuantiFERON® SARS-CoV-2 IGRA will serve as a simple but effective tool for cell-mediated immunity evaluation after COVID-19 vaccination, as reflected by recent studies that only incorporate this assay in their cellular analysis.47,48

Regarding safety, most of the observed AE were like those reported in randomized trials and observational studies conducted in KT recipients.26,27,30,49 mRNA vaccines were well tolerated without significant safety issues in renal patients. As expected, the second dose was worse tolerated than the first one,27,28 and some AE were more frequent with the mRNA-1273 vaccine.

Strengths in our study were the inclusion of a direct comparison of a KT cohort with healthy controls and control patients with advanced CKD on PD or HD programs, who underwent simple and reliable monitoring of humoral and cellular response to mRNA vaccines. The main limitation is the reduced number of KT recipients during their first year of postransplantation follow-up, which precludes detailed analyses of some factors potentially associated with lack of response. As technical limitations, we recognize the lack of results regarding neutralizing activity and durability of immune responses. However, the kit used to quantify anti-S IgG has a good correlation with a microneutralization test,50 therefore data on antibody levels presented in this study could highly relate with serum neutralizing capacity. As opposed to other studies that used the same kit,35,39 we diluted samples that exceeded assay measuring range to obtain a more accurate value of antibody

**FIGURE 4** Percentages of T cell responses after vaccination in the different groups of patients and controls

**FIGURE 5** Median antibody levels in positive and negative individuals for T cell responses in each group of PD controls, HD controls, and KT recipients (*p < .001, **p < .01). HD, hemodialysis; KT, kidney transplant; PD, peritoneal dialysis
levels. Concerning durability, this project will keep ongoing and evaluate cellular and humoral immunity at 6 and 12 months. However, Boyarsky et al. have demonstrated that antibody levels increase or remain stable between months 1 and 3 post-vaccination in 64% of solid organ transplant recipients. The incorporation of IGRA, as an easier way to assess cellular immunity, may be key for the complete follow-up of many patients at risk of COVID-19.

Vaccination is the best way to prevent SARS-CoV-2 infection. Nevertheless, KT patients develop weaker responses than healthy individuals and dialysis patients, probably related to the immunosuppression associated with anti-rejection treatment. Precautions still need to be taken in order to protect this vulnerable population, as COVID-19 cases in vaccinated KT recipients have already been described. Authorities have approved the administration of a third mRNA vaccine dose in immunocompromised individuals, which includes transplant recipients and patients on dialysis. Following this recommendation, a study with 396 solid organ transplant recipients observed an increase of the seropositive rate from 41.4% to 67.9% 4 weeks after receiving a third BNT162b2 dose. Another alternative, known as the cocoon strategy, would be prioritizing vaccination of patients’ relatives to create a safe environment with a lower risk of SARS-CoV-2 infection. This is of particular interest in recent transplant recipients, who infrequently develop immune responses after vaccination. In this regard, it is of utmost importance to find out if the response to the vaccine obtained on the waiting list persists despite the intense initial immunosuppression at transplantation.

In summary, a small percentage of KT recipients developed humoral responses 28 days after vaccination with mRNA vaccines,
and the median antibody level was considerably low in responders, with a shorter time since transplantation associated to impaired response. Regarding cell-mediated immunity, a similar trend was observed, in which patients with higher antibody levels were more likely to mount T cell responses. KT patients, especially within the first year after transplantation, must be followed to prevent possible infections as we cannot ensure that they are fully protected against SARS-CoV-2. In addition, the immunological memory endurance in renal patients must be evaluated so that other approaches can be carried out if the vaccine effects wane.

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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