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Predictors of Nonseroconversion to SARS-CoV-2 Vaccination in Kidney Transplant Recipients

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Background. Kidney transplant recipients (KTRs) are still at risk of severe COVID-19 disease after SARS-CoV-2 vaccination, especially when they have limited antibody formation. Our aim was to understand the factors that may limit their humoral response. **Methods.** Our data are derived from KTRs who were enrolled in the Dutch Renal Patients COVID-19 Vaccination consortium, using a discovery cohort and 2 external validation cohorts. Included in the discovery (N = 1804) and first validation (N = 288) cohorts were participants who received 2 doses of the mRNA-1273 vaccine. The second validation cohort consisted of KTRs who subsequently received a third dose of any SARS-CoV-2 vaccine (N = 1401). All participants had no history of SARS-CoV-2 infection. A multivariable logistic prediction model was built using stepwise backward regression analysis with nonseroconversion as the outcome. **Results.** The discovery cohort comprised 836 (46.3%) KTRs, the first validation cohort 124 (43.1%) KTRs, and the second validation cohort 358 (25.6%) KTRs who did not seroconvert. In the final multivariable model, 12 factors remained predictive for nonseroconversion: use of mycophenolate mofetil/mycophenolic acid (MMF/MPA); chronic lung disease, heart failure, and diabetes; increased age; shorter time after transplantation; lower body mass index; lower kidney function; no alcohol consumption; ≥2 transplantations; and no use of mammalian target of rapamycin inhibitors or calcineurin inhibitors. The area under the curve was 0.77 (95% confidence interval [CI], 0.74-0.79) in the discovery cohort after adjustment for optimism, 0.81 (95% CI, 0.76-0.86) in the first validation cohort, and 0.67 (95% CI, 0.64-0.71) in the second validation cohort. The strongest predictor was the use of MMF/MPA, with a dose-dependent unfavorable effect, which remained after 3 vaccinations. **Conclusions.** In a large sample of KTRs, we identify a selection of KTRs at high risk of nonseroconversion after SARS-CoV-2 vaccination. Modulation of MMF/MPA treatment before vaccination may help to optimize vaccine response in these KTRs. This model contributes to future considerations on alternative vaccination strategies.

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INTRODUCTION

In the general population, seroconversion was observed in practically all participants of clinical severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) mRNA vaccination

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**The RECOVAC consortium and collaborators were involved in collection of the data. P.B., A.L.M., and M.H.H. were mostly involved in collection of the LESS-CoV-2 study data, as S.C.F., A.L.M., R.T.G., L.B.H., M.E.J.R., J.-S.F.S., and F.J.B. were mostly involved in collection of the IR study data. S.C.F., HPS, P.B., F.J.B., and S.E.G. were involved in the design of this study. S.C.F. did the statistical analysis together with H.P.-S. and drafted the article, whereas all authors took part in its revision. S.C.F. had final responsibility for the decision to submit for publication and is the guarantor for the study.*

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trials.[1,2] Higher anti-S1 IgG antibody concentrations, and especially higher concentrations of virus neutralizing antibodies, are associated with a lower risk of infection and disease.[3-7] However, kidney transplant recipients (KTRs) show a decreased seroconversion rate after 2 doses of mRNA vaccination ranging from 30% to 57%.[8-14] Although this rate increases after 3 vaccine doses, a significant number of KTRs did not seroconvert and are still at risk of severe coronavirus disease 2019 (COVID-19) after vaccination.[5,15-20]

Antibody measurement can identify these patients, but not all countries advise the implementation of antibody assessment into clinical practice. We developed and validated a set of clinical predictors of nonseroconversion after basic immunization with 2 SARS-CoV-2 mRNA vaccine doses in KTRs to analyze the factors that may disrupt the primary humoral response. We subsequently validated the model in a cohort after 3 vaccine doses to make a selection of KTRs who remain at high risk of nonseroconversion. Our aim was to develop a model that can assist individualized patient counseling and guide immunosuppressive drug treatment strategy to optimize vaccine response in KTRs.

MATERIALS AND METHODS

Study Population

Our data are derived from KTRs who were enrolled in the Dutch Renal Patients COVID-19 Vaccination (RECOVAC) consortium. The discovery cohort is derived from the RECOVAC Long-term Efficacy and Safety of SARS-CoV-2 Vaccination (LESS CoV-2) study arm, of which the design has previously been published in detail elsewhere.[21] In this study, antibodies were measured in high-risk kidney patients (patients with chronic kidney disease [CKD] stages G4 to G5, dialysis patients, and KTRs) in a large nationwide prospective cohort. From April to June 2021, blood samples were obtained through self-obtained sample collection by use of a home-based finger prick set. Participants were included when the antibody measurement was performed ≥2 wk to ≤8 wk after the second vaccination. A separate cohort was used as the first external validation cohort, derived from the RECOVAC Immune Response (IR) study arm. The design of this study has been published previously in detail.[22] The study was performed between February 1 and May 31, 2021, at the outpatient clinics of 4 university medical centers in the Netherlands. This study included healthy controls, patients with CKD stages G4 to G5, dialysis patients, and KTRs. Antibody measurement was performed at 28 ± 3 d after the second vaccination. Measurement of vital signs and additional laboratory values were included. The second external validation cohort was derived from the RECOVAC LESS CoV-2 follow-up study arm. Blood samples were obtained from November 2021 to January 2022 through self-obtained sample collection. Antibody measurement was performed ≥2 and ≤8 wk after the third vaccination.

All participants included in the prediction model were aged 18 y or older and were at least 6 wk after transplantation. All participants received 2 doses of the mRNA-1273 SARS-CoV-2 vaccine (Moderna), and participants of the second validation cohort subsequently received a third dose of any SARS-CoV-2 vaccine. Subjects with a history of SARS-CoV-2 infection were excluded. Ethical approval was obtained for both of the nationwide RECOVAC IR and RECOVAC LESS CoV-2 studies, and informed consent has been given by all participants; therefore, this study was exempt from ethical approval from our institutional review board.

Antibody Measurement

Insufficient response to vaccination (nonseroconversion) was determined as anti-spike IgG in serum <50 binding antibody units (BAU)/mL when using the Sanquin anti-SARS-CoV-2 RBD IgG ELISA assay in the LESS CoV-2 study or <10 BAU/mL when using a validated fluorescent bead-based multiplex immunoassay (RIVM) in the IR study.[21,22] Cutoff points of both assays have been validated and published before. Antibodies were measured on average 30.8 d (SD 5.0) post second vaccination in the discovery cohort, 28.5 d (SD 1.3) post second vaccination in the first validation cohort, and 42.2 d (SD 7.3) post third vaccination in the second validation cohort. Antibody measurement included both the spike (S1) antigen and the nucleocapsid (N) antigen in both cohorts.[23] Combining these antibody measurements allows us to distinguish the response to a natural infection from an antibody response after S1-based vaccination for the exclusion of participants with previous COVID-19, together with the self-reported survey information collected.

Statistical Analysis

Variables are presented as mean ± SD if normally distributed or as median (interquartile range) in case of nonnormal distribution. *P* values were calculated using independent sample *t* test for normally distributed continuous variables, the Mann-Whitney U test in case of nonnormally distributed continuous variables, and the chi-square test in case of categorical variables.

In the discovery set, missing values were imputed by Multivariate Imputation by Chained Equations algorithm with a predictive mean matching modeling type.[24] We created 10 imputed datasets with 50 iterations each and randomly chose 1 imputed dataset for further analysis. A complete case analysis was performed as sensitivity analyses. There was negligible missing information in both external validation cohorts (see **Table S1, SDC**, http://links.lww.com/TXD/A464). All available variables and their 2-way interactions were assessed in a multivariable logistic backward-selection regression with the Akaike information criterion as a stopping rule to determine the independent factors associated with nonseroconversion. To assess the linearity of continuous predictor variables, we used 3-knot restricted cubic spline analysis and evaluated the nonlinear terms with Wald tests univariately. All predictors met the assumption of linearity, and no significant interactions were determined between predictors. The selected predictors from the discovery set were subjected to internal validation using a bootstrap method (N = 500) with resampling. The performance of the optimism-corrected model was assessed by discrimination using area under the ROC curve (AUC) and predictive accuracy by calibration plot. These statistics were also reported for the 2 external validation sets. Separate multivariable analysis of the final model was performed in the second external validation cohort to define the importance of these predictors after 3 vaccinations. Laboratory variables that were only available in the first validation set were univariately added to the final prediction score to evaluate if these were of added discriminative value. Additional sensitivity analyses were performed: (1) 2 machine learning algorithms (glmnet and gradient boosting machines) were deployed to investigate increase in performance compared to logistic regression and (2) validation analysis in a subpopulation of the discovery cohort including patients with antibody measurements at 28 ± 3 d after the second vaccination

(N = 989) to compare the model performance with the ≥2 wk to ≤8 wk antibody measurement inclusion cohort.

To investigate the impact of immunosuppressive treatment on nonseroconversion in more detail, explorative analyses were performed of the most commonly used immunosuppressive drug regimens in the Netherlands combining the data of discovery and first validation cohort. Also, available data of the first validation cohort on the doses of immunosuppressive agents were analyzed. Of these 288 patients, 191 used mycophenolate mofetil/mycophenolic acid (MMF/MPA), of which 6% was MPA. In the analysis, MPA dose was converted to MMF dose. Statistical analysis was performed using RStudio, version 4.0.3. A 2-sided *P* value of <0.05 was considered as statistically significant, except when stated otherwise. All results are presented according to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis Or Diagnosis guidelines.[25]

RESULTS

In total, 1804, 288, and 1401 eligible KTRs were designated to the discovery, first external validation and second external validation, cohort, respectively (Figure 1, see **Table S2, SDC**, http://links.lww.com/TXD/A464, for characteristics of the exclusion cohort). Table 1 shows demographic, physiological, and laboratory characteristics for the 3 cohorts. The median age and gender distribution were comparable. After the second mRNA-1273 vaccination, 836 (46.3%) KTRs in the discovery cohort and 124 (43.1%) KTRs in the first validation cohort did not seroconvert. In the second validation cohort, the nonseroconversion rate was 25.6% after the third vaccination, using mRNA-1273 (N = 96), BNT162b2 (N = 1262), ChAdOx-nCov19 (N = 4), Ad26.CoV2.S (N = 1), or undefined (N = 38).

In the discovery set, a total of 12 independent variables were found to be important to separate seroconversion (N = 968) from nonseroconversion (N = 836) after stepwise regression with backward elimination. The selected predictors are MMF/MPA use, chronic lung disease, heart failure, diabetes, age, time after transplantation, body mass index (BMI), estimated glomerular filtration rate (eGFR), alcohol consumption, number of transplantations, and the use of mammalian target of rapamycin (mTOR) inhibitors or calcineurin inhibitors. Table 2 shows the final multivariable model of the discovery cohort (see **Table S3, SDC**, http://links.lww.com/TXD/A464, for unadjusted estimates). The association with the outcome of every single predictor is depicted in **Figures S1A-D and S2, SDC**, http://links.lww.com/TXD/A464. The AUC was 0.77 (95% confidence interval (CI), 0.74-0.79) in internal validation after adjustment for optimism and 0.81 (95% CI, 0.76-0.86) in the first validation cohort. In the second validation cohort, the AUC was 0.67 (95% CI, 0.64-0.71). The calibration accuracy of the discovery cohort and validation cohorts is shown in Figure 2. Calibration was optimal in the discovery and first validation cohorts, whereas predictions were slightly overestimated in the higher range in the second validation cohort. A complete case analysis (N = 1362) showed comparable results to the imputed data analyses (**Figure S3, SDC**, http://links.lww.com/TXD/A464).

In previous nonseroconverted KTR after 2 vaccinations, we found an additional seroconversion rate of 44% (N = 244) after 3 vaccinations. A subsequent 56% (N = 316) remained without seroconversion. To define which factors remained

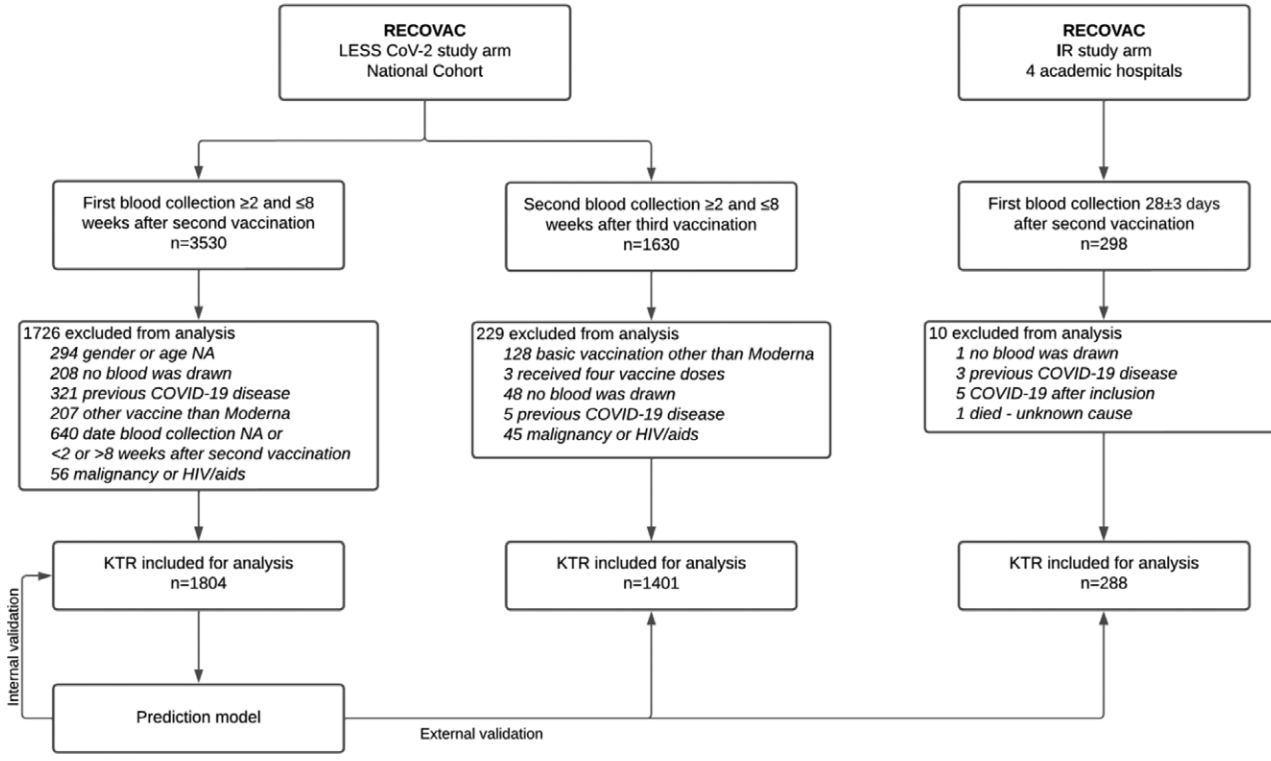

FIGURE 1. A conceptual framework of the study design and on the internal and external validation of the prediction model. Internal validation is the process of determining internal validity; we used the bootstrap method (N = 500). The external validation is the process of determining generalizability to the KTR in another cohort. The design of the LESS CoV-2 and RECOVAC IR studies has been published previously in detail.[21,22] COVID-19, coronavirus disease 2019; IR, Immune Response; KTR, kidney transplant recipients; LESS-CoV-2, Long-term Efficacy and Safety of SARSCoV-2 vaccination; NA, not available; RECOVAC, REnal patients COvid-19 VACcination.

TABLE 1.

Descriptive statistics of discovery and 2 external validation cohorts

	Discovery cohort, total (N = 1804)	First validation cohort, total (N = 288)	Second validation cohort, total (N = 1401)
Male, n (%)	1061 (58.8)	160 (55.6)	788 (56.2)
Caucasian, n (%)	1641 (92.9)	263 (91.6)	1286 (93.5)
Age, y	57.2 (11.7)	56.1 (14.0)	57.8 (11.6)
BMI, kg/m^2	26.0 (4.5)	26.9 (4.6)	25.8 (4.2)
Current smoking, n (%)	99 (5.5)	29 (10.1)	80 (5.7)
Current alcohol consumption, n (%)	809 (45.0)	117 (40.9)	622 (44.5)
SBP, mm Hg	NA	146.6 (21.1)	NA
DBP, mm Hg	NA	84.7 (10.9)	NA
Heart rate, bpm	NA	74.2 (12.9)	NA
Body temperature, °C	NA	36.7 (0.5)	NA
Primary renal diagnosis, n (%)			
Congenital/familial/hereditary renal disease	44 (3.6)	76 (29.3)	39 (4.2)
Diabetic kidney disease	88 (7.2)	10 (3.9)	68 (7.4)
Glomerulonephritis	309 (25.5)	57 (22.0)	220 (23.9)
Vascular disease	111 (9.1)	29 (11.2)	81 (8.8)
Interstitial nephritis/pyelonephritis/drug-induced nefropathy/urolithiasis	108 (8.9)	14 (5.4)	78 (8.5)
Secondary glomerular/other multisystemic disease	74 (6.1)	14 (5.4)	61 (6.6)
Other	391 (32.2)	41 (15.8)	309 (33.6)
Unknown	89 (7.3)	18 (6.9)	63 (6.9)
Comorbidities, n (%)			
Cardiovascular disease	204 (11.3)	NA	153 (10.9)
Peripheral vascular disease	59 (3.3)	NA	44 (3.1)
Heart failure	104 (5.8)	13 (4.5)	72 (5.1)
Diabetes	369 (20.5)	61 (21.2)	276 (19.7)
Hypertension	1531 (84.9)	233 (80.9)	1185 (84.6)
Past malignancy	NA	44 (15.3)	NA
Stroke	87 (4.8)	NA	70 (5.0)
Dementia	0 (0)	NA	0 (0)
Chronic lung disease	118 (6.5)	15 (5.2)	90 (6.4)
Liver cirrhosis	17 (0.9)	NA	13 (0.9)
Coronary artery disease	NA	38 (13.2)	NA
Autoimmune disease	NA	15 (5.2)	NA
eGFR, mL/min/1.73m^2	51.5 (18.8)	49.5 (18.6)	51.0 (18.9)
Transplant characteristics			
First kidney transplant, n (%)	1226 (85.8)	227 (78.8)	941 (85.5)
Time after transplantation, y	7.6 [4.0, 13.6]	6.9 [2.6, 13.3]	8.2 [4.3, 13.7]
Last transplant			
Living, n (%)	936 (65.5)	200 (69.4)	695 (63.2)
Preemptive, n (%)	NA	107 (37.2)	NA
Graft failure, n (%)	127 (8.9)	NA	103 (9.4)
Cause of graft failure, n (%)			
Patient died with functioning transplant	1 (0.8)	NA	0 (0.0)
Recurrent primary renal disease	2 (1.6)	NA	2 (1.9)
Rejection while taking immunosuppressive drugs (acute/chronic)	10 (7.8)	NA	9 (8.7)
Technical problems	1 (0.8)	NA	0 (0.0)
Thrombosis/infarction	1 (0.8)	NA	1 (1.0)
Unknown	113 (88.3)	NA	90 (87.4)
Other	0 (0.0)	NA	1 (1.0)
Laboratory values			
Hb, mmol/L	NA	7.8 (1.1)	NA
Platelet count, 10^9/L	NA	242.1 (66.8)	NA
Lymphocytes, 10^9/L	NA	1.5 (1.3)	NA
Total leukocyte count, 10^9/L	NA	8.2 (2.5)	NA
Neutrophils, 10^9/L	NA	6.0 (2.3)	NA
Glucose, mmol/L	NA	6.7 (1.9)	NA
Urea, mmol/L	NA	11.3 (6.6)	NA

Continued next page

TABLE 1. (Continued)

Descriptive statistics of discovery and 2 external validation cohorts

	Discovery cohort, total (N = 1804)	First validation cohort, total (N = 288)	Second validation cohort, total (N = 1401)
Creatinine, µmol/L	136.7 (69.4)	140.2 (56.0)	137.7 (74.4)
ALAT (U/L)	NA	21.8 (11.1)	NA
Potassium, mmol/L	NA	4.3 (0.5)	NA
Albumin, g/L	NA	41.1 (4.3)	NA
CRP, mg/L	NA	3.8 (6.5)	NA
Immunosuppressive treatment, n (%)			
Steroids	1074 (75.9)	219 (76.0)	841 (77.4)
Azathioprine	147 (10.4)	34 (11.8)	102 (9.4)
MMF/MPA	923 (65.2)	197 (68.4)	700 (64.5)
Calcineurin inhibitor	1166 (82.4)	236 (81.9)	899 (82.8)
mTOR inhibitor	104 (7.3)	17 (5.9)	96 (8.8)
Thymoglobulin	NA	0.0 (0.0)	NA
Alemtuzumab	NA	0.0 (0.0)	NA
Cyclophosphamide	NA	0.0 (0.0)	NA
Other biologicals	NA	0.0 (0.1)	NA
Other chemotherapy	NA	0.0 (0.0)	NA
Other	29 (2.0)	NA	19 (1.7)
Vaccine type, n (%)			
mRNA-1273	1804 (100)	288 (100)	96 (6.9)
BNT162b2	0 (0.0)	0 (0.0)	1262 (90.1)
ChAdOx-nCov19	0 (0.0)	0 (0.0)	4 (0.3)
Ad26.CoV2.S	0 (0.0)	0 (0.0)	1 (0.1)
Other	0 (0.0)	0 (0.0)	19 (1.4)
Do not know	0 (0.0)	0 (0.0)	19 (1.4)
Nonseroconversion, n (%)[a]	836 (46.3)	124 (43.1)	358 (25.6)
Death, n (%)	3 (0.2)	1 (0.3)	0.0 (0.0)

[a]Nonseroconversion was defined with a level of SARS-CoV-2 spike S1-specific IgG antibodies of <50 BAU/mL (anti–SARS-CoV-2 RBD IgG ELISA assay) after the second vaccination in the discovery cohort or third vaccination in the second validation cohort and <10 BAU/mL (fluorescent bead-based multiplex immunoassay) after the second vaccination in the first validation cohort.
ALAT, alanine aminotransferase; BAU, binding antibody units; BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; IgG, immunoglobulin G; MMF/MPA, mycophenolate mofetil/mycophenolic acid; mTOR, mammalian target of rapamycin; NA, not available; S1, subunit 1; SBP, systolic blood pressure;.

important after 3 vaccine doses, Table 2 shows the significance of our predictors in the second validation cohort separately. Seven predictors remained significant after multiple vaccination: MMF/MPA use, chronic lung disease, diabetes, age, time after transplantation, eGFR, and the use of mTOR inhibitors.

Type of third vaccine appeared not to be predictive of nonseroconversion when added to the final model, taking mRNA-1273 as reference (BNT162b2 $P = 0.651$, ChAdOx-nCov19 $P = 0.582$, Ad26.CoV2.S $P = 0.786$). Performance of the final model in KTRs who received a third vaccination with mRNA-1273 (N = 96) or BNT162b2 (N = 1262) is shown in **Figure S4, SDC**, http://links.lww.com/TXD/A464. Higher antibody levels after the second dose were associated with a lower risk of nonseroconversion when added to the model (OR, 0.05 per log BAU/mL; 95% CI, 0.03-0.07, $P < 0.0001$) and improved the AUC to 0.89 (95% CI, 0.86-0.91). We next evaluated additional laboratory variables, selected from items only available in the first validation set. Lymphocyte count appeared

TABLE 2.

Multivariable analysis of discovery cohort and second validation cohort

Predictors	Discovery cohort OR [95% CI]	*P*	Second validation cohort OR [95% CI]	*P*
MMF/MPA	5.45 (4.25-7.03)	<0.001	1.57 (1.17-2.13)	0.003
Chronic lung disease	1.91 (1.23-2.99)	0.004	1.69 (1.04-2.71)	0.031
Heart failure	1.83 (1.14-2.95)	0.013	1.17 (0.67-1.99)	0.6
Diabetes	1.65 (1.26-2.15)	<0.001	1.51 (1.11-2.06)	0.009
Age, y	1.02 (1.02-1.03)	<0.001	1.02 (1.01-1.03)	<0.001
Time after transplantation, y	0.95 (0.93-0.96)	<0.001	0.95 (0.93-0.97)	<0.001
BMI, kg/m^2 per 5	0.86 (0.73-0.95)	0.004	0.86 (0.73-1.00)	0.054
eGFR, mL/min/1.73 m^2 per 10	0.82 (0.82-0.90)	<0.001	0.82 (0.74-0.82)	<0.001
Current alcohol use	0.76 (0.61-0.94)	0.012	0.97 (0.75-1.26)	0.8
First kidney transplant	0.65 (0.47-0.88)	0.006	0.78 (0.55-1.11)	0.2
mTOR inhibitor	0.59 (0.37-0.93)	0.025	0.48 (0.28-0.80)	0.006
Calcineurin inhibitor	0.52 (0.38-0.72)	<0.001	0.69 (0.46-1.03)	0.066

BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; MMF/MPA, mycophenolate mofetil/mycophenolic acid; mTOR, mammalian target of rapamycin.

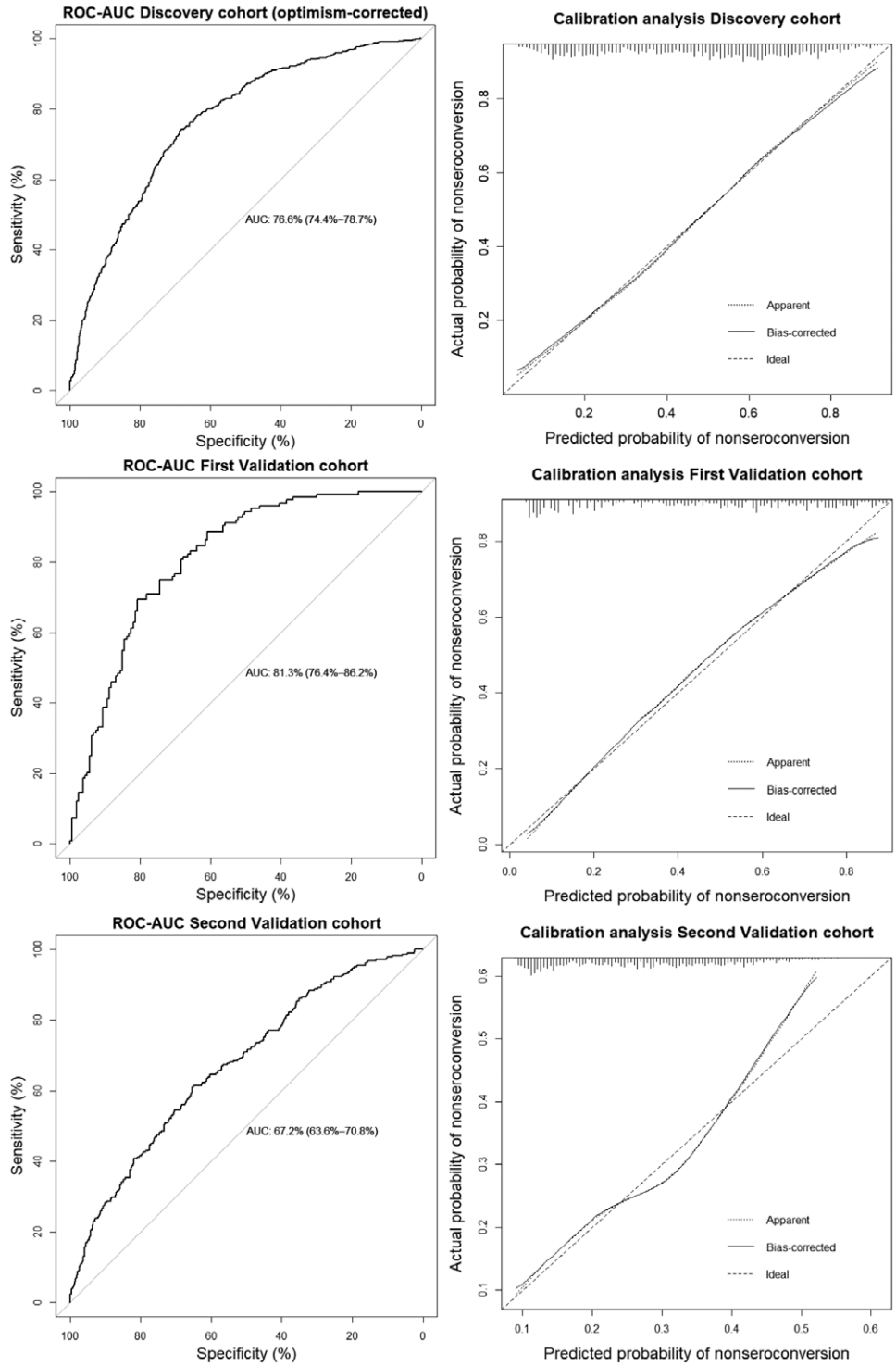

FIGURE 2. Top: Performance and calibration of the optimism-corrected discovery cohort. Middle: Performance and calibration of the first validation cohort. Bottom: Performance and calibration of the second validation cohort. AUC, area under the curve; ROC, receiver operating characteristic.

important in the prediction of nonseroconversion (OR, 0.71; 95% CI, 0.51-0.99; $P = 0.047$) and slightly improved the AUC to 0.82 (95% CI, 0.77-0.87) (**Figure S1E, SDC**, http://links.lww.com/TXD/A464). Also, adding hemoglobin count had a significant effect (OR, 0.46; 95% CI, 0.31-0.68; $P < 0.001$) and improved the AUC to 0.84 (95% CI, 0.79-0.88) (**Figure S1F, SDC**, http://links.lww.com/TXD/A464).

As a sensitivity analysis, we first evaluated the external validation with 2 machine learning methods. Neither of these methods was able to increase discrimination compared with conventional logistic regression (**Figure S5A and B, SDC**, http://links.lww.com/TXD/A464). Second, we validated the model in a cohort including patients with antibody measurements at 28 ± 3 d after the second vaccination (N = 989),

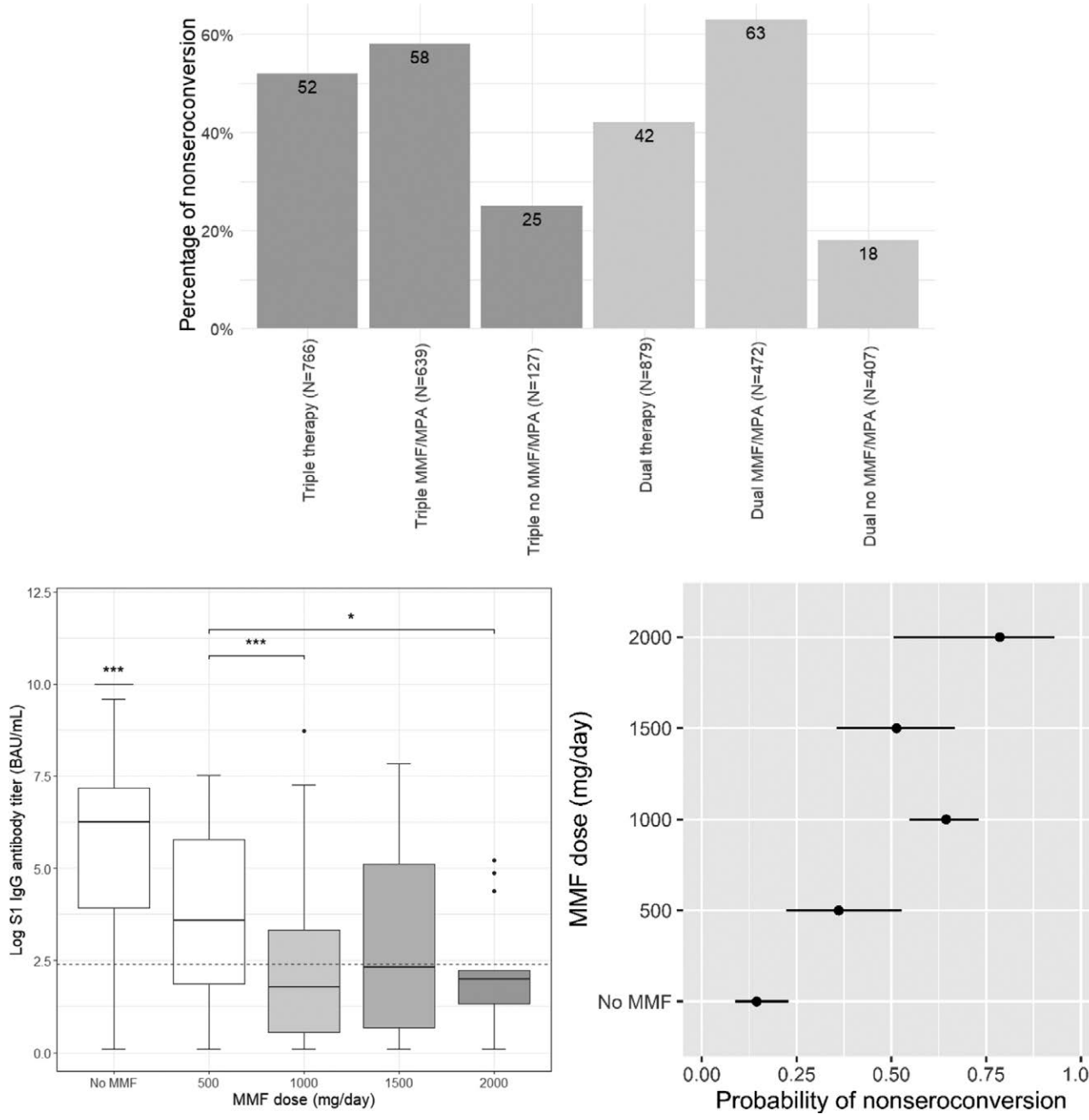

FIGURE 3. Explorative analysis of immunosuppressive therapy. Top: The impact of combination immunosuppressive therapies on the probability of nonseroconversion combining discovery and external validation cohort. Bottom: Subanalysis on MMF dose in the external validation cohort (N = 288). Left: The negative association between the use of MMF and S1 IgG antibody titer (log scale) with reference line for cutoff of nonseroconversion. Right: The effect of MMF dose on the probability of nonseroconversion. BAU, binding antibody units; IgG, immunoglobulin G; MMF/MPA, mycophenolate mofetil/mycophenolic acid; S1, subunit 1.

and it showed similar performance compared with the ≥2 wk to ≤8 wk inclusion cohort (AUC of 0.74; 95% CI, 0.71-0.78) (**Figure S5C, SDC,** http://links.lww.com/TXD/A464).

Lastly, we performed further exploratory analysis regarding the most commonly used immunosuppressive drug regimens in KTRs in the Netherlands. Including the data of both the discovery and first validation cohort, KTRs who were on triple immunosuppressive therapy (N = 766) had a higher percentage of nonseroconversion to the second mRNA-1273 vaccine than KTRs who were on dual immunosuppressive therapy (N = 879) (Figure 3). In particular, if the immunosuppressive regimen contained MMF/MPA in triple therapy (N = 639) or dual therapy (N = 472), the nonseroconversion rate was 2 to 4 times higher than when the immunosuppressive regimen did not contain MMF/MPA. In subanalysis in KTRs of the first validation cohort in whom doses of the immunosuppressive agents were registered (N = 288) (Figure 3), a significant negative association ($P < 0.001$) existed between every MMF daily dose (500 mg, 1000 mg, 1500 mg and 2000 mg) and the S1 IgG antibody titer (BAU/mL). The use of 500 mg/d was associated with higher antibody titer than 1000 mg/d ($P < 0.001$), 1500 mg/d ($P = 0.057$), and 2000 mg/d ($P < 0.05$). Consequently, an MMF dose of ≥1g/d increased the probability of nonseroconversion. No associations with the S1 IgG antibody titer were found

for any other immunosuppressive agents, which included azathioprine (P = 0.096), cyclosporine (P = 0.348), tacrolimus (P = 0.462), and prednisone (P = 0.728).

DISCUSSION

In a large sample of 2092 KTRs, we developed and externally validated a set of predictors based on routinely available clinical and laboratory information for nonseroconversion after SARS-CoV-2 vaccination. Characteristics of the inclusion and exclusion cohort were comparable, with the exception of a few patient characteristics and the nonseroconversion rate. The final model comprised 12 independent predictors for nonseroconversion: the use of MMF/MPA, 3 comorbidities (chronic lung disease, heart failure, and diabetes), increased age, shorter time after transplantation, lower BMI, lower eGFR, no alcohol consumption, ≥2 transplantations, and no use of mTOR inhibitors or calcineurin inhibitors. First validation of this model indicated excellent discrimination, and after analysis of the second validation cohort, MMF/MPA persisted to be an important factor in the prediction of nonseroconversion after 3 vaccinations.

In this study, we identified the use of MMF/MPA as the strongest predictor of nonseroconversion after SARS-CoV-2 mRNA vaccination in KTRs in our model, which remained highly important after 3 vaccine doses. This effect of MMF/MPA is consistent with results from previous studies on SARS-CoV-2 vaccines in KTRs with smaller sample sizes.[4,8,11,26,27] We show that MMF/MPA, as part of the immunosuppressive regimen, has an overall unfavorable effect on antibody formation. An MMF/MPA dose of ≥1g/d increases the probability of nonseroconversion drastically, suggesting a dose-dependent unfavorable effect. This is in concordance with the findings of Kantauskaite et al.[28] The findings for MMF/MPA are also in concordance with literature describing the IR to vaccination against hepatitis B, influenza, and *Streptococcus pneumonia*.[29] MMF/MPA depletes guanosine nucleotides preferentially in T and B lymphocytes and inhibits their proliferation, thereby suppressing cell-mediated IRs and antibody formation.[30] This fits with our finding that lower lymphocyte count is predictive for nonseroconversion in the first validation cohort.[27] Anemia has a multifactorial etiology. Remarkably, no negative associations were found for any other immunosuppressive agent and thus other mechanisms of action. Our findings that the use of calcineurin inhibitors and the use of mTOR inhibitors are positively associated with seroconversion in our model can possibly be explained by a concomitant decreased use of MMF/MPA. However, the aim of this study was to accurately predict the outcome using the combination of all predictors in the model and not to reveal a single association adjusted for confounders.

The association between diabetes has previously been made with cellular and/or humoral nonresponse after mRNA SARS-CoV-2 vaccination in KTRs.[9,31] No previous reports are available describing a negative effect on seroconversion rates in patients with chronic lung disease or heart failure. Age is a well-established risk factor for nonseroconversion regarding other vaccines,[32] and it also has been reported for SARS-CoV-2 vaccination.[12,13,27] Our results are in concordance with these studies.

Graft function is also associated with a reduced response to SARS-CoV-2 vaccination, which is in line with previous studies.[12,27] A similar phenomenon has been reported for influenza vaccination in KTRs.[33-35] Renal failure is associated with an impaired IR, mainly due to dysfunctional T cells.[36] Remarkably, we and others demonstrated that CKD G4/5 patients only have a marginally reduced antibody and T cell response after SARS-CoV-2 vaccination, despite their average kidney function being much lower than that of KTRs,[4,11] suggestive of immunosuppressive drugs as stronger determinants of antibody response to vaccination than impaired renal function.

Nutritional and behavioral factors might also influence how individuals respond to vaccines. Our observations that a lower BMI and abstinence from alcohol consumption are predictive for nonseroconversion to SARS-CoV-2 vaccination have not been reported before.[37] Shorter time after transplantation is associated with low seroconversion rates among KTRs who received the SARS-CoV-2 vaccine.[8,13,27] An obvious explanation is the more stringent immunosuppressive state in the early phase after transplantation both by lagging effects of induction therapy and by higher doses of maintenance therapy.

In the past 2 y, the SARS-CoV-2 virus has shown a high mutation rate, and the variants differ in infectivity and virulence and also develop the ability to escape vaccine-induced immunity in KTRs.[38] The current SARS-CoV-2 variant B.1.1.529 (Omicron) is highly transmissible and has reduced sensitivity to neutralization by antibodies induced by the currently used mRNA vaccines,[39] making the interpretation of antibody levels more difficult than before. Understanding the mechanisms of nonseroconversion might help to develop more successful vaccination strategies for KTRs to generate antibody levels able to combat future strains. Repeated vaccination against SARS-CoV-2 increases the seroconversion rate in KTRs with high interindividual variability. We and others see improved rates following a third mRNA dose in KTRs,[40] but still a significant number of patients remained seronegative and, thus, very likely inadequately protected against COVID-19. A fourth mRNA vaccine dose in strictly nonresponder KTRs induced a humoral response in almost half of participants; however, this response remained globally weak and was probably not protective enough.[41,42] Preventive preexposure SARS-CoV-2–specific monoclonal antibody therapy could provide protection for these patients.[43,44] Our results and others suggest that dose reduction or temporary withdrawal of MMF/MPA before vaccination may help to improve vaccine response in these KTRs.[40,45,46] The risk of rejection should be taken into consideration individually, although no acute rejection episodes have yet been reported.[47] We investigate the third dose of the mRNA-1273 vaccine in KTRs with discontinuation of MMF/MPA. The study is registered in www.ClinicalTrials.gov (NCT05030974).

Strengths of our study are the use of a large national cohort with a prospective design, including independent external validation in 2 cohorts. Participants were well characterized, which made it possible to analyze a relatively large number of factors associated with nonseroconversion in detail. Based on these cohorts, we provide valuable insight into the predictive value of clinical and laboratory variables for nonseroconversion in KTRs. Although our model is based on data from mid-2021, the highly discriminative predictors selected in the second vaccination model are stable in the third

vaccination model, for which data were collected until the beginning of 2022. In this time period, the B.1.1.7 (Alpha) variant was followed by the B.1.617.2 (Delta) variant as the dominant strain in the Netherlands.[48] Thus, we speculate that the predictors can play a role after multiple vaccinations and the emergence of new strains to select a group of KTRs at high risk of nonseroconversion, in which modulation of MMF/MPA could generate a protective response to repeated vaccination. A subject of debate is the recent knowledge that KTR can mount delayed IgG antibody responses compared with immunocompetent individuals.[49] This raises the question of whether obtaining blood samples at 28 d after the second vaccination was too early to detect antibodies in all patients; however, we show similar discrimination in the discovery cohort comparing a smaller time window. The data in the discovery cohort and second validation cohort were subject to a higher proportion of missingness, as comes with national registry databases. However, the missingness did not likely influence outcomes because the imputation analyses yielded similar results as compared with the complete case analyses. The collection of data in the first validation cohort was of high accuracy with hardly any missing data, which may explain the higher AUC (discrimination) in this cohort than in the discovery cohort. Regarding our study population, some specificities exist that can lead to limited generalization to other populations. Nonseroconversion rates after 2 vaccinations were relatively low compared with other studies using mRNA-based SARS-CoV-2 vaccines, which could be due to the cohorts consisting of long-term KTRs (median time after transplantation is 7.6 and 6.9 y) with 60% to 70% of them using MMF/MPA. Also, all fully vaccinated KTRs received the mRNA-1273 vaccine, which has higher seroconversion rates and clinical effectiveness than BNT162b2 in KTRs with breakthrough infections,[50,51] which aids in the discussion of whether mRNA-1273 should be the preferred vaccine in these patients. Although the type of third vaccine did not influence the prediction of nonseroconversion, we see an improved discrimination in the much smaller mRNA-1273 cohort, the type of vaccine on which the model was originally built. The less optimal predictive accuracy in the second validation cohort could be explained by an extra vaccine intervention associated with new seroconversion rates. The level of antibody response after basic immunization plays a major role, as expected.[27,45] Lastly, antibody measurement was not performed at baseline, and the absence of anti-N antibody is not sufficient to exclude for previous infection and thus, the inclusion of patients with asymptomatic SARS-CoV-2 infection, in this study could not be ruled out.

In conclusion, KTRs at high risk of nonseroconversion after SARS-CoV-2 vaccination can readily be identified using an easy-to-approach clinical model. Modulation of MMF/MPA treatment before vaccination may help to improve vaccine response in these KTRs. Future research should investigate the effect of MMF/MPA modulation in repeated SARS-CoV-2 vaccination and how nutritional and/or behavioral factors could be of influence. This model can contribute to the development of alternative strategies to optimize vaccine response in this complex patient group.

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REFERENCES

1. Polack FP, Thomas SJ, Kitchin N, et al; C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med*. 2020;383:2603–2615.
2. Baden LR, El Sahly HM, Essink B, et al; COVE Study Group. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2021;384:403–416.
3. Khoury DS, Cromer D, Reynaldi A, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med*. 2021;27:1205–1211.
4. Sanders JF, Bemelman FJ, Messchendorp AL, et al; RECOVAC Collaborators. The RECOVAC immune-response study: the immunogenicity, tolerability, and safety of COVID-19 vaccination in patients with chronic kidney disease, on dialysis, or living with a kidney transplant. *Transplantation*. 2022;106:821–834.
5. Caillard S, Chavarot N, Bertrand D, et al; French Society of Transplantation. Occurrence of severe COVID-19 in vaccinated transplant patients. *Kidney Int*. 2021;100:477–479.
6. Wajnberg A, Amanat F, Firpo A, et al. Robust neutralizing antibodies to SARS-CoV-2 infection persist for months. *Science*. 2020;370:1227–1230.
7. Feng S, Phillips DJ, White T, et al; Oxford COVID Vaccine Trial Group. Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. *Nat Med*. 2021;27:2032–2040.
8. Benotmane I, Gautier-Vargas G, Cognard N, et al. Low immunization rates among kidney transplant recipients who received 2 doses of the mRNA-1273 SARS-CoV-2 vaccine. *Kidney Int*. 2021;99:1498–1500.
9. Cucchiari D, Egri N, Bodro M, et al. Cellular and humoral response after MRNA-1273 SARS-CoV-2 vaccine in kidney transplant recipients. *Am J Transplant*. 2021;21:2727–2739.
10. Boyarsky BJ, Werbel WA, Avery RK, et al. Antibody response to 2-Dose SARS-CoV-2 mRNA vaccine series in solid organ transplant recipients. *JAMA*. 2021;325:2204–2206.
11. Grupper A, Rabinowich L, Schwartz D, et al. Reduced humoral response to mRNA SARS-CoV-2 BNT162b2 vaccine in kidney transplant recipients without prior exposure to the virus. *Am J Transplant*. 2021;21:2719–2726.

12. Rozen-Zvi B, Yahav D, Agur T, et al. Antibody response to SARS-CoV-2 mRNA vaccine among kidney transplant recipients: a prospective cohort study. *Clin Microbiol Infect*. 2021;27:1173.e1–1173.e4.
13. Dębska-Ślizień A, Ślizień Z, Muchlado M, et al. Predictors of humoral response to mRNA COVID19 vaccines in kidney transplant recipients: a longitudinal study-the COViNEPH Project. *Vaccines (Basel)*. 2021;9:1165.
14. Marion O, Del Bello A, Abravanel F, et al. Safety and immunogenicity of Anti-SARS-CoV-2 messenger RNA vaccines in recipients of solid organ transplants. *Ann Intern Med*. 2021;174:1336–1338.
15. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature*. 2020;584:430–436.
16. ERA-EDTA Council. ERACODA Working Group. Chronic kidney disease is a key risk factor for severe COVID-19: a call to action by the ERA-EDTA. *Nephrol Dial Transplant*. 2021;36:87–94.
17. Appelman B, Oppelaar JJ, Broeders L, et al; CovidPredict Study Group. Mortality and readmission rates among hospitalized COVID-19 patients with varying stages of chronic kidney disease: a multicenter retrospective cohort. *Sci Rep*. 2022;12:2258.
18. Stumpf J, Tonnus W, Paliege A, et al. Cellular and humoral immune responses after 3 doses of BNT162b2 mRNA SARS-CoV-2 vaccine in kidney transplant. *Transplantation*. 2021;105:e267–e269.
19. Schrezenmeier E, Rincon-Arevalo H, Stefanski AL, et al. B and T cell responses after a third dose of SARS-CoV-2 vaccine in kidney transplant recipients. *J Am Soc Nephrol*. 2021;32:3027–3033.
20. Tsapepas D, Paget K, Mohan S, et al. Clinically significant COVID-19 following SARS-CoV-2 vaccination in kidney transplant recipients. *Am J Kidney Dis*. 2021;78:314–317.
21. Bouwmans P, Messchendorp AL, Sanders JS, et al; RECOVAC Collaborators. Long-term efficacy and safety of SARS-CoV-2 vaccination in patients with chronic kidney disease, on dialysis or after kidney transplantation: a national prospective observational cohort study. *BMC Nephrol*. 2022;23:55.
22. Kho MML, Reinders MEJ, Baan CC, et al; RECOVAC Collaborators. The RECOVAC IR study: the immune response and safety of the mRNA-1273 COVID-19 vaccine in patients with chronic kidney disease, on dialysis or living with a kidney transplant – a prospective, controlled, multicenter observational cohort by the REnal patients COVID-19 VACcination (RECOVAC) consortium COVID-19 VACcination (RECOVAC) consortium. *Nephrol Dial Transplant*. 2021;36:1761–1764.
23. Vogelzang EH, Loeff FC, Derksen NIL, et al; Amsterdam University Medical Center COVID-19 Biobank Study Group. Development of a SARS-CoV-2 total antibody assay and the dynamics of antibody response over time in hospitalized and nonhospitalized patients with COVID-19. *J Immunol*. 2020;205:3491–3499.
24. Buuren van S, Groothuis-Oudshoorn K. MICE: Multivariate imputation by chained equations in R. *J Stat Softw*. 2011;45:1–67.
25. Collins GS, Reitsma JB, Altman DG, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *J Clin Epidemiol*. 2015;68:134–143.
26. Boyarsky BJ, Werbel WA, Avery RK, et al. Immunogenicity of a single dose of SARS-CoV-2 messenger RNA vaccine in solid organ transplant recipients. *JAMA*. 2021;325:1784–1786.
27. Benotmane I, Gautier G, Perrin P, et al. Antibody response after a third dose of the mRNA-1273 SARS-CoV-2 vaccine in kidney transplant recipients with minimal serologic response to 2 doses. *JAMA*. 2021;326:1063–1065.
28. Kantauskaite M, Müller L, Kolb T, et al. Intensity of mycophenolate mofetil treatment is associated with an impaired immune response to SARS-CoV-2 vaccination in kidney transplant recipients. *Am J Transplant*. 2022;22:634–639.
29. Reddy S, Chitturi C, Yee J. Vaccination in chronic kidney disease. *Adv Chronic Kidney Dis*. 2019;26:72–78.
30. Allison AC. Mechanisms of action of mycophenolate mofetil. *Lupus*. 2005;14 Suppl 1:s2–s8.
31. Prendecki M, Thomson T, Clarke CL, et al; Imperial Renal COVID-19 vaccine study group in collaboration with the OCTAVE Study Consortium. Immunological responses to SARS-CoV-2 vaccines in kidney transplant recipients. *Lancet*. 2021;398:1482–1484.
32. Lang PO, Govind S, Bokum AT, et al. Immune senescence and vaccination in the elderly. *Curr Top Med Chem*. 2013;13:2541–2550.
33. Mulley WR, Visvanathan K, Hurt AC, et al. Mycophenolate and lower graft function reduce the seroresponse of kidney transplant recipients to pandemic H1N1 vaccination. *Kidney Int*. 2012;82:212–219.
34. Manuel O, Pascual M, Hoschler K, et al. Humoral response to the influenza A H1N1/09 monovalent AS03-adjuvanted vaccine in immunocompromised patients. *Clin Infect Dis*. 2011;52:248–256.
35. Birdwell KA, Ikizler MR, Sannella EC, et al. Decreased antibody response to influenza vaccination in kidney transplant recipients: a prospective cohort study. *Am J Kidney Dis*. 2009;54:112–121.
36. Betjes MGH. Uremia-associated immunological aging and severity of COVID-19 infection. *Front Med (Lausanne)*. 2021;8:675573.
37. Zimmermann P, Curtis N. Factors that influence the immune response to vaccination. *Clin Microbiol Rev*. 2019;32:e00084–e00018.
38. Benning L, Morath C, Bartenschlager M, et al. Neutralization of SARS-CoV-2 variants of concern in kidney transplant recipients after standard COVID-19 vaccination. *Clin J Am Soc Nephrol*. 2022;17:98–106.
39. Cao Y, Wang J, Jian F, et al. Omicron escapes the majority of existing SARS-CoV-2 neutralizing antibodies. *Nature*. 2022;602:657–663.
40. Osmanodja B, Ronicke S, Budde K, et al. Serological response to three, four and five doses of SARS-CoV-2 vaccine in kidney transplant recipients. *J Clin Med*. 2022;11:2565.
41. Masset C, Benotmane I, Dantal J, et al. A fourth SARS-CoV-2 mRNA vaccine in strictly seronegative kidney transplant recipients. *Kidney Int*. 2022;101:825–826.
42. Caillard S, Thaunat O, Benotmane I, et al. Antibody response to a fourth messenger RNA COVID-19 vaccine dose in kidney transplant recipients: a case series. *Ann Intern Med*. 2022;175:455–456.
43. O'Brien MP, Forleo-Neto E, Musser BJ, et al; Covid-19 Phase 3 Prevention Trial Team. subcutaneous REGEN-COV antibody combination to prevent COVID-19. *N Engl J Med*. 2021;385:1184–1195.
44. Levin MJ, Ustianowski A, De Wit S, et al; PROVENT Study Group. Intramuscular AZD7442 (tixagevimab-cilgavimab) for prevention of COVID-19. *N Engl J Med*. 2022;386:2188–2200.
45. Yahav D, Rahamimov R, Mashraki T, et al. Immune response to third dose BNT162b2 COVID-19 vaccine among kidney transplant recipients-a prospective study. *Transpl Int*. 2022;35:10204.
46. Schrezenmeier E, Rincon-Arevalo H, Jens A, et al. Temporary antimetabolite treatment hold boosts SARS-CoV-2 vaccination-specific humoral and cellular immunity in kidney transplant recipients. *JCI Insight*. 2022;7:e157836.
47. Pascual J, van Hooff JP, Salmela K, et al. Three-year observational follow-up of a multicenter, randomized trial on tacrolimus-based therapy with withdrawal of steroids or mycophenolate mofetil after renal transplant. *Transplantation*. 2006;82:55–61.
48. National Institute for Public Health and the Environment. *Variants of the coronavirus SARS-CoV-2*. 2022. Available at https://www.rivm.nl/en/coronavirus-covid-19/virus/variants. Accessed August 21, 2022.
49. Cravedi P, Ahearn P, Wang L, et al. Delayed kinetics of IgG, but not IgA, antispike antibodies in transplant recipients following SARS-CoV-2 infection. *J Am Soc Nephrol*. 2021;32:3221–3230.
50. Mazuecos A, Villanego F, Zarraga S, et al; Spanish Society of Nephrology COVID-19 Group. Breakthrough infections following mRNA SARS-CoV-2 vaccination in kidney transplant recipients. *Transplantation*. 2022;106:1430–1439.
51. Verleye A, Wijtvliet V, Abrams S, et al. Seroconversion rate after primary vaccination with two doses of BNT162b2 versus mRNA-1273 in solid organ transplant recipients: a systematic review and meta-analysis. *Nephrol Dial Transplant*. 2022;37:1566–1575.