Impact of immunosuppressive treatment and type of SARS-CoV-2 vaccine on antibody levels after three vaccinations in patients with chronic kidney disease or kidney replacement therapy

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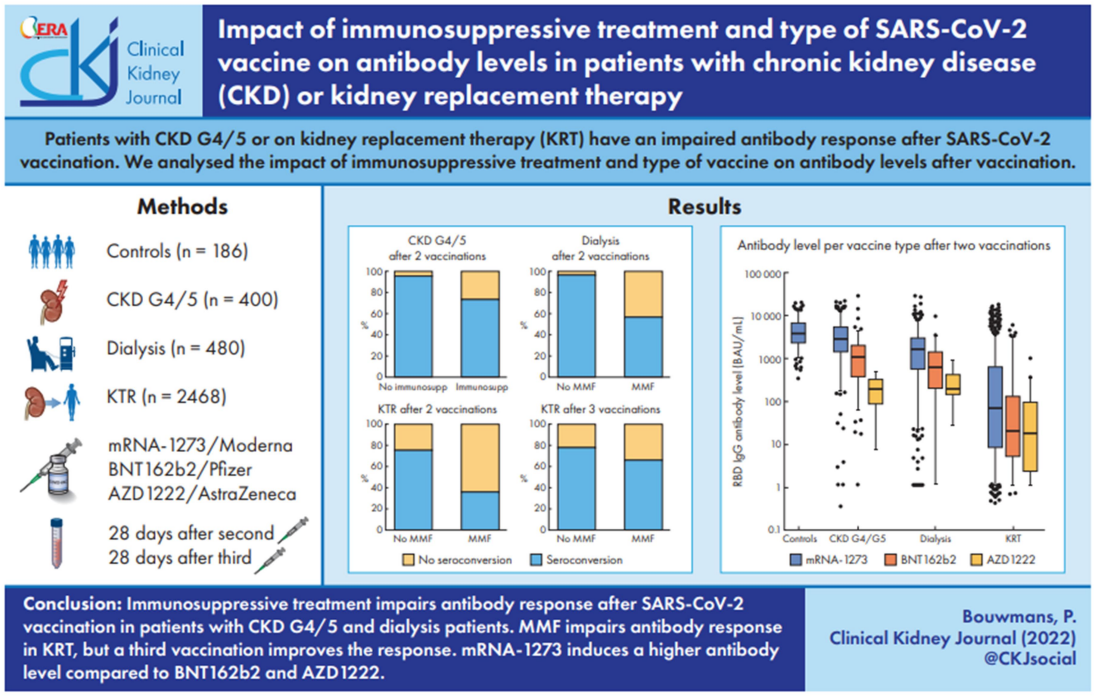
GRAPHICAL ABSTRACT



ABSTRACT

Background. Patients with chronic kidney disease or kidney replacement therapy demonstrate lower antibody levels after SARS-CoV-2 vaccination compared to healthy controls. In a prospective cohort, we analysed the impact of immunosuppressive treatment and type of vaccine on antibody levels after three SARS-CoV-2 vaccinations.

Methods. Control subjects (n=186), patients with CKD G4/5 (n=400), dialysis patients (n=480) and kidney transplant recipients (KTR) (n=2468) were vaccinated with either mRNA-1273 (Moderna), BNT162b2 (Pfizer-BioNTech) or AZD1222 (Oxford/AstraZeneca) in the Dutch SARS-CoV-2 vaccination programme. Third vaccination data were available in a subgroup of patients (n=1829). Blood samples and questionnaires were obtained one month after the second and third vaccination. Primary endpoint was the antibody level in relation to immunosuppressive treatment and type of vaccine. Secondary endpoint was occurrence of adverse events after vaccination.

Results. Antibody levels after two and three vaccinations were lower in patients with CKD G4/5 and dialysis patients with immunosuppressive treatment compared to patients without immunosuppressive treatment. After two vaccinations, we observed lower antibody levels in KTR using mycophenolate mofetil (MMF) compared to KTR not using MMF (20 BAU/ml [3-113] versus 340 BAU/ml [50-1492], p<0.001). Seroconversion was observed in 35% of KTR using MMF, compared to 75% of KTR not using MMF. Of the KTR who used MMF and did not seroconvert, eventually 45% seroconverted after a third vaccination. mRNA-1273 induces higher antibody levels as well as a higher frequency of adverse events compared to BNT162b2 in all patient groups.

Conclusions. Immunosuppressive treatment adversely affects the antibody levels after SARS-CoV-2 vaccination in patients with CKD G4/5, dialysis patients and KTR. mRNA-1273 vaccine induces a higher antibody level and higher frequency of adverse events.

Keywords: antibody response, chronic kidney disease, dialysis, kidney transplantation, SARS-CoV-2 vaccination

INTRODUCTION

Patients with chronic kidney disease (CKD) or receiving kidney replacement therapy have a lower response to SARS-CoV-2 vaccination and therefore remain at higher risk for COVID-19[1-4]. It is well known, that the use of immunosuppressive drugs, especially mycophenolate mofetil (MMF), severely affects the response to vaccination. While a third vaccination can enhance antibody levels in KTR[5], this is only described in relatively small cohorts using MMF[6, 7]. Limited data are available on the impact of immunosuppressive treatment on the antibody levels in patients with CKD G4/5 and dialysis patients after SARS-CoV-2 vaccinations[8-11].

Recent systematic reviews showed that the highest level of protection against symptomatic COVID-19 in the general population was reached with mRNA-based SARS-CoV-2 vaccines[12], although vector-based vaccines such as AZD1222 (Oxford/AstraZeneca) were also reported to be effective[13]. Of the two available mRNA-based vaccines, the mRNA-1273 (Moderna) vaccine is associated with higher

antibody levels and lower rates of breakthrough infections than the BNT162b2 (Pfizer-BioNTech) vaccine in the general population[14, 15]. Higher antibody levels after mRNA-1273 in comparison to BNT162b2 have also been reported in patients with kidney disease, although differences in safety outcomes between these vaccines have not yet been reported[2, 3, 16-19].

In this prospective observational cohort study, we assessed the impact of immunosuppressive treatment and type of vaccine on antibody levels and safety outcomes after two and three SARS-CoV-2 vaccinations in patients with CKD G4/5, dialysis patients and KTR.

MATERIALS AND METHODS

Study design

In this study, we measured antibody levels and adverse events (AEs) in control subjects and patients with kidney disease after two and three vaccinations with either mRNA-1273 (Moderna), BNT162b2 (Pfizer-BioNTech) or AZD1222 (Oxford/AstraZeneca) in the Dutch COVID-19 vaccination programme[20-22]. Kidney patients were prioritized for the first two vaccinations in April-May 2021, and for the third vaccination in October-November 2021, except for patients with CKD G4/5 without immunosuppressive treatment who were not prioritized for the third vaccination.

Study participants

Subjects were included for analysis from two different cohort studies of the REnal patients COVID-19 VACcination (RECOVAC) consortium. The main cohort is established from the LESS CoV-2 study, of which the design has been registered in clinicaltrials.gov (NCT04841785), and has previously been published[23]. In this study, patients with CKD G4/5 were recruited from the Santeon hospitals, a cooperation of seven non-university hospitals. Dialysis patients and KTR were recruited from all dialysis centres and hospitals in the Netherlands. Patients older than 80 years were not invited since they were prioritized in the vaccination campaign, and the timing of their second vaccination

preceded the start of this study by more than 28 days. Subjects provided informed consent in writing or electronically, in accordance to the ICMJE recommendations. Ethical approval was obtained from the Medical Ethics Committee at the University Medical Center Groningen (2021/099).

We have additionally included control subjects, and patients with CKD G4/5 from the RECOVAC IR-study[24]. In this study, 186 control subjects and 160 participants with CKD G4/5 were included. Control subjects were eligible for inclusion if they were partners or siblings of participants with CKD G4/5, dialysis patients or KTR. Non-transplant subjects who used immunosuppressive drugs were excluded from participation. Participants were vaccinated twice with mRNA-1273, after which blood samples were collected at 28 days after the second vaccination.

Data collection

Blood samples were obtained by home based finger prick kits (Sanquin, Amsterdam, The Netherlands). Blood samples and questionnaires were collected at 28 days after the second and third vaccination. Questionnaires requested for information on patient characteristics, including previous COVID-19 and medication use, and AEs within seven days after each vaccination. AEs were categorized in local AEs (pain or erythema at injection site and myalgia) or systemic AEs (fever, arthralgia, fatigue, headache, and other). We asked participants whether they used corticosteroids, calcineurin inhibitors, MMF, mycophenolic acid, mTOR-inhibitors, or azathioprine. Mycophenolic acid was considered as MMF for further analysis.

Additional information on characteristics of dialysis patients and KTR was extracted from the Dutch Renal Registry (RENINE) and the Dutch Organ Transplant Registry (NOTR). Data on the use of immunosuppressive drugs in KTR was collected from the NOTR. Primary kidney disease was defined following the European Renal Association (ERA) coding system[25].

For analysis, we included patients with complete information on demographics, vaccine type, date of SARS-CoV-2 vaccination, date of blood sample collection, and successful measurement of antibody

concentration. Patients were excluded, if their blood was obtained less than 14 days or more than 56 days after the second or third vaccination, or if they were diagnosed with COVID-19 before blood collection.

Antibody measurement

We analysed blood samples for the presence of antibodies against the receptor binding domain (RBD) of the SARS-CoV-2 spike protein (IgG anti-RBD antibody) using an in-house anti-SARS-CoV-2 RBD IgG ELISA assay (Sanquin)[26]. We combined this assay with an in-house anti-SARS-CoV-2 nucleocapsid protein (NP) bridging ELISA to detect an antibody response due to previous COVID-19 infection. RBD IgG antibody levels are expressed in BAU/ml[27]. The cut-off value for assessing seroconversion rates was set at ≥50 BAU/ml[28]. In addition, we used an arbitrary cut-off value of >1000 BAU/ml to assess the proportion of patients with high-level antibody response.

Statistical analysis

We assessed characteristics in patients who received at least two vaccinations, and in a subcohort of patients who received three vaccinations using Student's t-test for normally distributed data, Mann-Whitney-U test for non-normally distributed data and Pearson's chi-squared test for categorical data. In addition, we compared characteristics between patients with data on third vaccination and those without data on third vaccination to assess potential selection bias.

Antibody levels between patient groups and vaccine types were compared using Wilcoxon rank-sum test. Additionally, antibody levels and seroconversion rates were stratified for use of immunosuppressive drugs (yes vs. no) in patients with CKD G4/5 and dialysis patients, and for use of MMF (yes vs. no) in KTR. Seroconversion rates were compared by Pearson's chi-squared test. In patients who were vaccinated three times, we assessed the change in antibody level compared to the antibody level after two vaccinations. We also compared antibody levels between three-vaccination schemes.

We analysed the association between type of vaccine and antibody levels after two vaccinations by multivariable linear regression analysis (BNT162b2 or AZD1222 compared to mRNA-1273). Primarily, we adjusted for age, sex, and ethnicity. Additionally, we adjusted for variables that could be of influence on antibody levels. These variables were selected if they reached a statistically significant difference (α=0.1) between patient groups receiving different vaccine types in univariate analysis. As a result, we adjusted for eGFR in patients with CKD G4/5 and KTR, and transplant type in KTR. We also adjusted for use of immunosuppressive drugs (yes vs. no) in patients with CKD stages G4/5 and dialysis patients, and for type of immunosuppressive treatment in KTR.

AEs after each vaccination were compared using Pearson's chi-squared test. We analysed the association between type of vaccine and the occurrence of AEs after any of the first two vaccinations by using multivariable logistic regression analysis. We adjusted for variables in concordance with the previously mentioned regression analysis. Lastly, we show the occurrence of different AEs separately after each vaccination (e.g. pain at injection site, fever, myalgia, arthralgia, fatigue, headache, allergy, and other).

RESULTS

Participant characteristics

After two SARS-CoV-2 vaccinations, 186 control subjects, 400 patients with CKD G4/5, 480 dialysis patients and 2468 KTR were enrolled in the study (Figure S1). The average age was 59$\pm$12 years in control subjects, 65$\pm$11 years in patients with CKD G4/5, 65$\pm$12 years in dialysis patients, and 59$\pm$13 years in KTR (Table 1). The proportion of males was 39% in the controls and approximately 60% in the three patient groups. The eGFR was 82$\pm$18 ml/min/1.73m^2 in control subjects, 20$\pm$9 ml/min/1.73m^2 in patients with CKD G4/5, and 51$\pm$18 ml/min/1.73m^2 in KTR. The majority of the patients was of Caucasian origin. The most frequently administered vaccine was mRNA-1273 (CKD G4/5: 68%, dialysis: 86%, KTR: 93%), followed by BNT162b2 (CKD G4/5: 29%, dialysis: 11%, KTR: 5%)

and AZD1222 (<5% in all groups). Immunosuppressive drugs were used by 22 of 400 (6%) of the patients with CKD G4/5, and 84 of 480 (18%) of the dialysis patients and all KTR. Only 36 KTR (1%) were transplanted within six months before vaccination.

A subcohort of 40 patients with CKD G4/5, 242 dialysis patients and 1547 KTR received a third SARS-CoV-2 vaccination followed by a second blood sample. In total, 1519 patients were excluded of which 73 patients with COVID-19 between second and third vaccination (Figure S1). In this subcohort, 9 patients with CKD G4/5 (23%) and 38 dialysis patients (16%) used immunosuppressive drugs. Patients predominantly received BNT162b2 vaccine as third vaccination (Table 1). Baseline characteristics of dialysis patients and KTR included for analysis after three vaccinations did not differ from dialysis patients and KTR who were excluded for analysis. CKD G4/5 patients included for analysis after three vaccinations were significantly older (67±9 vs. 64±12 years) and more often used immunosuppressive drugs (23% vs. 4%) as compared to CKD G4/5 patients who were excluded for analysis (Table S1).

Antibody level after SARS-CoV-2 vaccination

The median (IQR) RBD IgG antibody level after two vaccinations was 3713 (2291-6451) BAU/ml in control subjects and all these subjects seroconverted. In comparison to control subjects, antibody levels and seroconversion rates were significantly lower in patients with CKD G4/5 (2097 [828-4077] BAU/ml and 96% seroconversion; p=<0.001 and p=0.006 resp.), in dialysis patients (1375 [431-2896] BAU/ml and 92% seroconversion; both p<0.001), and in KTR (66 [8-573] BAU/ml and 50% seroconversion; both p<0.001).

Antibody level and seroconversion rate did not increase in patients with CKD G4/5 after a third vaccination (Figure 1A-B). In contrast, a rise in antibody levels after third vaccination was observed in both dialysis patients (p<0.001) and KTR (p<0.001). Seroconversion after a third vaccination was observed in 26% of dialysis patients and 43% of KTR who did not respond after two vaccinations. An

antibody level more than 1000 BAU/ml after three vaccinations was induced in 55% of patients with CKD G4-5, 63% of dialysis patients and 25% of KTR (Table 2a-b).

The antibody levels and seroconversion rates in patients with CKD G4/5 and dialysis patients were lower in those with immunosuppressive treatment as compared to those without immunosuppressive treatment (Table 2a). No difference in change of antibody levels between second and third vaccination was observed in patients with CKD G4/5 and dialysis patients according to the use of immunosuppressive treatment (data not shown).

After two vaccinations, KTR who use MMF had lower antibody levels and a lower seroconversion rate compared to KTR without MMF (20 [3-113] BAU/ml versus 340 [50-1492] BAU/ml, and 35% versus 75%, respectively, p<0.001; Table 2b). The third vaccination resulted in a stronger increase in antibody level in KTR using MMF compared to KTR without MMF (+81 [0, +470] vs. 0 [-20, +340] BAU/ml, p<0.001]. In KTR using MMF who have not responded after two vaccinations, 164 KTR (45%) did seroconvert after a third vaccination. In KTR not using MMF, only 20 previously non-responding KTR (26%) seroconverted after a third vaccination.

Two vaccinations with mRNA-1273 resulted in higher antibody levels in all three patients groups compared to two vaccinations with BNT162b2 or AZD1222 (p<0.001, Figure 2A). This finding was confirmed after multivariable linear regression analysis (Table S2). We also observed higher antibody levels in vaccination schemes containing three vaccinations of mRNA-1273 compared to three vaccinations of BNT162b2 in dialysis patients and KTR (Figure 2B).

Adverse events after SARS-CoV-2 vaccination

The frequency of any AE within the first 7 days after the second mRNA-1273 vaccination was lower in patients with CKD G4/5 (84%), dialysis patients (60%) and KTR (63%) in comparison with control subjects (94%, p≤0.001, Table 3). More systemic and local AEs were reported after the second vaccination with mRNA-1273 in comparison with BNT162b2 in all three patient groups (p<0.01, Table

S3). This could be confirmed after multivariable logistic regression analysis (Table S4). No statistically significant differences in local or systemic AEs were observed between administration of BNT162b2 and mRNA-1273 after the third vaccination (Table S3). The most frequently reported AE was pain at the injection site for all three-vaccine types in all patient groups (Table S5).

DISCUSSION

In the present study, we found that immunosuppressive treatment in patients with CKD G4/5 and dialysis patients, as well as MMF use in KTR, leads to lower antibody levels and seroconversion rates after three SARS-CoV-2 vaccinations. Remarkably, 45% of the KTR using MMF who did not respond to the first two vaccinations had seroconversion after a third vaccination. In addition, we observed that mRNA-1273 in comparison to BNT162b2 and AZD1222 induced higher antibody levels, which was accompanied by higher rates of short-term reported AEs.

To date, only two small series described the effect of immunosuppressive treatment on the immune response after SARS-CoV-2 vaccination in patients with CKD G4/5. In one study, 36 patients with CKD G4/5 that were mainly treated with rituximab demonstrated lower antibody levels[2]. Another study in 18 patients with CKD G4/5 using immunosuppressive drugs also demonstrated lower antibody levels after inactivated whole virus SARS-CoV-2 vaccination[11]. Our data show an adverse effect of immunosuppressive treatment on antibody level and seroconversion rate in the largest cohort of patients with CKD G4/5 being described so far. In dialysis patients, more data are available on the effect of immunosuppressive treatment on the immune response after SARS-CoV-2 vaccination. Several studies show lower antibody levels after two[3, 29] and three[8-10] vaccinations, as we could likewise observe in our cohort. Both CKD G4-5 and dialysis patients who receive immunosuppressive treatment and do not respond to vaccination may be at a persistent higher risk of a severe course of COVID-19.

The effect of immunosuppressive treatment on the immune response after SARS-CoV-2 vaccination in KTR has extensively been studied, albeit in much smaller cohorts than in our study[30]. We demonstrate a higher antibody level and seroconversion rate after the second as well as the third vaccination in KTR not using MMF compared to KTR using MMF. Of the KTR using MMF that did not respond after two vaccinations, eventually 45% seroconverted after a third vaccination. This is a higher response than in non-responding KTR without MMF of whom 26% eventually seroconverted after a third vaccination. This shows that repeated vaccination is an effective strategy to improve antibody levels in KTR, especially those using MMF.

The lower immune response in KTR using MMF raises the question whether the response to SARS-CoV-2 vaccination in KTR can be optimized by temporary discontinuation of MMF[6, 31, 32]. One randomized controlled trial recently investigated withdrawal of MMF one week before and after a third or fourth vaccination in 103 previous non-responding KTR[33]. No difference in antibody response was found between the intervention and the placebo group. The authors argue that the withdrawal period of 2 weeks could have been too short to identify any differences. Similar studies with a longer withdrawal period of MMF or switch to another immunosuppressant agent should be performed to further investigate this issue.

The use of mRNA-1273 has previously been shown to yield higher antibody concentrations than BNT162b2 in the general population[12]. This has also been demonstrated in patients with kidney disease[2, 3, 16-18, 34-37], but a comparison between mRNA-1273 and AZD1222 has not been previously reported for patients with CKD G4/5 and KTR. In dialysis patients, conflicting results have been reported when comparing antibody levels after vector-based and mRNA-based SARS-CoV-2 vaccination[17, 19, 38, 39] . Differences in IgG antibody levels are thought to be of importance, since higher antibody levels are correlated with higher virus neutralization titres[40], and a higher protection against severe COVID-19[41]. We could confirm higher antibody levels with mRNA-1273 versus BNT162b2 in a large cohort of patients with CKD G4/5, dialysis patients and KTR. It may be that a

higher dose of mRNA in mRNA-1273 versus BNT162b2 is responsible for the difference in antibody levels. Due to the low representation of AZDZ1222 in our cohort, we cannot generalize our findings on vaccination with AZD1222 for the involved kidney patient groups.

As the COVID-19 pandemic further evolves with new variants of concern, currently used vaccines (targeted at the ancestral SARS-CoV-2 strain) will become less effective. Against the emerging Omicron variant, strongly reduced cross-neutralization was observed[42-45]. Nevertheless, a lower risk of severe disease after infection with this variant was described[46]. This is potentially due to inherent differences in viral properties between the Omicron and previously circulating variants. In addition, immunological mechanisms other than virus neutralization are also involved in cross-protection against severe disease. Examples are, beside functions of virus-specific T-cells, effector functions mediated by non-neutralizing antibodies such as antibody-dependent cellular cytotoxicity, phagocytosis, and complement deposition.

We assume that the induction of higher level of antibody levels is a desirable outcome in these patients at high- risk of severe COVID-19. Our study demonstrates that a third vaccination induces antibody levels above 1000 BAU/ml in the majority of patients with CKD G4/5 and dialysis patients. However, only a minority of dialysis patients using immunosuppressive drugs and KTR have antibody levels above 1000 BAU/ml after the third vaccination. Recently, an antibody level above 1000 BAU/ml was shown to correlate with in vitro neutralization against the Omicron variant 28 days after vaccination[40]. Furthermore, high-level antibody response is associated with clinical protection against SARS-CoV-2 infection[47] and severe COVID-19[48].

We observed a lower rate of AEs after BNT162b2 compared to mRNA-1273 in all patient groups. The reported AEs were mild and self-limiting. Given the vulnerability of the kidney patient groups for severe COVID-19, we consider the impact of higher AE rates of lesser importance than the beneficial immunogenicity of mRNA-1273.

The main strength of our study is the real-life representation of all high-risk patient groups with kidney disease. Recently, Quiroga et al. also described antibody responses in a cohort including

high-risk patients with kidney disease after two and three vaccinations[37, 49]. In contrast to these studies, we report on the impact of immunosuppressive treatment in patients with CKD G4/5 and dialysis patients. Furthermore, we have stratified the regression analysis for the three subgroups of patients with kidney disease. Our cohort also contains the largest number of KTR so far, enabling us to perform detailed analysis on the impact of type of immunosuppressive drugs and vaccine type on antibody levels. We also performed NP antibody measurement to exclude previous COVID-19 in patients who have not self-reported a previous COVID-19 diagnosis. Doing so, we minimize the possibility of asymptomatic infections influencing our results. A specific strong feature of this study is the measurement of antibody levels by home-based fingerprick sampling of blood. This prevented additional workload for hospital workers and circumvented visits of patients to health care centres during the pandemic.

The study has some limitations. First, we complied to the Dutch vaccination programme, in which different vaccines were administered in different age groups. Nevertheless, our main findings remain unchanged after adjustment for age. Second, we did not measure neutralizing antibodies after vaccination. The antibody level, however, is correlated with neutralizing capacity after SARS-CoV-2 vaccination or infection[40, 41]. Therefore, we also expect our findings to apply on neutralizing capacity. Third, we lost a part of our initial cohort for the analysis after third vaccination. We found no differences between characteristics of dialysis patients and KTR with and without data on third vaccination, what suggests no indication of selection bias. In contrast, patients with CKD G4/5 with data on third vaccination had a higher percentage of immunosuppressive treatment at baseline compared to those without data on third vaccination. This is a direct result of the prioritization of only CKD G4/5 patients with immunosuppressive treatment in the Dutch vaccination programme. Lastly, we did not collect data on reason and duration of immunosuppressive treatment, nor the dose of immunosuppressive drugs. The importance of immunosuppressive treatment dosage was previously reported for corticosteroids[50] and MMF[51].

In conclusion, the antibody level after SARS-CoV-2 vaccination is adversely affected by immunosuppressive treatment in patients with CKD G4/5, dialysis patients and KTR. The mRNA-1273 vaccine yields the highest antibody level with an acceptable increase of AEs. Repetitive SARS-CoV-2 vaccination is an effective strategy to establish antibody response in dialysis patients and KTR who did not respond to previous SARS-COV-2 vaccination, especially in KTR who use MMF.

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CONFLICT OF INTEREST STATEMENT

None declared.

AUTHORS' CONTRIBUTIONS

PB, LM, JS, RG, LH and MH drafted the manuscript. PB, PV, LM and MH were responsible for analysis. All authors provided intellectual content of critical importance to the study, and revised and approved the final manuscript. The RECOVAC collaborators contributed to the design of the consortium and data collection.

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DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

APPENDIX

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Table 1: Patient characteristics categorized by two or three SARS-CoV-2 vaccinations.

	Control	CKD G4/5		Dialysis		KTR	
	2 vaccinations	2 vaccinations	3 vaccinations	2 vaccinations	3 vaccinations	2 vaccinations	3 vaccinations
	n = 186	n = 400	n = 40	n = 480	n = 242	n = 2468	n = 1547
Age (years)	59 (12)	65 (11)	67 (9)	65 (12)	66 (10)	59 (13)	59 (12)
Sex, male, n (%)	72 (39)	241 (60)	25 (63)	294 (61)	143 (59)	1428 (60)	860 (56)
Ethnicity, n (%)							
• Caucasian	171 (92)	359 (90)	35 (88)	413 (86)	214 (88)	2229 (90)	1413 (91)
• Non-Caucasian	11 (6)	31 (8)	3 (8)	52 (11)	22 (9)	184 (78)	100 (6)
• Unknown	4 (2)	10 (2)	2 (5)	15 (3)	6 (2)	55 (2)	34 (2)
BMI (kg/m^2), mean (SD)	28 (5)	29 (6)	28 (7)	27 (6)	27 (6)	26 (7)	26 (7)
eGFR (ml/min/1.73m^2), mean (SD)	82 (18)	20 (9)	22 (13)	-	-	51 (18)	50 (19)
Comorbidities, n (%)							
• Cardiovascular disease	9 (5)	76 (19)	6 (15)	124 (26)	59 (24)	293 (12)	177 (11)
• Peripheral vascular disease	-	20 (8)	5 (13)	45 (9)	26 (11)	95 (4)	55 (4)
• Heart failure	3 (2)	53 (13)	6 (15)	81 (17)	45 (19)	152 (6)	83 (5)
• Diabetes	19 (10)	123 (30)	12 (30)	156 (33)	74 (31)	540 (22)	308 (20)
• Hypertension	53 (28)	294 (74)	26 (65)	293 (61)	147 (61)	1553 (63)	968 (63)
• Cancer	11 (6)	33 (8)	3 (8)	41 (9)	12 (5)	71 (3)	44 (3)
• Stroke	-	17 (7)	4 (10)	41 (9)	21 (9)	126 (5)	82 (5)
• Dementia	-	2 (1)	-	-	-	1 (0)	1 (0)
• Lung disease	16 (9)	45 (11)	6 (15)	71 (15)	34 (14)	166 (7)	94 (6)
• Liver cirrhosis	-	4 (2)	-	6 (1)	4 (2)	24 (1)	13 (1)
• HIV/aids	-	-	-	4 (1)	2 (1)	6 (0)	5 (0)
Primary kidney disease, n (%)							
• Diabetes	-	-	-	76 (18)	39 (18)	120 (5)	73 (6)
• Hypertension	-	-	-	110 (26)	57 (26)	156 (8)	91 (7)
• Glomerulonephritis	-	-	-	51 (12)	33 (15)	406 (20)	240 (19)
• Interstitial nephritis	-	-	-	37 (9)	16 (7)	151 (8)	90 (7)
• PCKD	-	-	-	41 (10)	25 (11)	343 (17)	240 (19)
• Congenital/hereditary	-	-	-	8 (2)	1 (0)	66 (3)	42 (3)
• Autoimmune disease	-	-	-	38 (9)	20 (9)	101 (5)	69 (6)
• Other	-	-	-	35 (8)	17 (7)	538 (27)	339 (27)
• Unknown	-	-	-	34 (8)	13 (6)	112 (6)	66 (5)
Dialysis modality, n (%)							
• Hemodialysis	-	-	-	334 (70)	166 (69)	-	-
• Peritoneal dialysis	-	-	-	78 (16)	42 (17)	-	-
• Unknown	-	-	-	68 (14)	34 (14)	-	-
Dialysis vintage, median (IQR), months	-	-	-	26 (11-50)	24 (11-50)	-	-
Previous transplantation, n (%)							
• Yes	-	-	-	66 (14)	31 (13)	-	-
Time between transplantation and 2nd or	-	-	-	-	-	92 (47-163)	104 (57-171)

3rd vaccination, median (IQR), months							
Time between transplantation and 2nd or 3rd vaccination, n (%)							
• < 6 months	-	-	-	-	-	36 (1)	2 (0)
• ≥ 6 months	-	-	-	-	-	1913 (78)	1210 (78)
• Unknown	-	-	-	-	-	519 (21)	335 (22)
Type of transplant, n (%)							
• DBD	-	-	-	-	-	430 (17)	282 (18)
• DCD	-	-	-	-	-	280 (11)	172 (11)
• Living	-	-	-	-	-	1239 (50)	758 (49)
• Unknown	-	-	-	-	-	519 (21)	335 (22)
Immunosuppressive treatment, n (%)							
• Yes	-	22 (6)	9 (23)	84 (18)	38 (16)	1583 (64)	964 (62)
• No	-	378 (95)	31 (78)	396 (83)	204 (84)	-	-
• Unknown	-	-	-	-	-	885 (36)	583 (38)
Type of immunosuppressive treatment[a], n (%)							
• Corticosteroids	-	17 (4)	6 (15)	66 (14)	31 (13)	1145 (72)	710 (74)
• CNIs	-	5 (1)	1 (3)	39 (8)	19 (8)	1297 (82)	781 (81)
• MMF	-	3 (1)	2 (5)	14 (3)	7 (3)	1029 (65)	609 (63)
• mTOR-inhibitors	-	1 (0)	1 (3)	2 (0)	2 (1)	116 (7)	90 (9)
• Azathioprine	-	5 (1)	2 (5)	3 (1)	2 (1)	166 (11)	97 (10)
• Other	-	-	0 (-)	0 (-)	0 (-)	21 (1)	10 (1)
Two-dose vaccination scheme, n (%)							
• mRNA-1273	186 (100)	273 (68)	-	411 (86)	-	2297 (93)	-
• BNT162b2	-	114 (29)	-	52 (11)	-	117 (5)	-
• AZD1222	-	13 (3)	-	17 (4)	-	54 (2)	-
Three-dose vaccination scheme							
• 3x mRNA-1273	-	-	2 (5)	-	16 (7)	-	99 (6)
• 2x mRNA-1273 – 1x BNT162b2	-	-	19 (48)	-	177 (73)	-	1280 (83)
• 3x BNT162b2	-	-	15 (38)	-	28 (12)	-	79 (5)
• other	-	-	4 (10)	-	21 (9)	-	89 (6)
Time between vaccination and antibody measurement, days, mean (SD)							
• 2nd vaccination to 1st antibody measurement	28 (1)	32 (7)	33 (10)	38 (9)	37 (8)	33 (8)	33 (7)
• 3rd vaccination to 2nd antibody measurement	-	-	37 (8)	-	41 (8)	-	42 (7)
Time between 2nd and 3rd vaccination, days, mean (SD)	-	-	172 (22)	-	177 (19)	-	178 (18)

[a] total numbers and % can vary because of missing values.

CKD: chronic kidney disease, CNIs: calcineurin inhibitors, KTR: kidney transplant recipients, BMI: body mass index, eGFR: estimated glomerular filtration rate, DBD: donation after brain death, DCD: donation after circulatory death, m-TOR inhibitors: mammalian target of rapamycin, MMF: mycophenolate mofetil, PCKD: polycystic kidney disease.

Table 2a: RBD IgG antibody levels after two and three vaccinations in patients with CKD stages G4/5 and dialysis patients categorized by use of immunosuppressive drugs.

	2 vaccinations				3 vaccinations			
		Immunosuppressive treatment				Immunosuppressive treatment		
	All	No	Yes	p*	All	No	Yes	p*
CKD G4/5, n (%)	400 (100)	378 (94)	22 (6)	-	40 (100)	31 (78)	9 (22)	-
RBD IgG Ab level (BAU/ml)	2097 (828-4077)	2186 (887-4160)	1110 (34-2456)	0.003	1551 (459-3225)	1680 (631-3466)	11 (3-739)	0.01
RBD IgG seroconversion rate, n (%)	384 (96)	368 (97)	16 (73)	<0.001	32 (80)	29 (94)	3 (33)	<0.001
RBD IgG antibody level > 1000 BAU/ml, n (%)	286 (72)	275 (73)	11 (50)	0.02	22 (55)	20 (65)	2 (22)	0.03
Dialysis patients, n (%)	480 (100)	396 (83)	84 (18)	-	242 (100)	204 (84)	38 (16)	-
RBD IgG Ab level (BAU/ml)	1375 (431-2896)	1798 (667-3073)	291 (29-748)	<0.001	1727 (570-4254)	2309 (867-4741)	200 (9-1102)	<0.001
RBD IgG seroconversion rate, n (%)	443 (92)	386 (97)	57 (68)	<0.001	222 (92)	199 (98)	23 (61)	<0.001
RBD IgG antibody level > 1000 BAU/ml, n (%)	274 (57)	260 (66)	14 (17)	<0.001	153 (63)	143 (70)	10 (26)	<0.001

* Not using immunosuppressive drugs versus using immunosuppressive drugs.

CKD: Chronic Kidney Disease. RBD: Receptor-Binding Domain, IgG: Immunoglobulin G, Ab: antibody, BAU: Binding Antibody Unit.

Table 2b: RBD IgG antibody levels after two and three vaccinations in KTR categorized by immunosuppressive regimen with or without mycophenolate mofetil.

	2 vaccinations				3 vaccinations			
		MMF				MMF		
	All	No	Yes	p*	All	No	Yes	p*
KTR, n (%)	1583 (100)	554 (35)	1029 (65)	-	964 (100)	355 (37)	609 (63)	-
RBD IgG Ab level (BAU/ml)	66 (8-573)	340 (50-1492)	20 (3-113)	<0.001	259 (26-1008)	437 (74-1445)	165 (16-791)	<0.001
RBD IgG seroconversion rate, n (%)	780 (49)	412 (75)	365 (35)	<0.001	675 (70)	277 (78)	398 (65)	<0.001
RBD IgG antibody level > 1000 BAU/ml, n (%)	263 (17)	182 (33)	81 (8)	<0.001	244 (25)	117 (33)	127 (21)	<0.001

* difference between “MMF yes” and “MMF no”

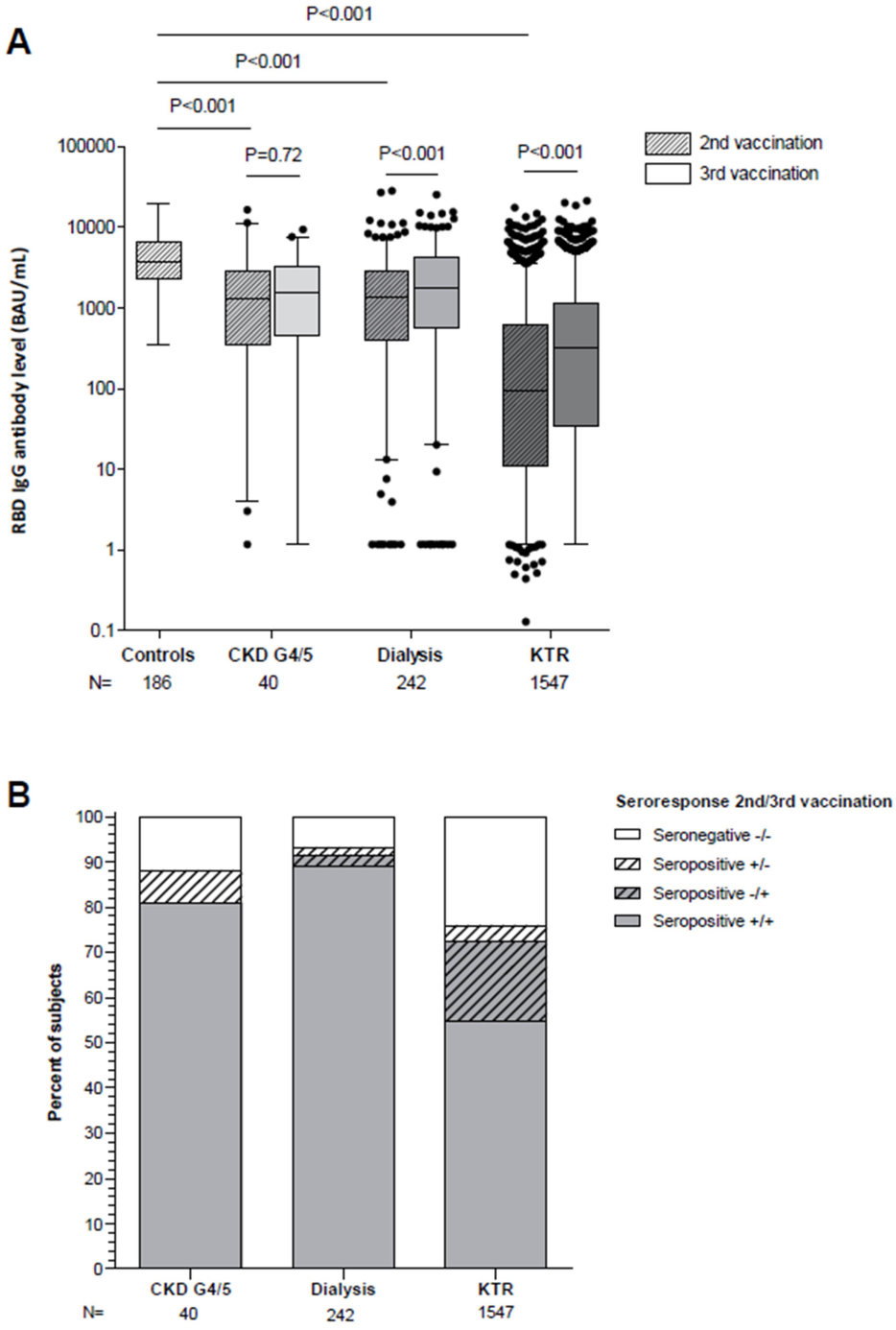
MMF: Mycophenolate Mofetil, KTR: Kidney Transplant Recipient, RBD: Receptor-Binding Domain, IgG: Immunoglobulin G, Ab: antibody, BAU: Binding Antibody Unit.

Table 3: Any adverse events after each SARS-CoV-2 vaccination in control subjects, patients with CKD G4/5, dialysis patients and kidney transplant recipients.

	mRNA-1273			BNT162b2			AZD1222	
	1	2	3	1	2	3	1	2
Controls, n (%)	166 (89)	175 (94)	-	-	-	-	-	-
CKD G4/5, n (%)	219 (80)	229 (84)	2 (100)	46 (40)	38 (33)	16 (44)	8 (62)	4 (31)
Dialysis, n (%)	254 (62)	245 (60)	8 (50)	13 (25)	11 (21)	84 (39)	8 (47)	7 (41)
KTR, n (%)	1723 (75)	1455 (63)	50 (50)	45 (38)	42 (36)	599 (43)	32 (59)	17 (36)

CKD: Chronic Kidney Disease, KTR: Kidney Transplant Recipients.

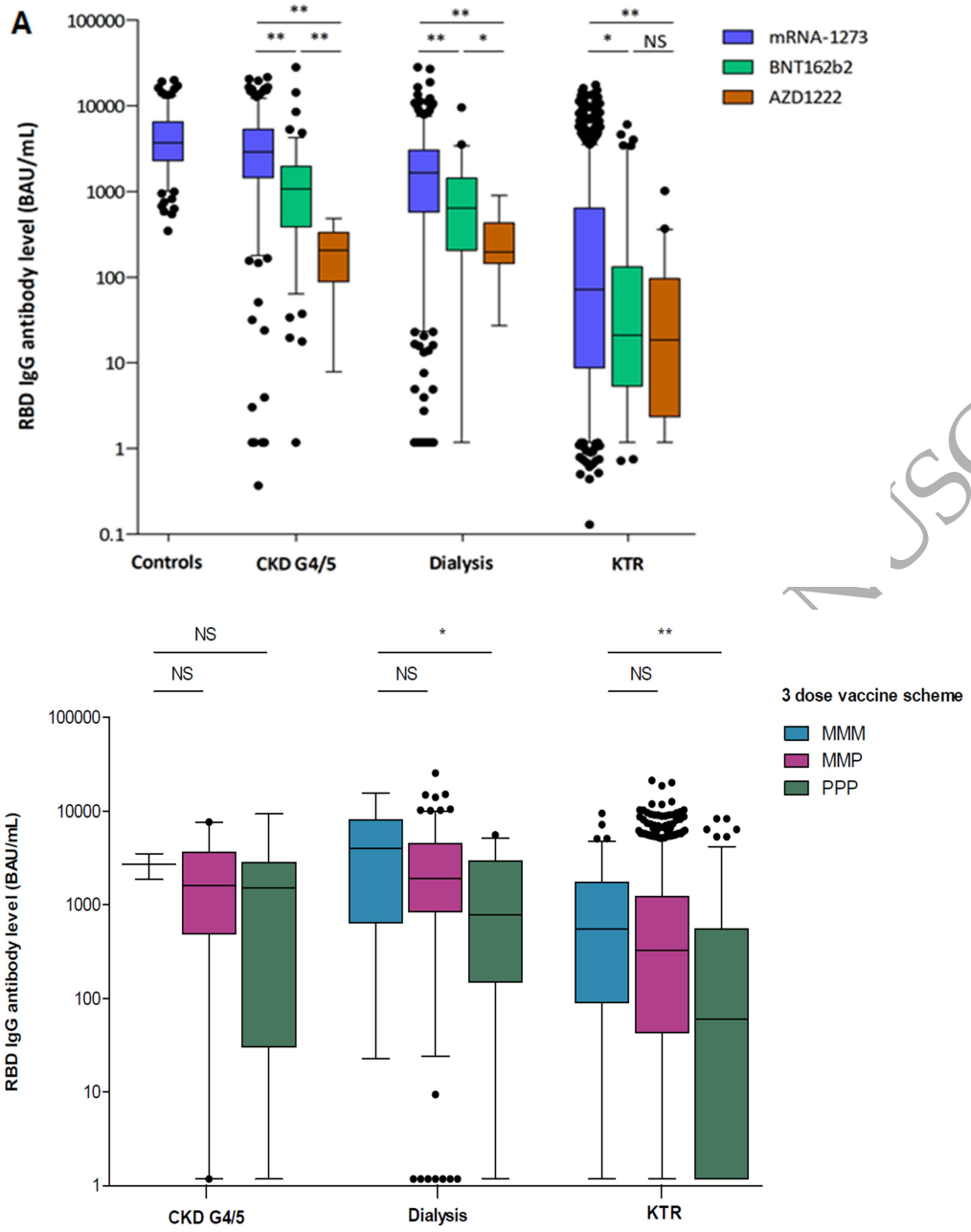
Figure 1: RBD IgG antibody levels (A) and seroconversion rates (B) after two and three SARS-CoV-2 vaccinations.



RBD: Receptor Binding Domain, IgG: Immunoglobulin G, BAU: Binding Antibody Unit. CKD: Chronic Kidney Disease. KTR: Kidney Transplant Recipient.

These figures describe antibody levels and response rates in patients with CKD G4/5, dialysis patients, and KTR who have data available on the first two vaccinations, and the third vaccination.

Figure 2: RBD IgG antibody levels after two vaccinations (A) and three vaccinations (B) in different patient groups categorized per vaccine type.



** p≤.01 **p≤0.001. RBD: Receptor Binding Domain, IgG: Immunoglublin G, BAU: Binding Antibody Unit, MMM: mRNA-1273 3x, MMP: mRNA-1273 2x – BNT162b2, PPP: BNT162b2 3x.*