The Impact of COVID-19 Third Dose Vaccination on the Magnitude of Antigen Specific T Cells in Kidney Transplant Patients

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Summary

Measuring T cell response can add information about antivirus immunity provided by antibody test results. The study evaluates the impact of a third mRNA COVID-19 vaccine dose on T cell response and antibody production in kidney transplant recipients (25 KTRs) versus healthy controls (26 Hc). Results show a significant rise in S-activated CD4+CD154+IFNγ+TNFα+ double producer cells in both KTRs ($p=0.025$) and Hc ($p=0.009$) as well as increased spike antibody response in KTRs ($p=0.00019$) and Hc ($p=3.10^{-8}$) third-month post-third dose. Moreover, the study revealed a drop in seronegative KTRs (non-responders) from 9/25 (36%) pre-third dose to 2/25 (7%) at 3 months post-third dose while 5/9 (56%) of non-responders post-second dose showed specific T cell responses. Notably, the third dose significantly improved seroconversion rates in both KTRs and Hc, although Hc individuals exhibited higher antibody levels.

Key words

mRNA COVID-19 vaccine • T cells • SARS-CoV-2 antibodies • Kidney transplantation • mRNA vaccination

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Introduction

In the era of the COVID-19 pandemic, understanding the efficacy of vaccines, especially in immunosuppressed populations like kidney transplant recipients (KTRs), has become crucial. The response of KTRs to COVID-19 vaccination is notably different from that of healthy individuals; while antibody response reaches approximately 96% detectability in healthy individuals, it is measurable in less than half of the KTRs after the second dose of the vaccine [1].

The persistence of antibody responses is also a key area of investigation. Findings from Ciao and Le Bert group [2] indicate that antibody responses to coronaviruses can diminish over time, with a significant decline in detectability within a few years. This observation has shifted focus towards T cell-specific immunity, which appears to offer longer-lasting protection. Recent publications have highlighted not only the presence of virus specific T cells capable of producing a single cytokine but also those capable of multiple cytokine production. Whereas the exact role of multifunctional T cells is not completely understood, they might contribute to a better protection given that quantities are elevated in individuals experiencing mild as compared to severe SARS-COV2 infections [3].

Our study investigates the impact of a third dose of an analogous mRNA vaccine on the levels of total specific T cell responses as well as antibodies against SARS-CoV-2, in kidney transplant recipients and healthy

controls. This research aims to provide a detailed understanding of both cellular and humoral immune responses to the vaccine in these distinct groups [4].

Methods

Patients

Between October 2021 and March 2022, 27 Kidney Transplant recipients (KTRs) and 26 Healthy controls (Hc) were included in the study. Two KTRs were later excluded from the study after the record of the experienced COVID-19 was found. None of Hc experienced COVID-19 before the third vaccine dose (confirmed based on the data from the Infectious Disease Information System (ISIN) database).

KTRs were enrolled consecutively from patients attending the outpatient care in our hospital who came to be vaccinated with the third vaccine dose. Kidney transplantation was performed at a median of 10.08 years (2.73-24.5) before blood collection. As a third dose, the Comirnaty® vaccine was used in all patients (BioNTech/Pfizer, Mainz, Germany). Of the 25 KTRs, 9 were previously vaccinated with two doses of Spikevax® (Moderna, Cambridge, Massachusetts), and two were previously vaccinated with two doses of ChAdOx1 (Astra Zeneca, Oxford, England), the first and second vaccination was dependent on the patient's domicile hospital.

As a healthy control group (Hc) we used blood samples from 26 volunteers, mainly healthcare professionals from our hospital. All of the Hc group volunteers were vaccinated in our hospital with three doses of Comirnaty® vaccine (BioNTech/Pfizer, Mainz, Germany). Seven Hc and 3 KTRs experienced COVID-19 after the third vaccination (confirmed based on ISIN database, Table 2). Patients and volunteers' variables are to be found in Table 1. The complete study design is illustrated in Figure 1.

Table 1. Demographic data of patients

	Hc (n=26)	**KTRs (n=25)**	**p**
Age (years ± SD)	46.6 (9.9)	55.4 (11.4)	*0.005*
Male (n, %)	10 (38 %)	17 (68 %)	*0.034*
Time since Tx (yrs, median (min-max))		10.08 (2.73-24.5)	
Deceased donor (n, %)		18 (72 %)	
Immunosuppression			
Tac+CS+MMF (n, %)		13 (52 %)	
Tac+CS (n, %)		7 (28 %)	
CsA+CS (n, %)		2 (8 %)	
mTOR+CS+MMF (n, %)		3 (12 %)	
Induction (n, %)		23 (92 %)	
eGFR at D0		0,83	
Rejection 3D-3M (n, %)		0 (0 %)	
IgG 3D (U/mL, median (min-max))	84.5 (3.5-1386)	33.7 (3.5-1925)	
IgG 3M (U/mL, median (min-max))	1925 (226-3740)	327 (3.5-6080)	
IgG negative before 3rd vaccine dose (n, %)	1 (4 %)	9 (36 %)	*0.007*
IgG negative after 3rd vaccine dose (n, %)	0 (0 %)	2 (7 %)	*0.16*
Sars-coV-2 within 3 months after 3rd vaccination (n, %)	6 (27 %)	3 (12 %)	*0.502*
blood withdrawal after 3rd vaccine dose (days, median (min, max))	90.5 (59-98)	91 (91-95)	
Vaccination scheme			
3*BNT162b2	25 (96 %)	14 (56 %)	*0.002*
2*mRNA-1273 + 1*BNT162b2	1 (4 %)	9 (36 %)	*0.011*
2*ChAdOx1 + 1*BNT162b2	0	2 (8 %)	*0.45*

Tx-transplantation; Tac-Tacrolimus; CsA-Cyclosporin A; MMF-mycofenolate mofetil, mTOR-mammalian target of rapamycin; eGFR-estimated glomerular filtration rate, 3rd-third

Table 2. Data of COVID positive patients

Group	Initial Vaccine	Third Vaccine	Age (years)	Gender	Time from Tx (years)	IS	IgG before Dose 3	IgG after Dose 3	COVID+ post 3rd vaccination (days)	COVID+ treatment
Tx	BNT162b2	BNT162b2	56	F	25	*CsA+CS*	*3,5*	*274*	*59*	Molnopuravir
Tx	BNT162b2	BNT162b2	63	M	17	*Tac+MM F+CS*	*3,5*	*191*	*82*	Molnopuravir
Tx	Moderna	BNT162b2	52	M	8	*Tac+MM F+CS*	*33,7*	*5040*	*69*	*not treated*
control	BNT162b2	BNT162b2	39	F			*53,8*	*2080*	*63*	*not treated*
control	BNT162b2	BNT162b2	45	F			*39,9*	*3340*	*3*	*not treated*
control	BNT162b2	BNT162b2	47	M			*3,5*	*2080*	*62*	*not treated*
control	BNT162b2	BNT162b2	51	F			*146*	*1046*	*8*	*not treated*
control	BNT162b2	BNT162b2	64	M			*58,3*	*226*	*84*	*not treated*
control	BNT162b2	BNT162b2	32	F			*123*	*800*	*75*	*not treated*
control	BNT162b2	BNT162b2	46	M			*92,4*	*2580*	*47*	*not treated*

Tx-transplantation; Tac-Tacrolimus; CsA-Cyclosporin A; CS-Corticosteroids; IS, immunosuppression; MMF-mycofenolate mofetil, mTOR-mammalian target of rapamycin; eGFR-estimated glomerular filtration rate, 3rd-third

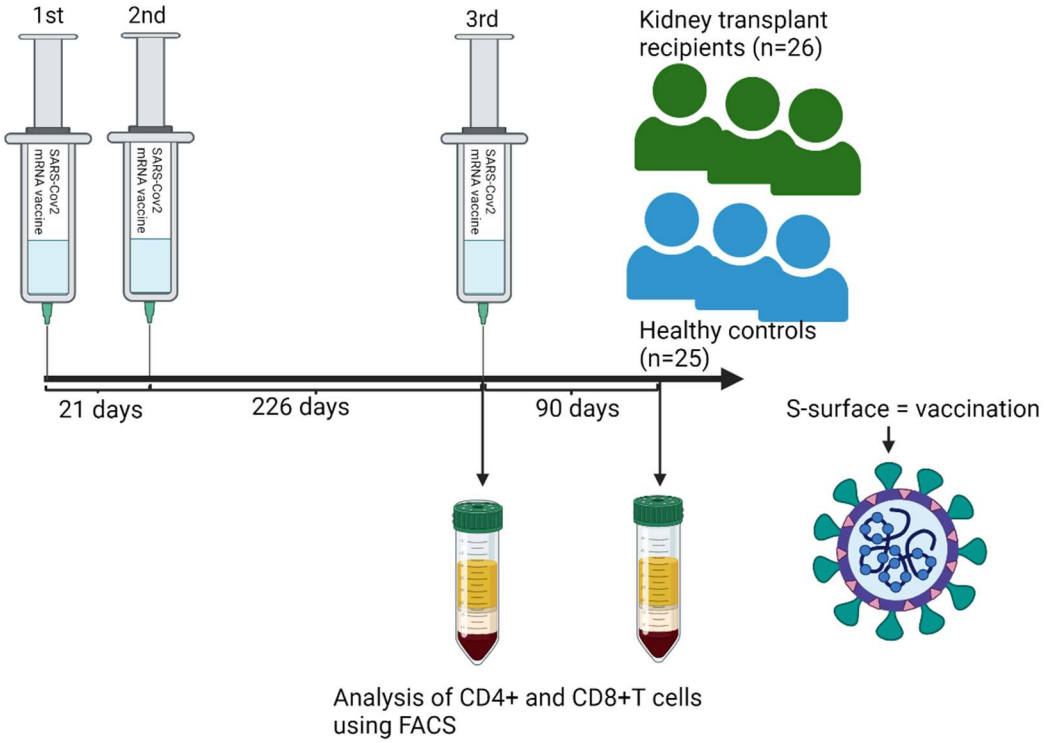

Fig. 1. Study design. Schematic timeline of the study; n, number of samples. 26 Kidney Transplant (KTRs) patients and 25 Healthy controls (Hc) were included in the study. Blood samples for antibody measurement and PBMC isolation were collected several hours before the third dose vaccination and 3 months after the third dose.

Safety

The study was approved by the Ethical Committee of IKEM number 30054/21; G-21-71. All patients and volunteers provided written informed consent.

Blood withdrawal and PBMC isolation

Peripheral blood was collected in Vacuette tube NH Sodium (Greiner, Austria). Collected blood was prediluted in phosphate-buffered saline (PBS/BSA) at a 1:1 ratio and isolated using the standard Ficoll-Hypaque

density gradient technique (GE Healthcare Bio-Sciences, Chicago, IL, United States). After isolation, PBMCs were cryopreserved in liquid nitrogen at the final concentration of 5-10 x 10^6 cells. In the final cryopreservation medium, the concentration was 10% DMSO (dimethyl sulfoxide), 40% heat-inactivated FCS (Fetal calf serum) and 20% RPMI.

PBMC thawing

The cryopreserved PBMCs (peripheral blood mononuclear cells) were thawed by incubating cryovials for 5 minutes at 37 °C in a water bath, washed twice in 37 °C RPMI 1640 medium (Life Technologies, USA) supplemented with 20% human AB serum (Merck, Darmstadt, Germany), 1% penicillin-streptomycin-glutamine (Sigma−Aldrich, USA) and 1% DNAseI (Merck, Darmstadt, Germany) and rested for 16 hours at 37 °C.

PBMC stimulation

Cells were washed, counted, and placed 10^6 per well in a 96-well plate. PBMC were stimulated for 6 hours with PepTivator® SARS-CoV-2 Prot_S at final amount of 0.06 nmol (Miltenyi Biotec, Germany) or left unstimulated (negative control) or stimulated with positive control (Cytostim™) (Miltenyi Biotec, Germany). After 2 hours, Brefeldin A was added to the culture to block the secretion of cytokines and effector molecules.

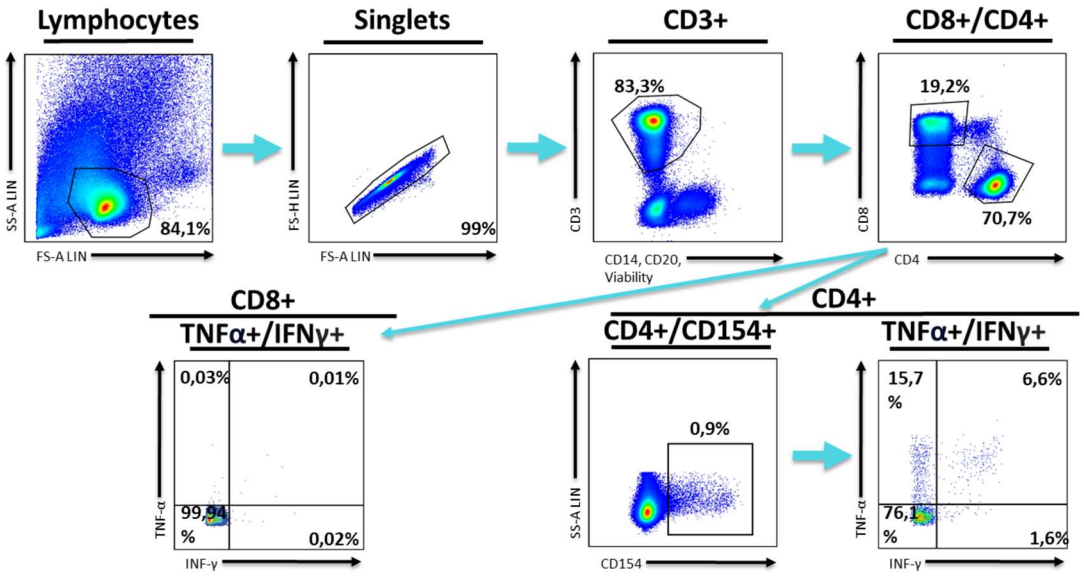

Fig. 2. Gating strategy. Gating strategy for the analysis of SARS-CoV-2 specific T cells. Lymphocytes were gated for size and granularity, doublets were excluded. Later CD3+ cells were gated based on viability, CD14 and CD20 negativity. CD4+ were gated on activation marker CD154+ and percentage of activated cells was inspected for TNFa+ and IFNg+ producers. CD8+ cells were inspected for TNFa+ and IFNg+ single and double producers.

Staining

Living single lymphocytes were analyzed for expression of CD3, CD4, and CD8. CD4+ T cells were analyzed for the expression of activation marker CD154. Both, CD4+ and CD8+ T cells were analyzed for expression of 2 cytokines: interferon γ (IFNγ), tumor necrosis factor α (TNFα). For the intracellular cytokine staining the permeabilization was performed using the Milteney Biotec Insidefix/InsidePerm™ solution according to the manufacturer's instructions. The gating strategy is to be seen on Figure 2.

Flow cytometric analysis

Data was acquired with the three laser, 10-color Navios™ Flow cytometer (Beckman Coulter, Marseille, France) with a blue diode Argon laser (488 nm, 22 mW), red diode Helium/Neon laser (638 nm, 25 mW) and violet air-cooled solid-state diode laser (405 nm, 50 mW). We have used MACS Comp Bead Kit, consisting of antibody-capture beads for our fluorescence compensation (Miltenyi Biotec, Germany, Single stains for IFNγ and TNFα, Fig. 6). A minimum of 400.000 relevant events were acquired per sample, while we aimed at acquiring 500.000 events per sample.

SARS-CoV-2 Neutralizing Antibody Measurement

Study subjects were tested for SARS-CoV-2-specific antibodies using LIAISON SARS-CoV-2 S1/S2 IgG chemiluminescence immunoassay (DiaSorin S.p.A.). This assay contains paramagnetic microparticles coated with spike proteins S1 and S2. According to previously published methodological procedures concerning the measurement methods [5,6] the method was validated using stored frozen samples obtained from subjects before the SARS-CoV-2 pandemic (n = 41) and from patients with SARS-CoV-2 infection verified by RT-PCR (n = 34). The optimized cut off (9.5 arbitrary units (AU/ml) with test sensitivity 91.2% (95% CI 76.3–98.1) and specificity 90.2% (95% CI 76.9–97.3) was determined using MedCalc Statistical Software version 19.1.

Quantification and statistical analysis

FACS data were analyzed in Flow Jo, version 7 (BD Biosciences, USA). The gating strategy is illustrated on Figure 2. Frequencies of SARS-CoV-2 specific CD4+ T cells expressing IFNγ+, TNFα+ or both (bifunctional) CD4+CD154+ T cells were calculated. Antigen-reactive responses were considered positive after the nonreactive background was subtracted with the use of negative controls. Negative values were set to zero.

Although there was no difference in the number of lymphopenic individuals, the variability in lymphocyte counts within groups was high. Therefore, the absolute number of S specific lymphocytes was calculated based on the ratios from FACS and the knowledge of the number of lymphocytes per L.

Statistics

Data were presented as medians with min, and max for continuous variables and counts with percentages for categorical variables. Continuous variables were compared by the Mann-Whitney U test and categorical variables by Pearson's chi-squared test. Paired measurements were compared by Wilcoxon signed rank test. P values of < 0.05 were considered significant. Statistical analysis was performed using R-studio version 4.2.2. (2022-10-31).

Results

Demographic data

Median ± min, max for the descriptive variables in the healthy controls and kidney transplant patients are shown in Table 1. Transplanted patients were significantly older (p=0.005) and had a lower proportion of patients vaccinated with three doses of Comirnaty® vaccine (BioNTech/Pfizer, Mainz, Germany). In the KTRs group, more patients were vaccinated twice with Spikevax® (Moderna, Cambridge, Massachusetts) and a third time with Comirnaty® vaccine (p=0.011).

S+ Activated lymphocytes

A significant increase was seen in the magnitude of double-producing S-reactive CD4+CD154+ IFNγ+TNFα+ T lymphocytes in KTR (p=0.025) as well as in the Hc group (p=0.009) after the third dose as visualized in Fig. 3.

Considering only the seronegative KTRs (n=9) after the 2nd dose, five patients already had detectable S-reactive CD4+CD154+ T lymphocytes before the third vaccination.

There was no significant difference in the magnitude of total S-reactive CD4+CD154+ cells neither before (3D, p=0.1244) nor 3 months after (3M, p=0.9244) vaccination between KTRs and Hc group.

There was no significant difference in the magnitude of total S-reactive CD4+CD154+ IFNγ+TNFα+ cells neither before (3D, p=0.2555) nor three months after (3M, p=0.1639) vaccination between KTRs and Hc group.

There was no difference in the magnitude of different subpopulations of CD8+ T lymphocytes in the KTRs and Hc groups after the third dose of vaccination.

Humoral response after third dose of vaccine

There was a significant increase in the levels of the anti-spike IgG levels after the third dose vaccination in KTRs (p = 3e-0.08) as well as in the Hc group (p = 0.00019) (Fig. 4).

When we compared the total anti-spike IgG levels between KTRs and Hc subjects, a significant difference was found at third month after the booster dose, with the higher production detected in the Hc group (p = 0.001) (Fig. 4).

The only individual showing seronegativity in the Hc group converted after the third vaccine dose. Out of nine seronegative KTRs, two remained seronegative even after the third vaccine dose.

In the Hc group, 6 volunteers experienced Covid after the third vaccination (Covid-negative group). The increase in antibody titer was seen in the Covid-negative group (p<0.001) as well as in the Covid-positive group (p=0.031) (Fig. 5).

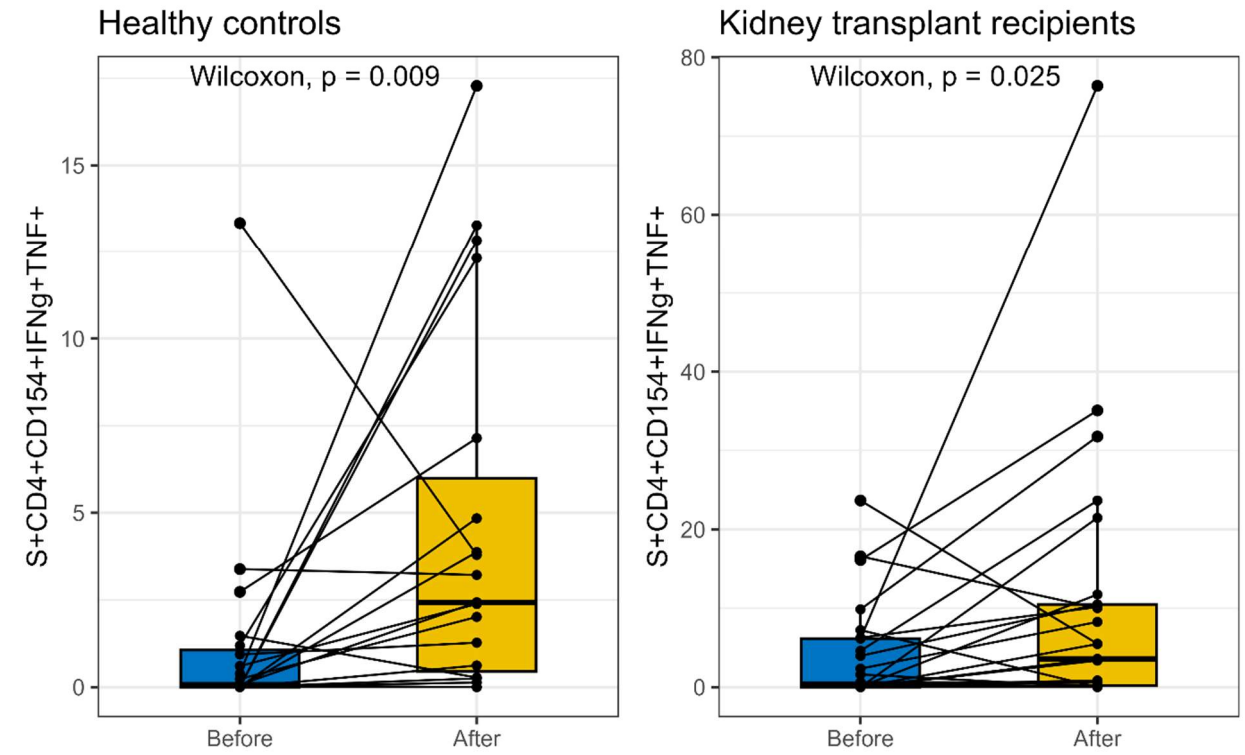

Fig. 3. S-reactive CD4+CD154+IFNg+TNF+ T cell response. Measurement of S-reactive CD4+CD154+IFNg+TNF+ T cell response in healthy controls and kidney transplanted patients before third vaccine dose (Before) and 3 months after 3dr vaccine dose (After).

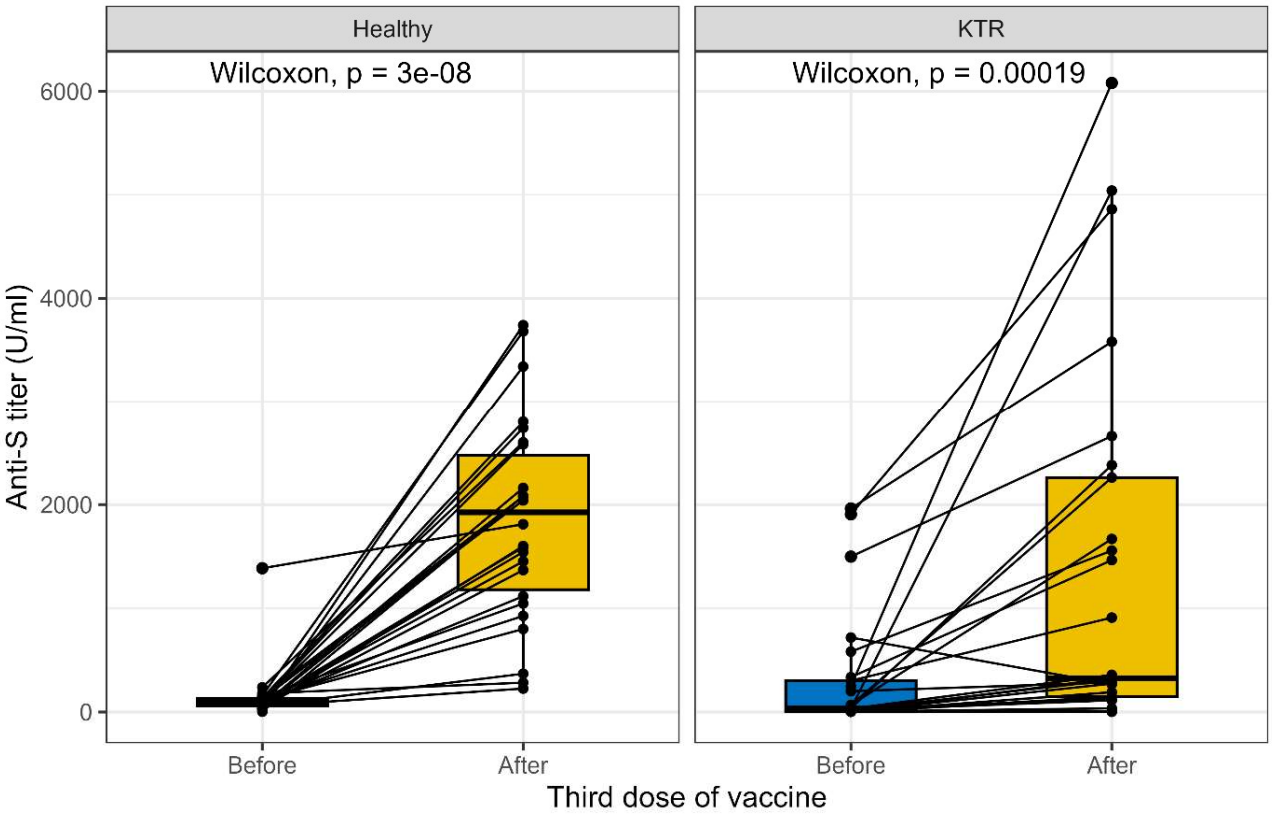

Fig. 4. Humoral spike antibody response. Measurement of anti SARS-CoV2 Ig in serum of healthy controls and kidney transplanted patients before third vaccine dose (Before) and 3 months after third vaccine dose (After).

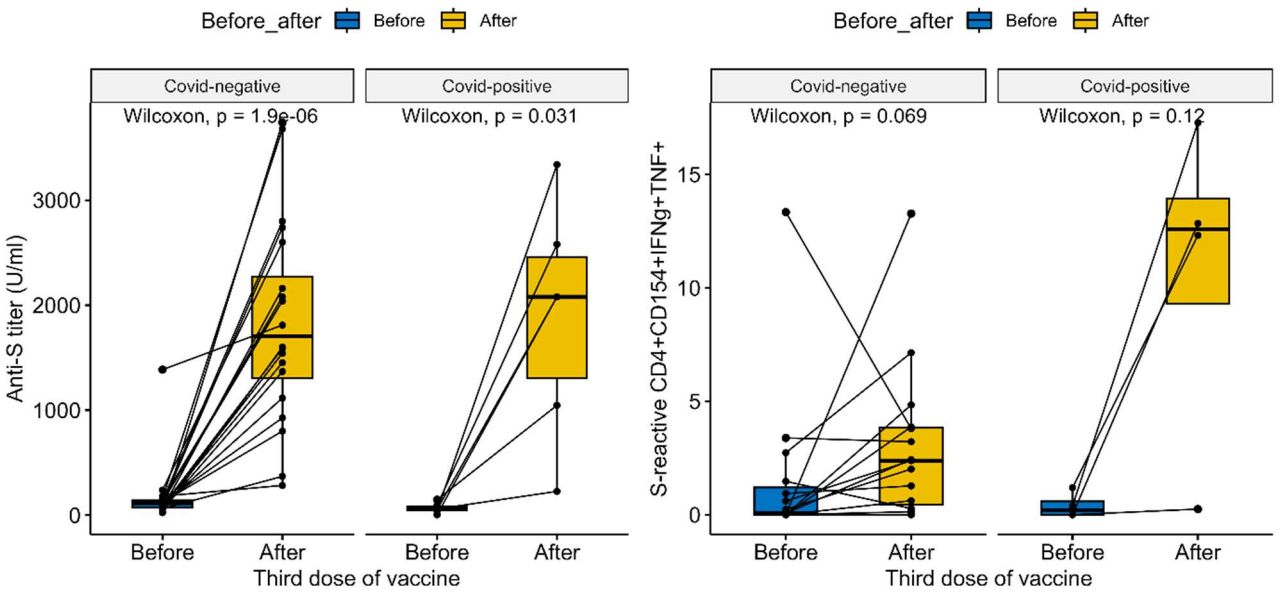

Fig. 5. Covid negative/positive healthy controls before and after the third dose of vaccine. (**A**) Humoral spike antibody response (**B**) S-reactive CD4+CD154+IFNγ+TNF+ T cell response. The group of healthy controls (Hc) divided into those who experienced covid after the third dose of vaccination (n=6) and who did not (n=20).

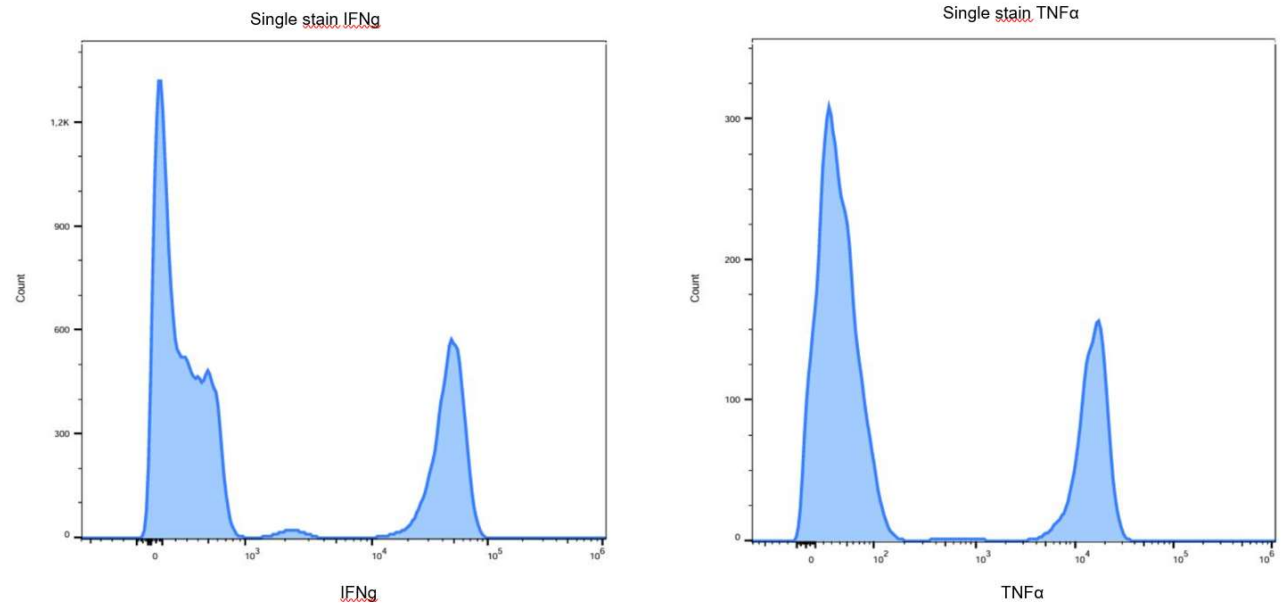

Fig. 6. Single stain control for compensation of IFNγ and TNFα.

Discussion

This study presents critical insights into the immune response to COVID-19 vaccination in kidney transplant recipients (KTRs), comparing them with healthy controls (Hc). Our findings align with recent studies highlighting the nuanced immune responses in immunocompromised populations, especially after vaccination [7-9].

The significant increase in S-reactive CD4+CD154+IFNγ+TNFα+ T lymphocytes in both KTRs and Hc group post-third vaccine dose mirrors findings by Westhoff [10] and [1] emphasizes enhanced cellular immunity following booster vaccinations. Grupper at al. reported enhanced antibody response and T cell reactive response to S-protein in a larger cohort of the slightly older population than we did [1]. Westhoff *et al.* showed a percentage increase in CD4+ S-specific T cells after the third dose, although with a wide range of responses in the small number of kidney recipients [10]. The studies showed that the most effective memory T cells are thought to produce high levels of a range of

cytokines, termed poly or multifunctional T cells [1,11]. The enhanced cellular immunity observed in S-reactive CD4+CD154+IFNγ+TNFα+ T lymphocytes by Guo *et al.* post-third vaccine dose, underscores the pivotal role of polyfunctional T cells, particularly those expressing both interferon γ and tumor necrosis factor α, in providing robust protection against SARS-CoV-2 [11]. Polyfunctional S-reactive T cells have been identified not only in the bloodstream of vaccinated individuals but are even more prevalent within the tissues [3].

Stratification for non-responders (seronegative KTRs) and responders of the standard two doses of vaccination based on their seropositivity in our study showed measurable levels of cellular immunity even in the seronegative population as well as in the work of Grupper [1]. These results are adding information to the essential question whether there is a protective capacity of CD4+ T cells in patients who fail to demonstrate SARS-CoV-2 Spike-IgG response [11,12].

In the current study, the third dose vaccination significantly increased the seroconversion rates that is consistent with multiple studies generally showing improved response to a third booster vaccine [13-16]. Immune response presented higher variability in kidney transplant patients than healthy controls, with nine seronegative (Anti S-titer ≤3.5U/ml) KTRs before the third vaccine compared to one in the Hc group. The unique seronegative person seroconverted in the control group after the third vaccine dose. The post-booster seropositivity rates were 88% and 100% for the KTRs and Hc, respectively. In the KTR two patients remained seronegative after three vaccine doses, potentially due to the profound impact of their immunosuppressive treatments, or other factors like kidney function status, age, and specific immune system characteristics such as thymic function and inflammatory status, which have been shown to influence the humoral response to vaccination [17,18]. Specifically, we noted that one patient received a reduced level of immunosuppression due to recurrent infections, while the other followed a standard protocol.

Contrary to our results, Thieme *et al.* [19] showed a response not only in CD4+ T cell pool but also to CD8+ T cell pool. The data suggest that the differential antibody titers, particularly the higher anti-spike IgG levels in Hc individuals compared to KTRs, indicate a disparity in vaccine-induced immunity among populations with varying degrees of immune competence. It might reflect the different timeframe of the study.

Furthermore, Sattler *et al.* clearly showed that the second dose of the BNT vaccine has little or almost no impact on specific antibody levels. Moreover, KTRs had lower concentrations of interleukin-2, interleukin-4, and interferon gamma -producing cells. Studies by [20] and [21] highlight the importance of examining varied immune responses across different vaccine types and dosing intervals.

Our study's limitations include a relatively small sample size, which could affect the generalizability of findings. Furthermore, it is important to acknowledge that our data may not fully capture all COVID-19 cases due to the prevalence of asymptomatic infections and under-reporting [22]. This limitation could influence the interpretation of our results, as these unreported cases may contribute to an incomplete understanding of the immune response to COVID-19 vaccination among KTRs and healthy controls. Additionally, early research suggests that mRNA vaccines may induce a stronger immune response in some immunocompromised populations, including kidney transplant recipients, compared to viral vector vaccines. However, the degree of response is still lower than in individuals with a healthy immune system [5,23]. Future research should focus on larger cohorts, to validate these observations.

In summary, our study adds to the growing body of literature on vaccine responses in immune-compromised individuals.

Author contribution

EG, PH and OV designed the study. EG, PH, JM and PM collected the samples and isolated PBMCs. EG JM, and PH performed the stimulation and FASC analysis. MF performed the IgG measurement. EG, PH and OV performed statistical analysis and prepared the manuscript.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

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Abbreviations

KTRs, kidney transplant recipients; Hc, Healthy control group; 3D, day of third vaccine dose, 3M, three months after third vaccine dose; S, spike protein; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2.

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