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Seroconversion rates in kidney transplant recipients following SARS-CoV-2 vaccination and its association with immunosuppressive agents: a systematic review and meta-analysis

Maria Riastuti Iryaningrum[1], Alius Cahyadi[1], Fachreza Aryo Damara[2], Ria Bandiara[3], Maruhum Bonar Hasiholan Marbun[4]

[1]Department of Internal Medicine, School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Jakarta; [2]Dr Hasan Sadikin Hospital, Faculty of Medicine, Universitas Padjadjaran, Bandung; [3]Department of Internal Medicine, Dr Hasan Sadikin Hospital, Faculty of Medicine, Universitas Padjadjaran, Bandung; [4]Department of Internal Medicine, Cipto Mangunkusumo Hospital, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

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Corresponding author: Fachreza Aryo Damara, MD
Dr Hasan Sadikin Hospital, Faculty of Medicine, Universitas Padjadjaran, 38th Eyckman, Bandung, West Java 40161, Indonesia
Tel: +62-022-84288888, Fax: +62-022-84288888
E-mail: fachrezaaryo21@gmail.com; fachreza15002@mail.unpad.ac.id

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This systematic and meta-analysis aims to evaluate humoral and cellular responses to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine among kidney transplant recipients (KTRs). We conducted a systematic literature search across databases to evaluate seroconversion and cellular response rates in KTRs receiving SARS-CoV-2 vaccines. We extracted studies that assessed seroconversion rates described as the presence of antibody *de novo* positivity in KTRs following SARS-CoV-2 vaccination published up to January 23rd, 2022. We also performed meta-regression based on immunosuppression therapy used. A total of 44 studies involving 5,892 KTRs were included in this meta-analysis. The overall seroconversion rate following complete dose of vaccines was 39.2% (95% confidence interval [CI], 33.3%–45.3%) and cellular response rate was 41.6% (95% CI, 30.0%–53.6%). Meta-regression revealed that low antibody response rate was significantly associated with the high prevalence of mycophenolate mofetil/mycophenolic acid (p=0.04), belatacept (p=0.02), and anti-CD25 induction therapy uses (p=0.04). Conversely, tacrolimus use was associated with higher antibody response (p=0.01). This meta-analysis suggests that postvaccination seroconversion and cellular response rates in KTRs are still low. And seroconversion rate was correlated with the type of immunosuppressive agent and induction therapy used. Additional doses of the SARS-CoV-2 vaccine for this population using a different type of vaccine are considered.

Keywords: Kidney transplant, SARS-CoV-2, Seroconversion, Transplantation, Vaccine

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has become one of the major problems worldwide for the past years. Extensive investigations have been undertaken to explore the characteristics of infection and possible intervention and prevention strategies within a specific group of the population. Kidney transplant recipients (KTRs) are among one of the most vulnerable populations to the SARS-CoV-2 infection poor outcomes. The mortality rate of SARS-CoV-2 infection in KTRs was 20%–40% [1,2]. Moreover, the risk of death increases with age and comorbidities [2-4].

Vaccination programs have been prioritized in many countries to reduce the risk of

SARS-CoV-2 infection-related adverse outcomes. Trials have been conducted to evaluate the vaccine's safety and efficacy and yet, KTRs were mostly excluded from the analysis [5,6]. Several studies that evaluate immunogenicity rates in the KTRs population have been published. However, postvaccination humoral and cellular response rates have not yet been reviewed systematically. Further, whether any factors substantially contribute to these immune responses remains elusive.

The primary objective of this systematic review and meta-analysis was to evaluate postvaccination seroconversion rates in KTRs. In addition, we also aimed to determine the contributing factors to the immune response from an essential set of variables with regard to baseline characteristics and immunosuppressive agent, and induction therapy used to be reported for studies to establish adequate SARS-CoV-2 vaccination strategies for KTRs.

Materials and Methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline [7]. This study protocol has also been registered in PROSPERO (CRD42022303956).

Search strategy and eligibility criteria

Two reviewers (M.R.I. and F.A.D.) systematically searched for relevant articles published up to January 23rd across Medline (PubMed) and EMBASE databases. Search strategies were designed with specific keywords to retrieve articles related to the SARS-CoV-2 vaccine immune response rate in KTRs (Supplement 1). We used the "related articles" feature and hand-searched the reference lists of the included articles to expand the search and obtain additional studies. Duplicate results were removed after the initial search.

The PICO (population, intervention, comparison or control, and outcome) structure design, outcomes definitions, and the subgroup of interest were established among authors prior to data collection [8]. We included all research articles on the KTR population receiving any kind of SARS-CoV-2 vaccine. Studies that met the criteria of reporting postvaccination antibody and/or cellular response were included in further analyses. Studies that reported the outcomes of the third dose (boost dose) of vaccine were excluded in this present study. Queries regarding the eligibility of the study were resolved by consensus. We did not apply any language or geographic restriction to the article selection process.

Outcome measurements

The primary outcome of this study was humoral immunogenicity rates after a complete dose of vaccination among KTRs. Humoral response rates were extracted from the data on de novo positivity of neutralizing antibody, anti-SARS-CoV-2 spike receptor-binding domain, or either immunoglobulin (Ig)G or IgA anti-spike protein that indicated above-normal quantification results. The secondary outcome was cellular response rates of KTRs following SARS-CoV-2 vaccination as defined by vaccine-induced *de novo* T-cellular immunity.

Data extraction

Data extraction was carried out independently by two authors (M.R.I. and F.A.D.). For each study, we extracted basic information using standardized forms that included author, date of publication, study design, study setting, sample size, sex, and age. In addition, the following relevant variables were also extracted; diagnostic modalities, numbers of subjects with prior SARS-CoV-2 infection, transplantation vintage, type of vaccine received, vaccination protocol, length of the follow-up period, type of immunosuppressive agents used, and type of induction therapy used by the KTRs.

For each cohort study, two reviewers (N.N.M.S. and F.A.D.) independently assessed the quality of cohort studies using the Newcastle-Ottawa scale (NOS) that contained predefined criteria covering three major domains; quality of the selection, comparability, and the outcome of study populations. A study was rated as low risk of bias if it scored 7 to 9, moderate risk if it scored 4 to 6, and high risk of bias if it scored less than 4 points on NOS [9].

Statistical analysis

The proportion of postvaccination humoral and cellular immunity in KTRs from the included studies was summarized using the DerSimonian-Laird random-effects model. The heterogeneity of the pooled estimate was assessed using I^2 statistic where a variation in outcome greater than 50% was considered to derive from heterogeneity [10]. To explore the potential source of heterogeneity, we performed subgroup analyses using mixed effects models on the following subsets; complete and incomplete vaccination protocols, and population with a previous history of SARS-CoV-2 infection and without prior SARS-CoV-2 infection. Further, we also conducted a restricted-maximum likelihood random-effects me-

ta-regression analysis to investigate the influence of the following covariates—sex, age, time since transplant to first vaccine dose, immunosuppressive therapy used, and induction therapy used.

Analyses of publication bias were done by initially using a funnel plot to screen for asymmetry in detecting publication bias and followed by a formal statistical test using Egger's linear regression test to indicate small-study effects [11,12]. Sensitivity analysis was performed under the leave-one-out method to single out the cause of study heterogeneity and statistical significance. All statistical analysis was performed using R ver. 4.0.4 (The R Foundation, Vienna, Austria).

Results

Search results

A literature search across Medline (PubMed) and EMBASE databases resulted in 542 potentially eligible studies (Fig. 1, Supplement 2). Titles and abstracts were initially screened followed by full-text reviews to further determine study eligibility. Of 64 studies that were included for full-text review, a total of 44 publications were included in our present analyses after the exclusion of irrelevant studies that did not report the outcome of interest [13-56] (Table 1).

Study characteristics

A total of 5892 KTRs were included in this present meta-analysis. The mean of age of the study participants was 57.8 years with 62.1% of them were male. The type of vaccine administered in this study was varied—BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), ChAdOx1 nCoV-19 (AstraZeneca), Ad26.CoV2.S (Johnson & Johnson), and whole-virion inactivated SARS-CoV-2 vaccine (CoronaVac). The mean time from kidney transplant to first dose vaccination was 6.97 years ranging from 1.65 to 13 years. All included studies had a low to moderate risk of bias (Supplement 3).

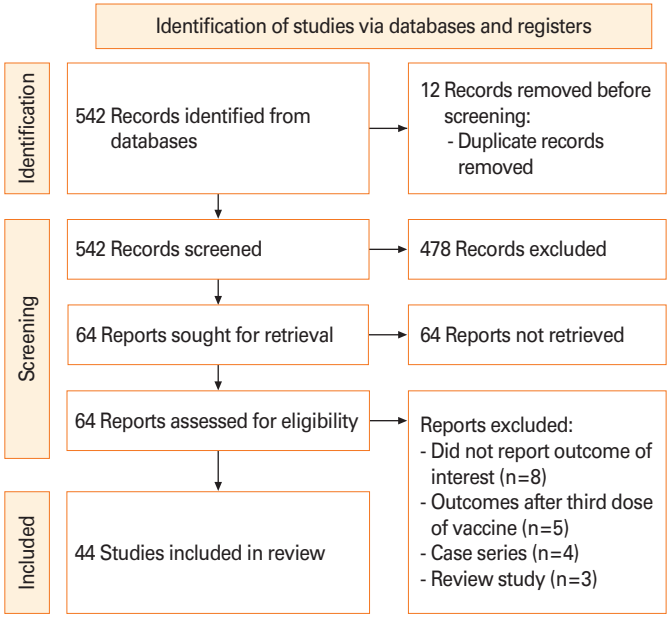

Fig. 1. Study inclusion flowchart.

Postvaccination seroconversion and cellular response rates

Our pooled analyses showed that the overall seroconversion rate in KTRs was 39.2% (95% confidence interval [CI], 33.3%–45.3%) with high level of heterogeneity (I^2=95%) (Fig. 2). In addition, we conducted meta-analysis to evaluate postvaccination cellular response rate in KTRs. This meta-analysis demonstrated that positive cellular response rate was 41.6% (95% CI, 30.0%–53.6%; I^2=91%; p<0.01) (Fig. 3). Sensitivity analysis on humoral response rate by single removing each study did not indicate any significant alteration in statistical robustness and study heterogeneity (Supplement 4).

Subgroup analysis and meta-regression

Subgroup analyses were performed under the following subsets–the completeness of vaccine protocol and the presence of prior SARS-CoV-2 infection. Humoral response rate was significantly lower in patients with incomplete vaccine protocol (11.1%; 95% CI, 5.4%–18.4%; I^2=93%; p<0.01) compared to complete vaccine protocol (39.2%; 95% CI, 33.3%–45.3%; I^2=95%; p<0.01) (Fig. 4A). Subsequently, KTRs with a previous history of SARS-CoV-2 infection had a higher humoral immune response after vaccination compared to those without prior infection (87.8%; 95% CI, 66.3%–99.9%; 37.2%; 95% CI, 32.2%–42.3%; p<0.01) (Fig. 4B)

Univariate meta-regression analyses indicated that tacrolimus was positively correlated with a higher proportion of postvaccination humoral response (regression coefficient, 0.4; 95% CI, 0.1–0.8; p=0.01). In contrast, mycophenolate mofetil/mycophenolate acid (MMF/MPA) and belatacept were significantly correlated with a lower humoral immune response rate (regression coefficient, -0.6; 95% CI, -1 to -0.04; p=0.04; regression coefficient, -0.4; 95% CI, -0.8 to -0.06; p=0.02, respectively) (Fig. 5). Additionally, we incorporated commonly reported induction therapy used by the KTRs into the regression analysis. Our results showed that anti-CD25 was inversely correlated with the proportion of positive hu-

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Table 1. Characteristics of included studies

Study	Study design	Age (yr)	Male (%)	Total subject	Prior COVID-19 (%)	Vaccine	Follow-up period after 2nd vaccination (day)	Time after transplantation (yr)	Diagnostic test
Azzi et al. [13] (2021)	Prospective cohort	62.2	59	76	0	BNT162b2, mRNA-1273, and Ad26.CoV2.S	NR	4	VITROS Anti-SARS-CoV-2 IgG CMIA (Ortho-Clinical Diagnostics)
Ben-Dov et al. [14] (2022)	Prospective cohort	53.5	66.7	252	9.1	BNT162b2	12–42	4	LIAISON SARS-CoV-2 S1/S2 IgG (DiaSorin) and ARCHITECT SARS-CoV-2 IgG II (Abbott) immunoassays
Benning et al. [15] (2022)	Prospective cohort	55	60	135	0	BNT162b2, mRNA-1273, and ChAdOx1 nCoV-19	21	7	Anti-RBD antibodies (Luminex)
Benotmane et al. [16] (2021)	Prospective cohort	57.7	63.8	204	0	mRNA-1273	28	6.2	ARCHITECT IgG II Quanttest (Abbott, USA)
Bertrand et al. [17] (2021)	Prospective cohort	63.5	51	45	0	BNT162b2	30	6.9	ARCHITECT IgG II Quanttest (Abbott, USA)
Bruminhent et al. [18] (2021)	Prospective cohort	50	60	35	0	Whole-virus SARS-CoV-2 vaccine (CoronaVac)	14	4.5	ARCHITECT IgG II Quanttest (Abbott, USA)
Buchwinkler et al. [19] (2021)	Prospective cohort	59.9	68	216	0	BNT162b2, mRNA-1273	63	NR	Abbott SARS-CoV-2 IgG II Quant Assay and Liaison SARS-CoV-2 S1/S2 IgG
Chavarot et al. [20] (2021)	Prospective cohort	64	67.3	101	0	BNT162b2	30	4.9	Humoral: SARS-CoV-2IgG II Quant antibody; Cellular: (EliSpot) measuring interferon-γ produced by specific SARS-CoV-2 T-cells test (Abbott)
Cucchiari et al. [21] (2021)	Prospective cohort	59	67.7	117	0	mRNA-1273	14	1.65	Humoral: Luminex; Cellular: ELIspot
Correia et al. [22] (2022)	Prospective cohort	59.3	64.9	131	0	BNT162b2, mRNA-1273, ChAdOx1 nCoV-19, and Ad26.CoV2.S	20.3	9.2	Alinity i SARS-CoV-2 IgG II CMIA
Crane et al. [23] (2021)	Prospective and retrospective cohort	19	56	25	12	mRNA vaccines	45	7.1	Siemens Atellica IM SARS-CoV-2 IgG CMIA
Crespo et al. [24] (2021)	Prospective cohort	59.7	61.1	90	0	mRNA-1273	28	3.5	Humoral: Liaison SARS-CoV-2 S1/S2 IgG; Cellular: QuantiFERON SARS-CoV-2 IGRA
Danthu et al. [25] (2021)	Prospective cohort	64.8	61.1	74	0	BNT162b2	28	6.42	LIAISON SARS-CoV-2 S1/S2 IgG (DiaSorin)
Dębska-Ślizień et al. [26] (2021)	Prospective cohort	54	58.5	142	0	BNT162b2, mRNA-1273	14–21	8	LIAISON SARS-CoV-2 S1/S2 IgG (DiaSorin)
Devresse et al. [27] (2021)	Prospective cohort	60	52	90	7.8	BNT162b2	30	8.5	Humoral: Elecsys anti SARS-CoV-2 Stest; Cellular: SARS-CoV-2 IGRA, Euroimmun
Ducloux et al. [28] (2021)	Prospective cohort	63.5	60.4	153	0	BNT162b2	75	8.1	Abbott SARS-CoV-2 IgG II Quant Assay
Duni et al. [29] (2021)	Prospective cohort	58.2	70.4	54	0	BNT162b2	14	11.9	ARCHITECT IgG II Quanttest (Abbott, USA)
Eren Sadioğlu et al. [30] (2021)	Cross-sectional and prospective cohort	46.4	44.7	85	0	Whole-virus SARS-CoV-2 vaccine (CoronaVac)	30	6.8	COVID-19 IgG antibody enzyme immunoassay kit (DIA.PRO)
Erol et al. [31] (2021)	Prospective cohort	NA	NA	38	0	BNT162b2 and whole-virus SARS-CoV-2 vaccine (CoronaVac)	28–42	NA	Abbott SARS-CoV-2 IgG II Quant Assay
Georgery et al. [32] (2021)	Prospective cohort	61	48	79	0	BNT162b2	28	8.75	Elecsys Anti SARS-CoV-2 Stest
Grupper et al. [33] (2021)	Prospective cohort	58.6	81.7	136	0	BNT162b2	30	3.27	LIAISON SARS-CoV-2 S1/S2IgG (DiaSorin)
Haskin et al. [34] (2021)	Prospective cohort	18.6	66	38	0	BNT162b2	37	7.22	ARCHITECT IgG II Quanttest (Abbott, USA)

(Continued on next page)

Table 1. Continued

Study	Study design	Age (yr)	Male (%)	Total subject	Prior COVID-19 (%)	Vaccine	Follow-up period after 2nd vaccination (day)	Time after transplantation (yr)	Diagnostic test
Hod et al. [35] (2021)	Case-control	59.7	80	120	0	BNT162b2	26.7	5.8	IgG against the RBD of SARS-CoV-2
Husain et al. [36] (2021)	Prospective cohort	66	61	28	10.7	BNT162b2 and mRNA-1273	28	8	Anti-spike IgG immunoassay Liaison assay (Dia-Sorin, Saluggia, Italy)
Kantauskaite et al. [37] (2021)	Prospective cohort	62	64.8	225	0	BNT162b2 and mRNA-1273	14	6.7	Anti-SARS-CoV-2-QuantiVac-ELISA (Euroimmun AG)
Korth et al. [38] (2021)	Case-control	57.7	48	23	0	BNT162b2	15.8	11.4	Anti-SARS-CoV-2 IgG CLIA
Massa et al. [39] (2021)	Prospective cohort	58	72.1	61	0	BNT162b2	28	4.5	ARCHITECT IgG II Quanttest (Abbott, USA)
Marion et al. [40] (2021)	Prospective cohort	NA	NA	271	NA	BNT162b2 and mRNA-1273	28	NA	SARS-CoV-2 total antibodies ELISA test (Beijing Wantai Biological Pharmacy Enterprise)
Midtvedt et al. [41] (2021)	Prospective cohort	67.4	56	141	0	BNT162b2		9.6	SARS-CoV-2 spike antibodies using bead-based flow cytometric assay
Miele et al. [42] (2021)	Case-control	57	81.2	16	NR	BNT162b2	20	NA	Humoral: LIAISON SARS-CoV-2 S1/S2IgG (DiaSorin); Cellular: IFN-γ-ELISpot assay (Mabtech)
Nazaruk et al. [43] (2021)	Retrospective cohort	54.4	45.9	61	8.2	BNT162b2	28–56	13	Abbott SARS-CoV-2 IgG II Quant Assay
Ou et al. [44] (2021)	Prospective cohort	58	40	609	0	BNT162b2 and mRNA-1273	21	NA	ELISA-based (Euroimmun, Lübeck, Germany) IgG
Pedersen et al. [45] (2021)	Case-control	56.9	41.4	58	NR	BNT162b2	28	6.8	LIAISON SARS-CoV-2 S1/S2IgG (DiaSorin)
Prendecki et al. [46] (2021)	Cohort	59	66.1	920	17	BNT162b2 and ChAdOx1 nCoV-19	31	6.6	Abbott SARS-CoV-2 IgG II Quant Assay
Quiroga et al. [47] (2021)	Prospective cohort	56	60	283	6	BNT162b2, mRNA-1273, ChAdOx1 nCoV-19, and Ad26.CoV2.S	28	NR	Quantitative chemiluminescence immunoassay (CLIA, COVID-19 Spike Quantitative Virclia IgG Monotest)
Rahav et al. [48] (2021)	Prospective cohort	60	79.3	111	0	BNT162b2	22	NR	IgG against the RBD of SARS-CoV-2 (Gert Zimmer)
Reischig et al. [49] (2021)	Prospective cohort	51	65	56	34	BNT162b2	28	8.3	Humoral: Chemiluminescent (CLIA) ACCESS SARS-CoV-2 IgG II assay; Cellular: quantitation of IFN-ɣ using ELISpot analysis (Mabtech)
Rincon-Arevalo et al. [50] (2021)	Case-control	62.4	70	40	2.5	BNT162b2	21–28	5	SARS-CoV-2 spike (S)protein ELISA
Rozen-Zvi et al. [51] (2021)	Prospective cohort	57.5	64	308	1.3	BNT162b2	28	7.1	SARS-CoV-2 IgG II Quant (Abbott) assay
Russo et al. [52] (2021)	Retrospective cohort	58.5	57.3	82	0	BNT162b2	43	5.75	LIAISON SARS-CoV-2 S1/S2IgG (DiaSorin)
Sattler et al. [53] (2021)	Case-control	14	71.8	39	0	BNT162b2	8–23	8.15	Humoral: ELISA-based (Euroimmun, Lübeck, Germany) IgG; Cellular: flow cytometry for spike specific CD4, CD8
Stumpf et al. [54] (2021)	Prospective cohort	57.3	65.5	368	0	BNT162b2 and mRNA-1273	56	9.9	Humoral: ELISA-based (Euroimmun, Lübeck, Germany) IgG; Cellular: flow cytometry forspike specific CD4, CD8
Vaiciuniene et al. [55] (2021)	Prospective cohort	55	62.4	136	0	BNT162b2	21–42	6.5	ELISA-based (Euroimmun, Lübeck, Germany) IgG
Villanego et al. [56] (2021)	Case-control	59	67	97	6.2	mRNA vaccines	30	5.3	Abbott SARS-CoV-2 IgG II Quant Assay

COVID-19, coronavirus disease 2019; NR, not reported; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; IgG, immunoglobulin G; CMIA, chemiluminescent microparticle immunoassay; RBD, receptor-binding domain; IGRA, interferon-γ release assay; NA, not applicable; ELISA, enzyme-linked immunosorbent assay; CLIA, Chemiluminescence immunoassay; IFN-ɣ, interferon-gamma.

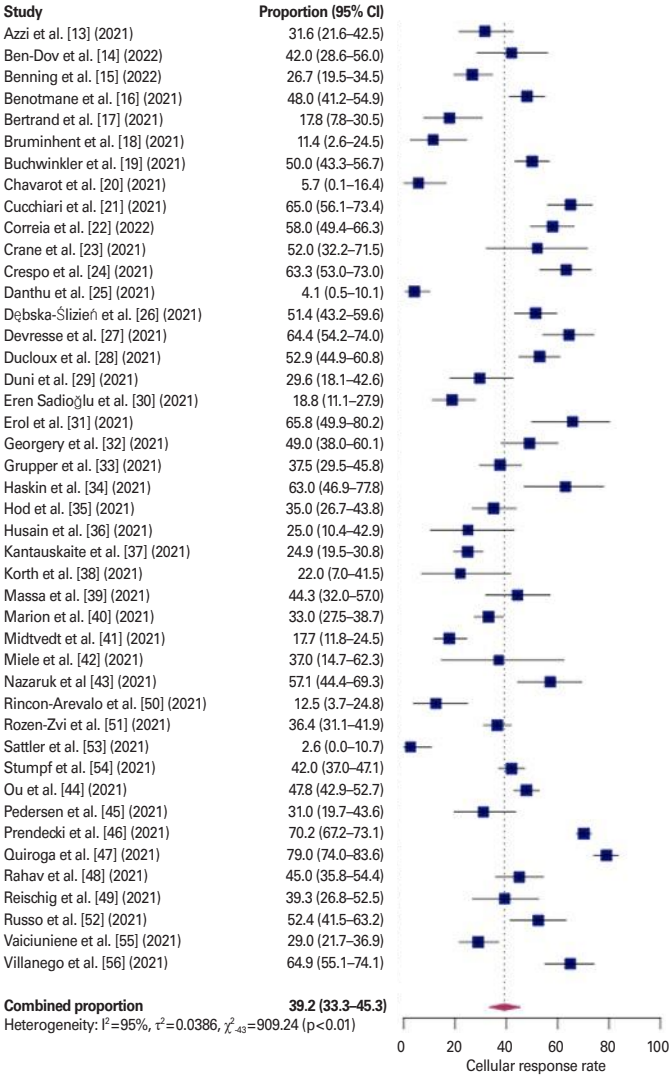

Fig. 2. Forest plot of seroconversion rate in kidney transplant recipients receiving severe acute respiratory syndrome coronavirus 2 vaccines. CI, confidence interval.

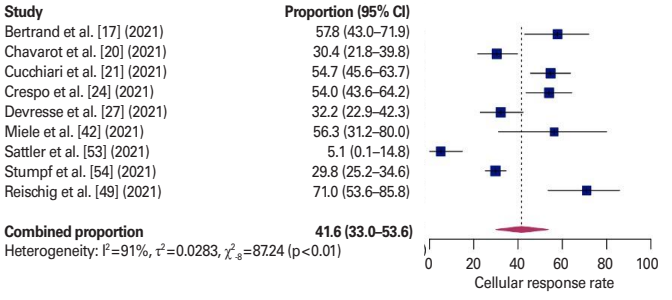

Fig. 3. Forest plot of cellular response rate in kidney transplant recipients receiving severe acute respiratory syndrome coronavirus 2 vaccines. CI, confidence interval.

moral response rate (regression coefficient, -0.3; 95% CI, -0.6 to -0.02; p=0.04) (Supplement 5). We did not find substantial associations between mean age (p=0.82), proportion of male (p=0.93), time since transplantation (p=0.86), cyclosporine (p=0.52), azathioprine (p=0.68), steroid (p=0.75), mechanistic target of rapamycin inhibitor (p=0.62), anti-thymocyte globulin (p=0.12), and humoral response rate (Supplements 5–12).

Publication bias

The funnel plot demonstrated asymmetry of data points, which qualitatively indicated the presence of publication bias (Supplement 13). Also, the Egger test showed a significant result (p<0.01) which implied the presence of publication bias within this meta-analysis.

Discussion

Several key findings were highlighted in this present meta-analysis. We have found that humoral and cellular immune response rates in KTRs following SARS-CoV-2 vaccination were 39.2% and 41.6%, respectively. Immune response rates were significantly increased after the second dose or complete vaccine protocol. Furthermore, immune response rates were found higher in patients with a previous history of SARS-CoV-2 infection. Humoral response rates were positively associated with tacrolimus and inversely correlated with MMF/MPA, belatacept, and anti-CD25 induction therapy.

Previous studies have addressed the antibody response to the complete dose of SARS-CoV-2 vaccination in solid organ transplant recipients [57,58]. In this study, we put an emphasis specifically on the KTR population. Our results revealed low overall immunogenicity rates in KTRs. This was consistent with previous studies which compared immune response rates between KTRs and healthy cohorts that showed transplant recipients have a significantly lower immunogenicity rate following SARS-CoV-2 vaccinations [25,31,35,47,59-61]. The dampened humoral immune responses to vaccination may be attributed to the inhibition of lymphocyte activation, alteration of antigen-presenting cells interaction, and overall reduction in B-cell memory responses [31,57].

Identification of cellular immunity to vaccination is required to accommodate an in-depth exploration of the functionality of immune response in KTRs. Here, we found that cellular response was accordant with humoral response demonstrating a significant reduction in KTRs. Apart from this phenomenon may also be a direct consequence of immunosuppressive therapy used in KTRs, this substantial reduction of reactive $CD4^+$ T helper (Th) cells producing Th1 cytokines can also impact the production of humoral re-

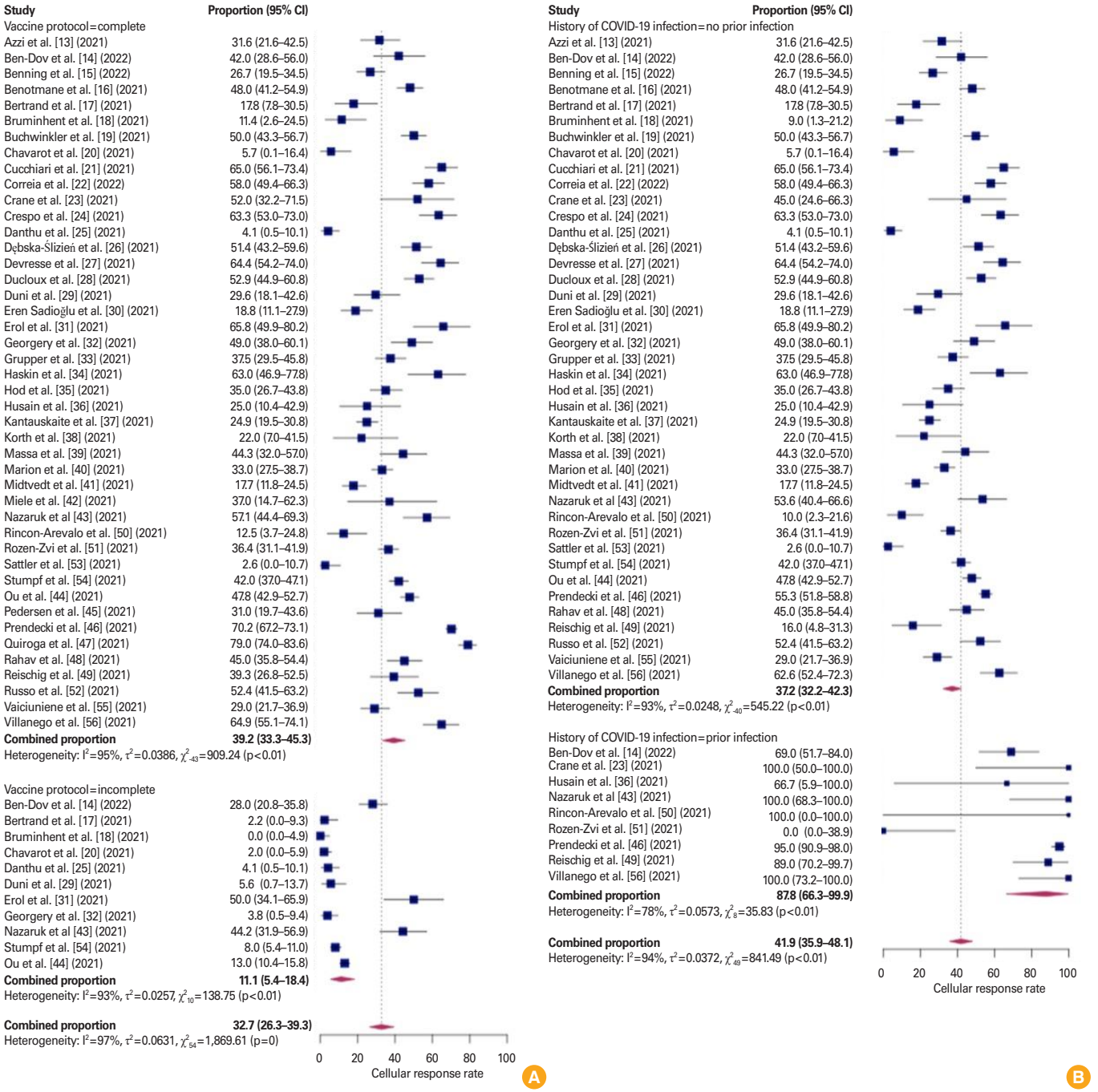

Fig. 4. Subgroup analysis of seroconversion rates in kidney transplant recipients receiving severe acute respiratory syndrome coronavirus 2 vaccine based on vaccine protocol (A) and history of infection (B). CI, confidence interval.

sponse resulting in a seroconversion failure [54].

Understanding immune reactivity to the SARS-CoV-2 vaccine can help in establishing a vaccination protocol strategy that supports not only the quantity of immunity against the virus but also its functionality. This meta-analysis showed a significant discrepancy in postvaccination humoral response before and after the complete vaccine protocol. Although the second dose of vaccine attenuated humoral response, it is still relatively inadequate when compared to the healthy cohort. Interestingly, we found that KTRs with a previous history of SARS-CoV-2 infection posed a comparable seroconversion rate relative to healthy individuals. This was consistent with previous studies that showed humoral response reactivity against SARS-CoV-2 was comparable between KTRs and immunocompetent populations that may be explained by the broader variety of antigenic stimuli provided by natural

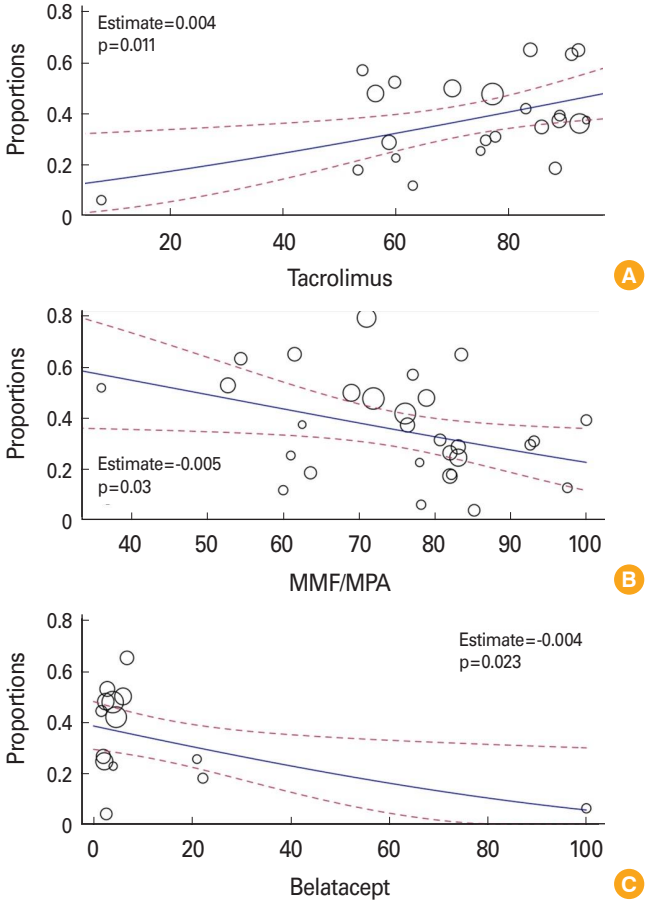

Fig. 5. Associations of tacrolimus (A), mycophenolate mofetil/mycophenolic acid (MMF/MPA) (B), and belatacept (C) on postvaccination seroconversion rate among kidney transplant recipients.

infection in comparison to a specific antigen of the vaccine [54,62,63]. Hence, an additional dose and a stronger or higher dose of vaccine should be implemented as an alternative vaccine strategy for KTRs.

Previous studies have attempted to explore a variety of factors that may be responsible for the small seroconversion rate in KTRs. However, whether the low antibody response to the SARS-CoV-2 vaccine in KTRs was caused by age, gender, or the type of immunosuppressive agent applied remains inconsistent. Here, we presented a summary of analyses yielding a larger cohort that may help to elucidate the potential factors contributing to the low antibody response. We demonstrated that the use of MMF/MPA and belatacept had a significant influence on a lower antibody response rate. A similar relationship between MMF/MPA use was also found in the previous studies that showed an inverse dose-response of MMF/MPA to immune response after vaccination [37,51,54]. It is also documented that MMF inhibits B-cell function and significantly influences antibody response to influenza vaccine [64,65]. Further, the negative correlation between belatacept uses and poor antibody response was also shown in the previous studies [20,44,54]. This was due to the direct effect of belatacept on overall humoral response activation by inhibiting major transcription factors that play an integral part in plasma cell functions and modulate B cell-T follicular helper crosstalk which causes substantial impairment of germinal center formation and antibody response [66,67]. In addition to the negative association of the aforementioned medications and seroconversion rate, we also demonstrate a significant correlation between the higher prevalence of anti-CD25 induction therapy use and the lower seroconversion rates. Anti-CD25 may cause little depletion of T cells by inhibiting α-chain (CD25) of the interleukin 2 receptor [68].

Interestingly, we found that tacrolimus alone was associated with a higher humoral response rate. Nazaruk et al. [43] and Ruether et al. [69] have found a positive correlation between tacrolimus and anti-S1 antibody response in liver transplant recipients. Although the exact mechanism underlying the positive influence of tacrolimus on SARS-CoV-2 vaccine seroconversion remains unclear, there are possible explanations for this discrepancy in the results. First, some studies analyzed the effect of tacrolimus as a component of a combined immunosuppressant regiment which can augment the blunting effect of antibody production [16,18,40]. Second, studies that include tacrolimus in regression analysis often combined it with cyclosporine as a calcineurin-inhibitors [14,54]. This can also mask the potential individual effect of tacrolimus in modulating antibody response to SARS-CoV-2 vaccination in KTRs. Ultimately, we did not find a significant association between age, sex, time since transplantation, or other immunosuppressive agents.

This study has limitations. Most of the included studies were cohort studies–which are prone to have a higher possibility of bias. The generalizability of the study results may be limited due to differences in immunogenicity which depended on the type of vaccine. However, subgroup analyses based on vaccine type was not possible due to the disproportion and paucity of different type of vaccines. The immunogenicity assessment was done in a wide range of follow-up days after vaccination which may result in different response rates. Included studies were carried out in different time ranges and regions which have different dominance in a particular SARS-CoV-2 variant. Our included studies utilized different diagnostic modalities to quantify both humoral and cellular

immune response rates as they may have different sensitivities and specificities [54]. Many of the articles were letters that did not include many baseline characteristics (e.g., comorbidities and induction therapy used) to help us to deduce factors that influence the low seroconversion rates in KTRs. Ultimately, this study aimed to evaluate the immune response to SARS-CoV-2 complete vaccination in KTRs. However, knowing that both antibody and cellular responses are low in this population, further studies on the effect of a third or booster dose are still needed.

ORCID

Maria Riastuti Iryaningrum *https://orcid.org/0000-0001-9980-7442*
Alius Cahyadi *https://orcid.org/0000-0001-7939-5479*
Fachreza Aryo Damara *https://orcid.org/0000-0003-2547-0474*
Ria Bandiara *https://orcid.org/0000-0001-8530-6022*
Maruhum Bonar Hasiholan Marbun *https://orcid.org/0000-0001-7505-0289*

Supplementary Materials

Supplementary materials are available at Clinical and Experimental Vaccine Research website (http://www.ecevr.org).

References

1. Udomkarnjananun S, Kerr SJ, Townamchai N, et al. Mortality risk factors of COVID-19 infection in kidney transplantation recipients: a systematic review and meta-analysis of cohorts and clinical registries. Sci Rep 2021;11:20073.
2. Kremer D, Pieters TT, Verhaar MC, et al. A systematic review and meta-analysis of COVID-19 in kidney transplant recipients: lessons to be learned. Am J Transplant 2021;21:3936-45.
3. Soetedjo NN, Iryaningrum MR, Damara FA, et al. Prognostic properties of hypoalbuminemia in COVID-19 patients: a systematic review and diagnostic meta-analysis. Clin Nutr ESPEN 2021;45:120-6.
4. Permana H, Soeriadi EA, Damara FA, Mulyani Soetedjo NN. The prognostic values of thyroid disorders in predicting COVID-19 composite poor outcomes: a systematic review and meta-analysis. Diabetes Metab Syndr 2022;16:102464.
5. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N Engl J Med 2020;383:2603-15.
6. Tenforde MW, Self WH, Adams K, et al. Association between mRNA vaccination and COVID-19 hospitalization and disease severity. JAMA 2021;326:2043-54.
7. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
8. Tierney JF, Fisher DJ, Vale CL, et al. A framework for prospective, adaptive meta-analysis (FAME) of aggregate data from randomised trials. PLoS Med 2021;18:e1003629.
9. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603-5.
10. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539-58.
11. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. J Clin Epidemiol 2008;61:991-6.
12. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.
13. Azzi Y, Raees H, Wang T, et al. Risk factors associated with poor response to COVID-19 vaccination in kidney transplant recipients. Kidney Int 2021;100:1127-8.
14. Ben-Dov IZ, Oster Y, Tzukert K, et al. Impact of tozinameran (BNT162b2) mRNA vaccine on kidney transplant and chronic dialysis patients: 3-5 months follow-up. J Nephrol 2022;35:153-64.
15. 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.
16. Benotmane I, Gautier-Vargas G, Gallais F, et al. Strong antibody response after a first dose of a SARS-CoV-2 mRNA-based vaccine in kidney transplant recipients with a previous history of COVID-19. Am J Transplant 2021;21:3808-10.
17. Bertrand D, Hanoy M, Edet S, et al. Antibody response to SARS-CoV-2 mRNA BNT162b2 vaccine in kidney transplant recipients and in-centre and satellite centre haemodialysis patients. Clin Kidney J 2021;14:2127-8.
18. Bruminhent J, Setthaudom C, Chaumdee P, et al. SARS-CoV-2-specific humoral and cell-mediated immune re-

sponses after immunization with inactivated COVID-19 vaccine in kidney transplant recipients (CVIM 1 study). Am J Transplant 2022;22:813-22.
19. Buchwinkler L, Solagna CA, Messner J, et al. Antibody response to mRNA vaccines against SARS-CoV-2 with chronic kidney disease, hemodialysis, and after kidney transplantation. J Clin Med 2021;11:148.
20. Chavarot N, Morel A, Leruez-Ville M, et al. Weak antibody response to three doses of mRNA vaccine in kidney transplant recipients treated with belatacept. Am J Transplant 2021;21:4043-51.
21. 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;21:2727-39.
22. Correia AL, Leal R, Pimenta AC, et al. The type of SARS-CoV-2 vaccine influences serological response in kidney transplant recipients. Clin Transplant 2022;36:e14585.
23. Crane C, Phebus E, Ingulli E. Immunologic response of mRNA SARS-CoV-2 vaccination in adolescent kidney transplant recipients. Pediatr Nephrol 2022;37:449-53.
24. Crespo M, Barrilado-Jackson A, Padilla E, et al. Negative immune responses to two-dose mRNA COVID-19 vaccines in renal allograft recipients assessed with simple antibody and interferon gamma release assay cellular monitoring. Am J Transplant 2022;22:786-800.
25. Danthu C, Hantz S, Dahlem A, et al. Humoral response after SARS-CoV-2 mRNA vaccination in a cohort of hemodialysis patients and kidney transplant recipients. J Am Soc Nephrol 2021;32:2153-8.
26. Debska-Slizien A, Slizien Z, Muchlado M, et al. Predictors of humoral response to mRNA COVID19 vaccines in kidney transplant recipients: a longitudinal study: the COVi-NEPH project. Vaccines (Basel) 2021;9:1165.
27. Devresse A, Saad Albichr I, Georgery H, et al. T-cell and antibody response after 2 doses of the BNT162b2 vaccine in a belgian cohort of kidney transplant recipients. Transplantation 2021;105:e142-3.
28. Ducloux D, Colladant M, Chabannes M, Bamoulid J, Courivaud C. Factors associated with humoral response after BNT162b2 mRNA COVID-19 vaccination in kidney transplant patients. Clin Kidney J 2021;14:2270-2.
29. Duni A, Markopoulos GS, Mallioras I, et al. The humoral immune response to BNT162b2 vaccine is associated with circulating CD19+ B lymphocytes and the naive CD45RA to memory CD45RO CD4+ T helper cells ratio in hemodialysis patients and kidney transplant recipients. Front Immunol 2021;12:760249.
30. Eren Sadioglu R, Demir E, Evren E, et al. Antibody response to two doses of inactivated SARS-CoV-2 vaccine (CoronaVac) in kidney transplant recipients. Transpl Infect Dis 2021;23:e13740.
31. Erol C, Yanik Yalcin T, Sari N, et al. Differences in antibody responses between an inactivated SARS-CoV-2 vaccine and the BNT162b2 mRNA vaccine in solid-organ transplant recipients. Exp Clin Transplant 2021;19:1334-40.
32. Georgery H, Devresse A, Yombi JC, et al. Very low immunization rate in kidney transplant recipients after one dose of the BNT162b2 vaccine: beware not to lower the guard! Transplantation 2021;105:e148-9.
33. Grupper A, Katchman E, Ben-Yehoyada M, et al. Kidney transplant recipients vaccinated before transplantation maintain superior humoral response to SARS-CoV-2 vaccine. Clin Transplant 2021;35:e14478.
34. Haskin O, Ashkenazi-Hoffnung L, Ziv N, et al. Serological response to the BNT162b2 COVID-19 mRNA vaccine in adolescent and young adult kidney transplant recipients. Transplantation 2021;105:e226-33.
35. Hod T, Ben-David A, Olmer L, et al. Humoral response of renal transplant recipients to the BNT162b2 SARS-CoV-2 mRNA vaccine using both RBD IgG and neutralizing antibodies. Transplantation 2021;105:e234-43.
36. Husain SA, Argyropoulos CP. Boosters and optimizing SARS-CoV-2 vaccine for transplantation: no time to wait. Am J Transplant 2022;22:328-9.
37. Kantauskaite M, Muller 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;22:634-9.
38. Korth J, Jahn M, Dorsch O, et al. Impaired humoral response in renal transplant recipients to SARS-CoV-2 vaccination with BNT162b2 (Pfizer-BioNTech). Viruses 2021;13:756.
39. Massa F, Cremoni M, Gerard A, et al. Safety and cross-variant immunogenicity of a three-dose COVID-19 mRNA vaccine regimen in kidney transplant recipients. EBioMedicine 2021;73:103679.
40. Marion O, Del Bello A, Abravanel F, et al. Predictive factors for humoral response after 2-dose SARS-CoV-2 vaccine in solid organ transplant patients. Transplant Direct 2021;8:e1248.
41. Midtvedt K, Tran T, Parker K, et al. Low immunization

rate in kidney transplant recipients also after dose 2 of the BNT162b2 vaccine: continue to keep your guard up! Transplantation 2021;105:e80-1.
42. Miele M, Busa R, Russelli G, et al. Impaired anti-SARS-CoV-2 humoral and cellular immune response induced by Pfizer-BioNTech BNT162b2 mRNA vaccine in solid organ transplanted patients. Am J Transplant 2021;21:2919-21.
43. Nazaruk P, Monticolo M, Jedrzejczak AM, et al. Unexpectedly high efficacy of SARS-CoV-2 BNT162b2 vaccine in liver versus kidney transplant recipients: is it related to immunosuppression only? Vaccines (Basel) 2021;9:1454.
44. Ou MT, Boyarsky BJ, Chiang TP, et al. Immunogenicity and reactogenicity after SARS-CoV-2 mRNA vaccination in kidney transplant recipients taking belatacept. Transplantation 2021;105:2119-23.
45. Pedersen RM, Bang LL, Tornby DS, et al. The SARS-CoV-2-neutralizing capacity of kidney transplant recipients 4 weeks after receiving a second dose of the BNT162b2 vaccine. Kidney Int 2021;100:1129-31.
46. Prendecki M, Thomson T, Clarke CL, et al. Immunological responses to SARS-CoV-2 vaccines in kidney transplant recipients. Lancet 2021;398:1482-4.
47. Quiroga B, Soler MJ, Ortiz A, et al. Safety and immediate humoral response of COVID-19 vaccines in chronic kidney disease patients: the SENCOVAC study. Nephrol Dial Transplant 2022;37:1868-78.
48. Rahav G, Lustig Y, Lavee J, et al. BNT162b2 mRNA COVID-19 vaccination in immunocompromised patients: a prospective cohort study. EClinicalMedicine 2021;41:101158.
49. Reischig T, Kacer M, Vlas T, et al. Insufficient response to mRNA SARS-CoV-2 vaccine and high incidence of severe COVID-19 in kidney transplant recipients during pandemic. Am J Transplant 2022;22:801-12.
50. Rincon-Arevalo H, Choi M, Stefanski AL, et al. Impaired humoral immunity to SARS-CoV-2 BNT162b2 vaccine in kidney transplant recipients and dialysis patients. Sci Immunol 2021;6:eabj1031.
51. 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.
52. Russo G, Lai Q, Poli L, et al. SARS-COV-2 vaccination with BNT162B2 in renal transplant patients: risk factors for impaired response and immunological implications. Clin Transplant 2022;36:e14495.
53. Sattler A, Schrezenmeier E, Weber UA, et al. Impaired humoral and cellular immunity after SARS-CoV-2 BNT162b2 (tozinameran) prime-boost vaccination in kidney transplant recipients. J Clin Invest 2021;131:e150175.
54. Stumpf J, Siepmann T, Lindner T, et al. Humoral and cellular immunity to SARS-CoV-2 vaccination in renal transplant versus dialysis patients: a prospective, multicenter observational study using mRNA-1273 or BNT162b2 mRNA vaccine. Lancet Reg Health Eur 2021;9:100178.
55. Vaiciuniene R, Sitkauskiene B, Bumblyte IA, et al. Immune response after SARS-CoV-2 vaccination in kidney transplant patients. Medicina (Kaunas) 2021;57:1327.
56. Villanego F, Cazorla JM, Vigara LA, et al. Protecting kidney transplant recipients against SARS-CoV-2 infection: a third dose of vaccine is necessary now. Am J Transplant 2022;22:1275-6.
57. 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;325:2204-6.
58. Aslam S, Adler E, Mekeel K, Little SJ. Clinical effectiveness of COVID-19 vaccination in solid organ transplant recipients. Transpl Infect Dis 2021;23:e13705.
59. Fernandez-Ruiz M, Almendro-Vazquez P, Carretero O, et al. Discordance between SARS-CoV-2-specific cell-mediated and antibody responses elicited by mRNA-1273 vaccine in kidney and liver transplant recipients. Transplant Direct 2021;7:e794.
60. Yanis A, Haddadin Z, Spieker AJ, et al. Humoral and cellular immune responses to the SARS-CoV-2 BNT162b2 vaccine among a cohort of solid organ transplant recipients and healthy controls. Transpl Infect Dis 2022;24:e13772.
61. Bergman P, Blennow O, Hansson L, et al. Safety and efficacy of the mRNA BNT162b2 vaccine against SARS-CoV-2 in five groups of immunocompromised patients and healthy controls in a prospective open-label clinical trial. EBioMedicine 2021;74:103705.
62. Candon S, Guerrot D, Drouot L, et al. T cell and antibody responses to SARS-CoV-2: experience from a French transplantation and hemodialysis center during the COVID-19 pandemic. Am J Transplant 2021;21:854-63.
63. Thieme CJ, Anft M, Paniskaki K, et al. The magnitude and functionality of SARS-CoV-2 reactive cellular and humoral immunity in transplant population is similar to the general population despite immunosuppression. Transplantation 2021;105:2156-64.

64. Boey L, Curinckx A, Roelants M, et al. Immunogenicity and safety of the 9-valent human papillomavirus vaccine in solid organ transplant recipients and adults infected with human immunodeficiency virus (HIV). Clin Infect Dis 2021;73:e661-71.
65. Natori Y, Shiotsuka M, Slomovic J, et al. A double-blind, randomized trial of high-dose vs standard-dose influenza vaccine in adult solid-organ transplant recipients. Clin Infect Dis 2018;66:1698-704.
66. Leibler C, Thiolat A, Henique C, et al. Control of humoral response in renal transplantation by belatacept depends on a direct effect on B cells and impaired T follicular helper-B cell crosstalk. J Am Soc Nephrol 2018;29:1049-62.
67. Chen J, Yin H, Xu J, et al. Reversing endogenous alloreactive B cell GC responses with anti-CD154 or CTLA-4Ig. Am J Transplant 2013;13:2280-92.
68. Orcurto A, Pascual M, Hoschler K, Aubert V, Meylan P, Manuel O. Impact of anti-T-cell therapy in the immunogenicity of seasonal influenza vaccine in kidney transplant recipients. Transplantation 2012;94:630-6.
69. Ruether DF, Schaub GM, Duengelhoef PM, et al. SARS-CoV2-specific humoral and T-cell immune response after second vaccination in liver cirrhosis and transplant patients. Clin Gastroenterol Hepatol 2022;20:162-72.