Kidney Diseases

Systematic Review

Kidney Dis 2024;10:107–117
DOI: 10.1159/000536308

Received: August 20, 2022
Accepted: January 12, 2024
Published online: January 19, 2024

Immunogenicity and Safety of the Three-Dose COVID-19 Vaccine Regimen in Patients Receiving Renal Replacement Therapy: A Systematic Review and Meta-Analysis

Becky Mingyao Ma[a] Anthony Raymond Tam[b] Kam Wa Chan[a] Ivan Fan Ngai Hung[b] Sydney Chi Wai Tang[a] Tak Mao Chan[a] Desmond Yat-Hin Yap[a]

[a]Division of Nephrology, Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong, China; [b]Division of Infectious Diseases, Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong, China

Keywords
COVID-19 · Vaccine · Third dose · Immunogenicity · Safety · Renal replacement therapy

Abstract
Background: A three-dose regimen is the current standard for COVID-19 vaccination, but systematic data on immunogenicity and safety in chronic kidney disease patients remains limited. ***Objectives:*** We conducted a meta-analysis on the immunogenicity and safety of three-dose COVID-19 vaccination in patients on renal replacement therapy (RRT). ***Methods:*** Systematic literature search in four electronic databases yielded twenty eligible studies (2,117 patients, 94% of whom received mRNA vaccines) for meta-analysis. ***Results:*** The overall seropositivity rate of anti-SARS-CoV-2 was 74.2% (95% CI: 65.0–83.4%) after three-dose COVID-19 vaccination. The seropositivity rate of anti-SARS-CoV-2 in kidney transplant recipients (KTRs) was 64.6% (95% CI: 58.7–70.5%), and 43.5% (95% CI: 38.5–48.6%) of non-responders after second dose became seropositive after third dose. The seropositivity rate of anti-SARS-CoV-2 was 92.9% (95% CI: 89.5–96.2%) in dialysis patients, and 64.6% (95% CI: 46.8–82.3%) of non-responders after second dose became seropositive after third dose. In KTRs, each year increase in transplant vintage was associated with 35.6% increase in anti-SARS-CoV-2 seropositivity (95% CI: 15.9–55.4%, $p = 0.01$). There were no serious adverse events attributed to vaccination in KTRs, and the commonest local and systemic adverse events were injection site pain and fatigue, respectively. ***Conclusion:*** Three-dose COVID-19 vaccination regimen in patients on RRT is associated with reduced immunogenicity, especially in KTRs. There are no adverse events associated with third-dose COVID-19 vaccine in KTRs.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), remains an important public health concern. As of May 12, 2023, over half a billion confirmed

karger@karger.com
www.karger.com/kdd

Correspondence to:
Desmond Yat Hin Yap, desmondy@hku.hk

cases of COVID-19 and more than 6.9 million cases of mortality have been reported to the World Health Organization [1]. Patients with chronic kidney disease (CKD) showed increased susceptibility to COVID-19 infection, with high rates of severe disease, intensive care unit (ICU) admissions, and mortality [2]. Patients receiving long-term renal replacement therapy (RRT), be it dialysis or kidney transplantation, are particularly vulnerable to COVID-19 infection. The reported mortality rate of COVID-19 in kidney transplant recipients (KTRs) (20–40%) was considerably higher than the overall mortality rates in patients requiring hospitalization (~10–15%) [3]. In dialysis population with COVID-19, the attributable mortality rate was 20%, which was 17-fold higher than dialysis patients without COVID-19 (mortality ~1.2%) [4].

The availability of oral antivirals, such as nirmatrelvir-ritonavir (also known as Paxlovid) and molnupiravir (a nucleoside analog), offers new hopes in combating the pandemic as they have been shown to reduce hospitalization and mortality in patients infected with COVID-19. However, there are many limitations and concerns in the use of these oral antiviral agents in KTRs and patients on long-term dialysis. In this context, nirmatrelvir-ritonavir, while being more potent than molnupiravir, can cause significant drug interactions and hence increase in calcineurin inhibitor (CNI) exposure in KTRs [5]. Moreover, its optimal dosing in patients with estimated glomerular filtration rate of less than 30 mL/min has not been established and is hence not recommended for patients with advanced CKD in current treatment guidelines. Although molnupiravir has the advantage of few drug-drug interactions and does not require dosage reduction in patients with kidney and liver impairment, its antiviral potency is relatively modest. Therefore, effective vaccination remains the cornerstone for preventing COVID-19 infections and improving clinical outcomes in patients on RRT. It is also recognized that vaccination mainly protects against severe disease and mortality, and postvaccination breakthrough infections can still occur [6].

The incidence of breakthrough infections in the general population is variable, ranging from 0.066% to 2.6%, though most of these infections were mild in disease severity [6]. The level of neutralizing antibodies has been shown to be an important predictor of postvaccination breakthrough infection in both healthy individuals and patients on RRT. Kidney impairment can lead to reduced vaccine immunogenicity, and putative mechanisms include impaired B-cell maturation and increased B-cell apoptosis, T-lymphocyte dysfunction, downregulation of toll-like receptors/co-stimulation molecules in immune-reactive cells, and the use of immunosuppression in KTRs [7]. Indeed, our previous meta-analysis showed that the immunogenicity after two-dose COVID-19 vaccines were 26.1%, 84.3%, and 92.4%, respectively, in KTRs, hemodialysis (HD), and peritoneal dialysis (PD) patients [8]. Such decreased immunogenicity corresponds well with recent reports of higher rates of breakthrough infections of 2.2–17.8% in dialysis and transplant population compared to the 4.3% reported in healthy individuals [9, 10]. Most breakthrough infections occur 3 to 4 months after second dose of vaccination due to waning of neutralizing antibodies over time [9]. Notably, over half of the KTRs developing breakthrough infections required hospital admissions, in which half of these hospitalized KTRs had severe disease manifestations that required ICU admission and were associated with high mortality [10]. A three-dose vaccination is the current standard immunization regimen for COVID-19. The main body of literature on the three-dose vaccination is relatable to the general population, and data on the immunogenicity and safety of this regimen in RRT patients remains relatively limited. In addition, the heterogeneity of existing reports also renders the interpretation of results difficult [11–30]. These backgrounds have prompted us to conduct a meta-analysis to investigate the overall immunogenicity and safety of the three-dose COVID-19 vaccine regimen in RRT patients and identify factors that affect vaccine immunogenicity. These data will enhance our knowledge of the immunogenicity of the three-dose COVID-19 vaccination protocol in patients on RRT and thereby help formulate the optimal immunization strategy in this highly vulnerable population.

Materials and Methods

Search Strategy

This study was registered under the international prospective register of systematic reviews (PROSPERO, registration ID: CRD42022311640) and followed the standards set forth by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [31]. We performed systematic literature search in PubMed, Cochrane Library, MEDLINE, and Embase to identify all published studies on CKD patients who had received three doses of COVID-19 vaccine up to January 31, 2022 (keywords used and search strategy were listed in online Suppl. Material S1; for all online suppl. material, see https://doi.org/10.1159/000536308). The search was limited to English-language papers.

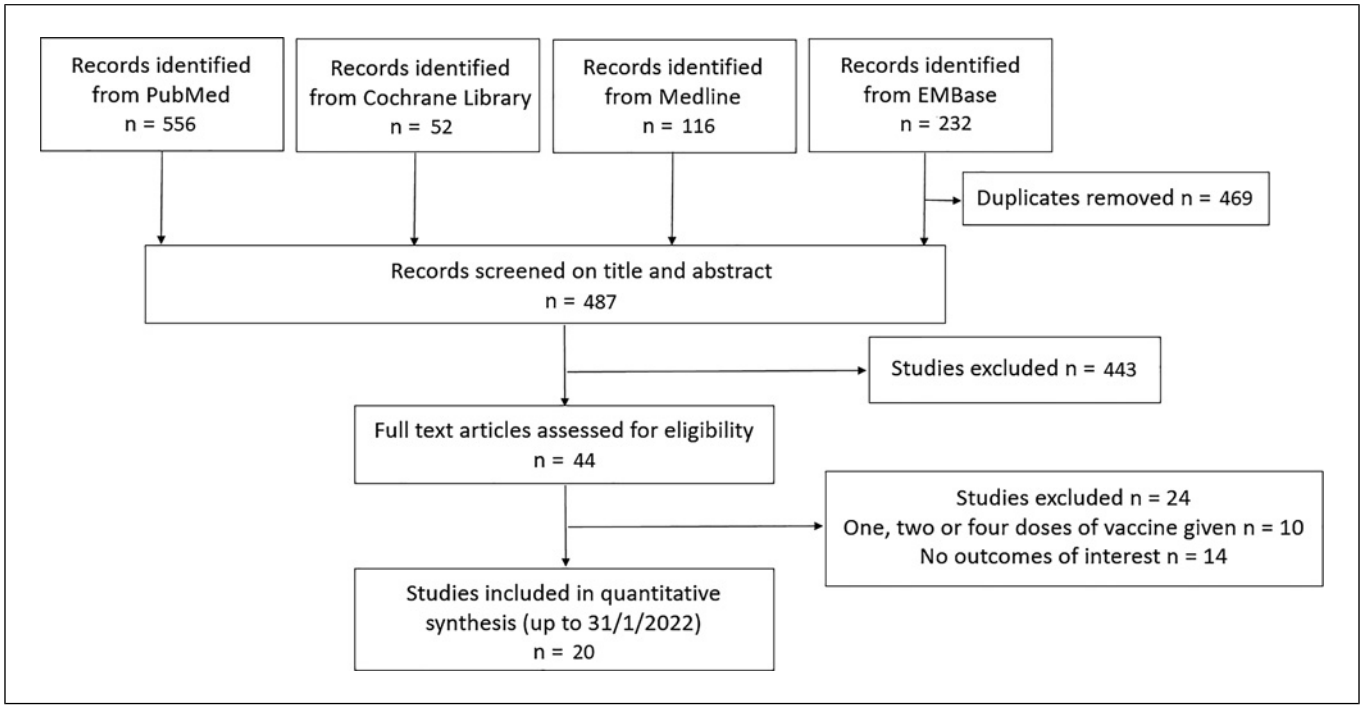

Fig. 1. Flowchart of study selection.

Study Selection

Clinical trials and cohort studies of adults with CKD on HD, PD, or KTRs without prior history of COVID-19 who have received three doses of COVID-19 vaccines and had their antibody titers tested were included. Reviews, case reports, commentaries, conference abstracts, and animal studies were excluded. Studies were also excluded if there was an overlap in subjects with another included study, such that study subjects were only included once in any given analysis.

Data Extraction and Quality Assessment

Two investigators (B.M. and A.T.) extracted and reviewed data independently, and disagreement was resolved by their consensus or consultation with the third author (D.Y.). Data on the journal publication date, first author, study design, sample size, patient demographics (including age, gender, modality of RRT, vintage of dialysis or transplantation, regimen of maintenance immunosuppression, history of diabetes mellitus), number of healthy controls, type and regimen of COVID-19 vaccination, antibody response after second and third doses of vaccination, and adverse reactions were retrieved. Risk of bias was assessed by the National Institute of Health Study Quality Assessment Tool (online suppl. Material S2) [32]. The Egger's test and a funnel of the standard error (SE) were used to evaluate publication bias (online suppl. Material S3).

Outcomes

Primary outcomes of our meta-analysis were the immunogenicity and safety of COVID-19 vaccine in patients on RRT. Immunogenicity was evaluated by antibody response to the receptor-binding domain of the spike protein or antibody to the spike protein of SARS-CoV-2, as measured by commercially available assays. Immunogenicity was expressed as the pooled percentage of seropositivity. Safety was evaluated by reports of any local or systemic adverse reaction.

Statistical Analysis

Continuous variables were expressed as mean ± SD. The rate of seropositivity after the third dose of COVID-19 vaccination was pooled, stratified across studies, and analyzed using random-effect models with inverse variance weighting. The magnitude of heterogeneity was estimated using the I^2 statistic, an estimate of the proportion of the total observed variance that is attributed to between-study variance. Categorical variables were analyzed by univariate meta-regression. All statistical analyses were performed using STATA version 17.0 (College Station, TX, USA), and p values of <0.05 were considered to imply statistical significance.

Results

Data Source and Patient Characteristics

A search of PubMed, Cochrane Library, MEDLINE, and Embase using pre-determined search criteria generated 956 studies initially (Fig. 1). Duplicates, in vitro studies, and studies using animal models or conducted in the pediatric population were excluded. Forty-four studies were retrieved for detailed evaluation by full-text

screening. Twenty-four studies were excluded since they did not report vaccine response or only reported serologic response after the first, second, or fourth dose of vaccine. Twenty studies from six countries were included in the final analyses (online suppl. Material S4). Healthy adults as the control group were only available in one study [20]. A total of 2,117 patients (1,840 KTRs, 246 receiving chronic HD, and 31 receiving PD) with no prior history of COVID-19 were included in the meta-analysis. The mean age (±SE) of patients was 61.4 ± 6.7 years. Majority of patients received mRNA platform vaccines (94%, n = 1,990), and the rest received viral vector vaccine. All studies adopted a three-dose vaccination protocol, with the third dose administered at 62.6 ± 6.7 days after the second dose. Blood sampling was performed at 27.5 ± 7.2 days after the third dose of the COVID-19 vaccine. The antibody response to the receptor-binding domain of the spike protein of SARS-CoV-2 was measured using eight different commercially available assays. The Egger's test and funnel plot showed no publication bias for the immunogenicity after three doses of COVID-19 vaccines in patients receiving RRT (p = 0.503) (Supplementary Material S3).

Antibody Response in Patients Receiving Different RRT Modalities

Meta-analysis of twelve studies (n = 1,543) showed that the overall seropositivity rate of anti-SARS-CoV-2 was 74.2% (95% CI: 65.0–83.4%) in patients on RRT having received the third dose vaccine (Fig. 2). For KTRs, a meta-analysis of eight studies (n = 1,840) revealed that 64.6% of patients developed anti-SARS-CoV-2 antibodies (95% CI: 58.7–70.5%) after the third dose of COVID-19 vaccine (Fig. 3). Among non-responders after the second dose of vaccine, 43.5% developed anti-SARS-CoV-2 antibodies after the third dose (95% CI: 38.5–48.6%) (Fig. 4).

Regarding patients on chronic dialysis, meta-analysis of four studies (n = 259) showed a seropositivity rate of 92.9% (95% CI: 89.5–96.2%) after three doses of COVID-19 vaccine (Fig. 5). Among non-responders after the second dose of vaccine, 64.6% became seropositive after the third dose (95% CI: 46.8–82.3%) (Fig. 6).

Factors Affecting Immunogenicity in Patients Receiving RRT

We next investigated the impact of different immunosuppressants and patient characteristics on the immunogenicity of COVID-19 vaccine after a three-dose regimen in KTRs. Our meta-regression demonstrated that for each year of increase in transplant vintage, the seropositivity rate for anti-SARS-CoV-2 antibody increased by 35.6% (95% CI: 15.9–55.4%, p = 0.01). The type of immunosuppressants including corticosteroids, CNIs, mycophenolic acid analog (MPAA), mammalian target of rapamycin inhibitors had no significant impact on seropositivity after a three-dose COVID-19 vaccine regimen (p > 0.05, for all). Age and the presence of diabetes mellitus also did not show any relationship with anti-SARS-CoV-2 seropositivity (p > 0.05, for both) (Table 1).

We also analyzed the effect of various demographic factors on the development of anti-SARS-CoV-2 antibodies in patients receiving long-term dialysis. No significant correlation between age and dialysis vintage and anti-SARS-CoV-2 seropositivity was observed among patients receiving long-term dialysis (p > 0.05 for all) (Table 1).

Adverse Events

Five studies (all in KTRs, n = 368) reported local or systemic adverse events after the third dose of COVID-19 vaccine (online Suppl. Material S4), but none were serious adverse events. Two studies (Bertrand et al. [13] and Massa et al. [21]) investigated the relationship between the third dose of COVID-19 vaccine and kidney allograft outcomes, which indicated that the administration of the third dose of COVID-19 vaccine did not increase the risk of acute rejection, development of de novo donor-specific antibodies, and kidney allograft loss up to 1-month postvaccination. Adverse events were reported in 66.7% of KTRs in three studies, with pain and fatigue being the most common local and systemic event, respectively.

Discussion

Accumulating data has consistently demonstrated the suboptimal humoral immune response among CKD patients following two doses of COVID-19 vaccines. One recent meta-analysis by our group indicated that, after a two-dose vaccination schedule, the overall seropositivity rate of anti-SARS-CoV-2 was 64% in patients on RRT [8]. Furthermore, only 26% of KTRs developed anti-SARS-CoV-2 antibodies, while patients on chronic HD and PD showed serologic responses of 84.3% and 92.4% respectively [8]. In this context, immunocompromised patients who fail to mount a robust immune response against SARS-CoV-2 or have rapidly waning immunity are prone to severe breakthrough infections [33]. Also, prolonged viral shedding in these patients has become a source of continuous unintended exposure to others and

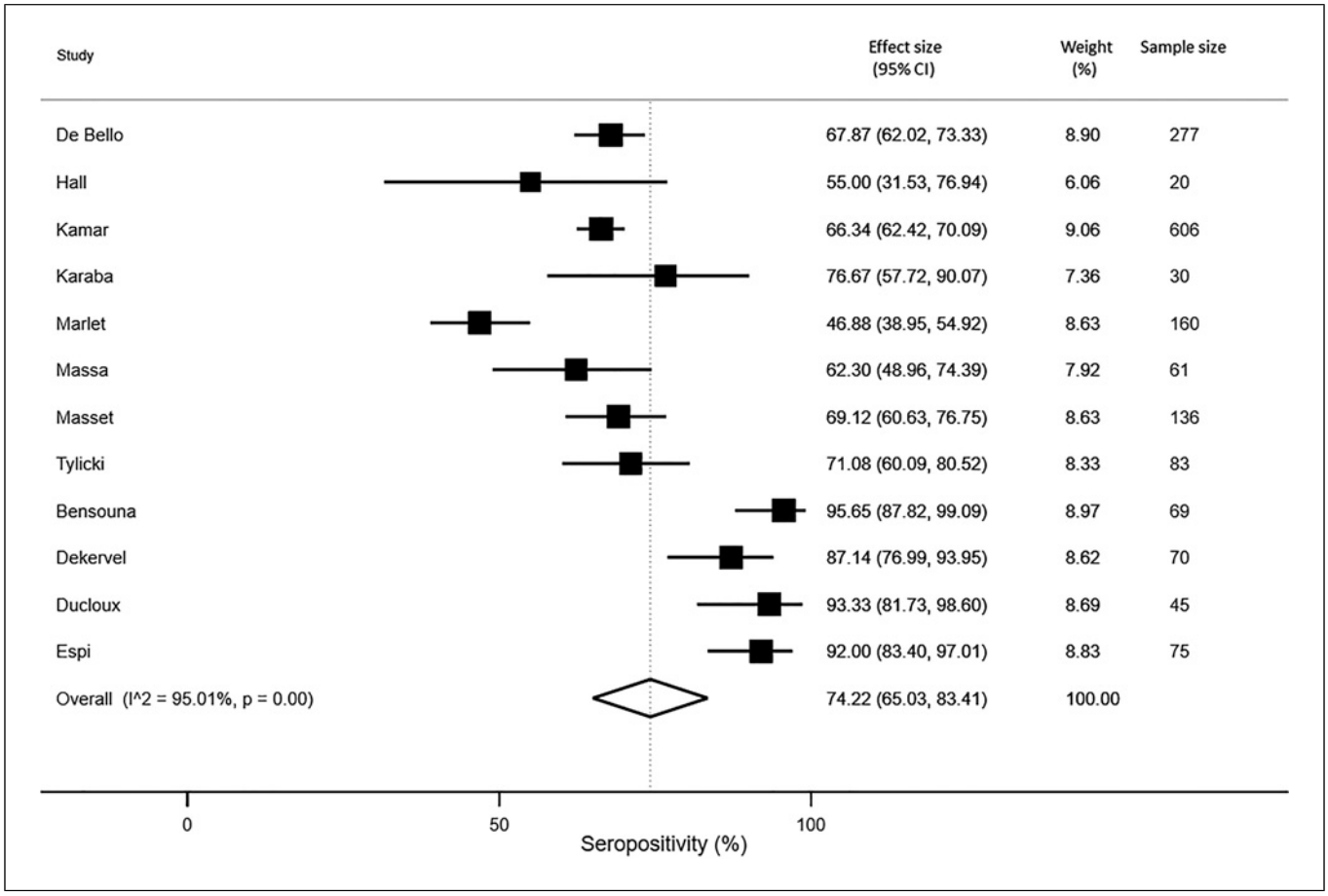

Fig. 2. Immunogenicity after three doses of COVID-19 vaccines in patients receiving RRT.

a potential niche for new variants [34]. Based on these rationales, the Center for Disease Control and Prevention (CDC) of the USA has recommended that patients who are moderately to severely immunocompromised should receive the third dose of COVID-19 vaccine since August 2021 [35]. Previous studies on three-dose COVID-19 vaccine regimen in CKD patients showed substantial heterogeneities in patient characteristics, type of vaccines administered, and healthcare settings, and therefore, systematic review and meta-analyses data will provide clinically useful evidence on the efficacy and safety of the three-dose COVID-19 vaccine regimen in RRT patients.

Our current meta-analysis demonstrated that, despite completing three doses of COVID-19 vaccines, only 74.2% patients on RRT were seropositive for anti-SARS-CoV-2 antibody and such seropositivity rate was significantly lower than that in the general population (~95–100%) [36]. The reduced overall seropositivity rates were largely driven by the low immunogenicity in KTRs. Nevertheless, the seropositivity rate of anti-SARS-CoV-2 increased from 26% after two doses to 64.6% following the third dose, suggesting this booster dose in KTRs was highly important [8]. The impaired immune responses to COVID-19 vaccines in KTRs are primarily contributed by the use of various immunosuppressive treatments. Standard immunosuppressive regimens for KTRs are a triple combination comprising corticosteroids, a CNI plus a mycophenolic acid analog (MPAA) or mTOR inhibitor, and with or without antibody induction (e.g., anti-thymocyte globulin (ATG) or anti-IL2 receptor antagonist) [37]. These immunosuppressive medications exert both specific and non-specific inhibitory effects on various immune-reactive cells including the neutrophils as well as B and T lymphocytes [38–40]. Benotmane et al. [11] reported that patients receiving the combination of corticosteroids, tacrolimus, and MPAA were less likely to develop anti-SARS-CoV-2 antibodies compared with those

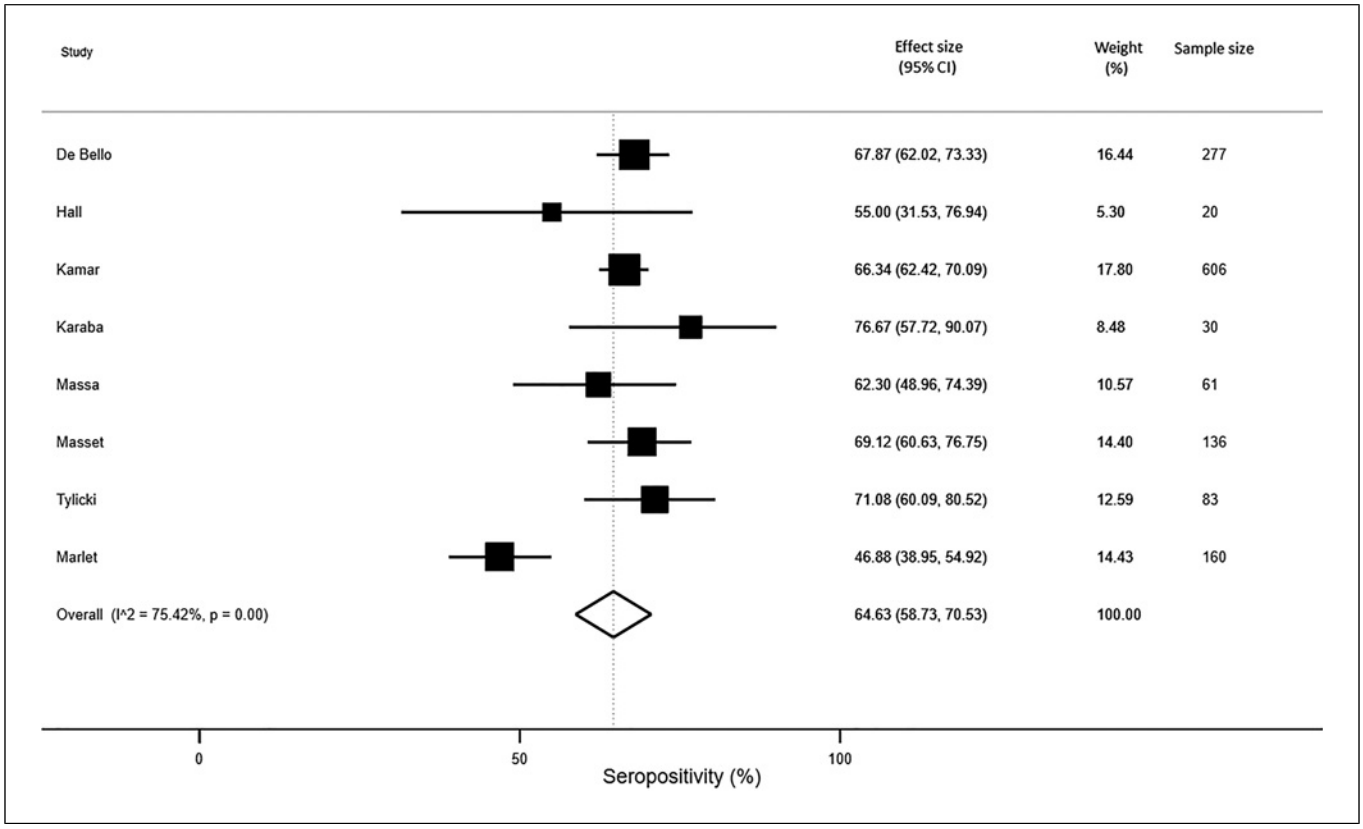

Fig. 3. Immunogenicity after three doses of COVID-19 vaccines in kidney transplant recipients.

treated with other regimens. Our previous meta-analysis also revealed that the use of MPAA would significantly reduce the likelihood of anti-SARS-CoV-2 seropositivity after two doses of COVID-19 vaccines [8]. Such findings may be explained by the potent suppressive effects of MPAA on B-cell proliferation and differentiation as well as T helper cell functions [40]. In this meta-analysis, no individual immunosuppressants showed a significant relationship with vaccine immunogenicity, implying a three-dose vaccination schedule may overcome the effect of individual immunosuppressive drugs including MPAA. Rather, the immunogenicity of COVID-19 vaccine is related to the overall degree of immunosuppression in KTRs, as the seropositivity rate of anti-SARS-CoV-2 tends to increase with transplant vintage. This finding was corroborated by one previous study which showed that the durability of anti-SARS-CoV-2 was related to the duration between transplantation and vaccination [19]. Our results also suggested that among KTRs who did not develop anti-SARS-CoV-2 antibodies after 2 doses of COVID-19 vaccine, almost 60% remained seronegative after the third dose. This insinuates that a considerable proportion of KTRs are still susceptible to SARS-CoV-2 infection despite the current standard three-dose vaccination regimen, and hence these patients should stay vigilant and adhere to important infection control measures (e.g., wearing of face mask and maintaining good hand hygiene). In addition, it is more justifiable to apply novel vaccination approaches in KTRs that may potentially improve the immunogenicity. These include the administration of the fourth dose vaccine, heterologous vaccination, intranasal/intradermal immunization, and peri-vaccination modification of the immunosuppressive regimens [41–45]. In this context, the current evidence supports the administration of the fourth dose of COVID-19 vaccine to immunocompromised hosts including KTRs [46]. The evidence on heterologous vaccinations has been conflicting. Two studies showed no statistically significant difference in immunogenicity when comparing homologous vaccination with heterologous vaccination, while another study demonstrated that employing heterologous viral vector vaccine as booster was associated with lower antibody titers when compared to homologous mRNA vaccine [47–49]. Pre-exposure

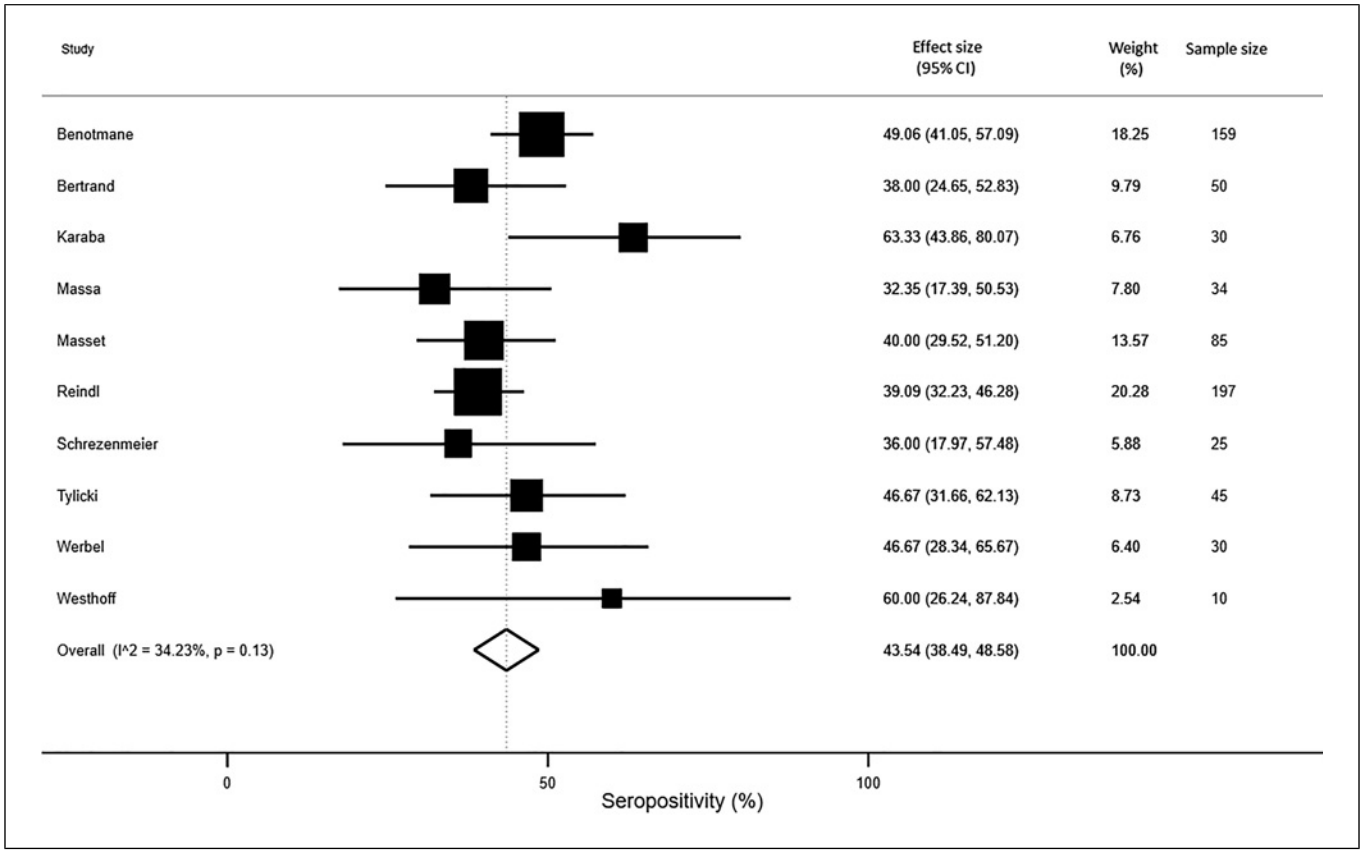

Fig. 4. Immunogenicity after three doses of COVID-19 vaccines in kidney transplant recipients who are non-responders or poor responders after two-dose vaccination.

prophylaxis using a long-acting monoclonal antibody combination (tixagevimab and cilgavimab) can be considered in KTRs [50], but its use is often limited by drug availability and should not be regarded as a substitute for effective immunization. Other useful strategies include ring vaccination of household members and close contacts in KTRs, especially for those with suboptimal immune response to vaccination.

Various immunological dysfunctions in CKD contribute to the reduced vaccination response, which include decreased expression of toll-like receptors and co-stimulation molecules on immune-reactive cells, impaired activation and proliferation of T lymphocytes, and diminished number and accelerated apoptosis of B cells in uremic environments [51]. Indeed, previous studies showed that anti-SARS-CoV-2 levels were significantly lower in HD patients compared with healthy controls, both after the second and third doses of COVID-19 vaccine [52, 53]. In our current meta-analysis, the immunogenicity of the three-dose COVID-19 vaccine regimen was affected to a lesser extent in dialysis patients when compared to KTRs. Here we demonstrated that 92.9% patients on chronic dialysis were seropositive for anti-SARS-CoV-2 antibodies after the third dose of COVID-19 vaccine, approximating the seropositivity rates (~95–100%) in healthy subjects. Furthermore, it is encouraging to see that among non-responders after the second dose of COVID-19 vaccine, two-thirds will develop anti-SARS-CoV-2 antibody after the third dose. One should also appreciate that these seroconversion rates only refer to the proportion of patients who have antibody levels above the detection limit of assay but do not reflect the quality and durability of humoral response. Also, whether such vaccine response is sufficient to protect vulnerable dialysis patients from severe COVID-19 disease and reduce the risk of outbreaks in dialysis units remains to be investigated.

Dialysis and kidney transplant patients, with substantial burden of medical co-morbidities and their immunocompromised states, are often worried about the side effects of COVID-19 vaccination, and this poses a barrier to achieve high vaccination uptake rates among these patients. Our present meta-analysis indicates that the third dose of COVID-19 vaccine is safe in patients on RRT, and no serious

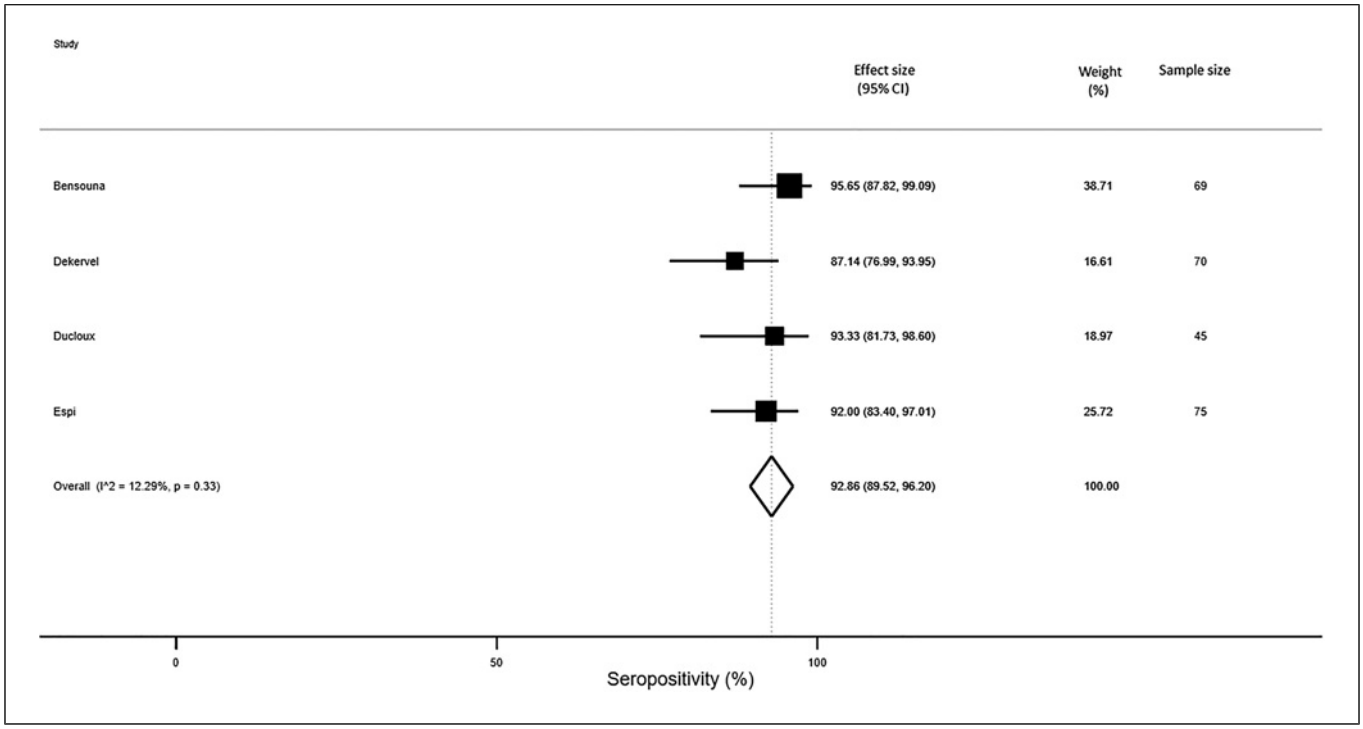

Fig. 5. Immunogenicity after three doses of COVID-19 vaccines in patients receiving chronic dialysis.

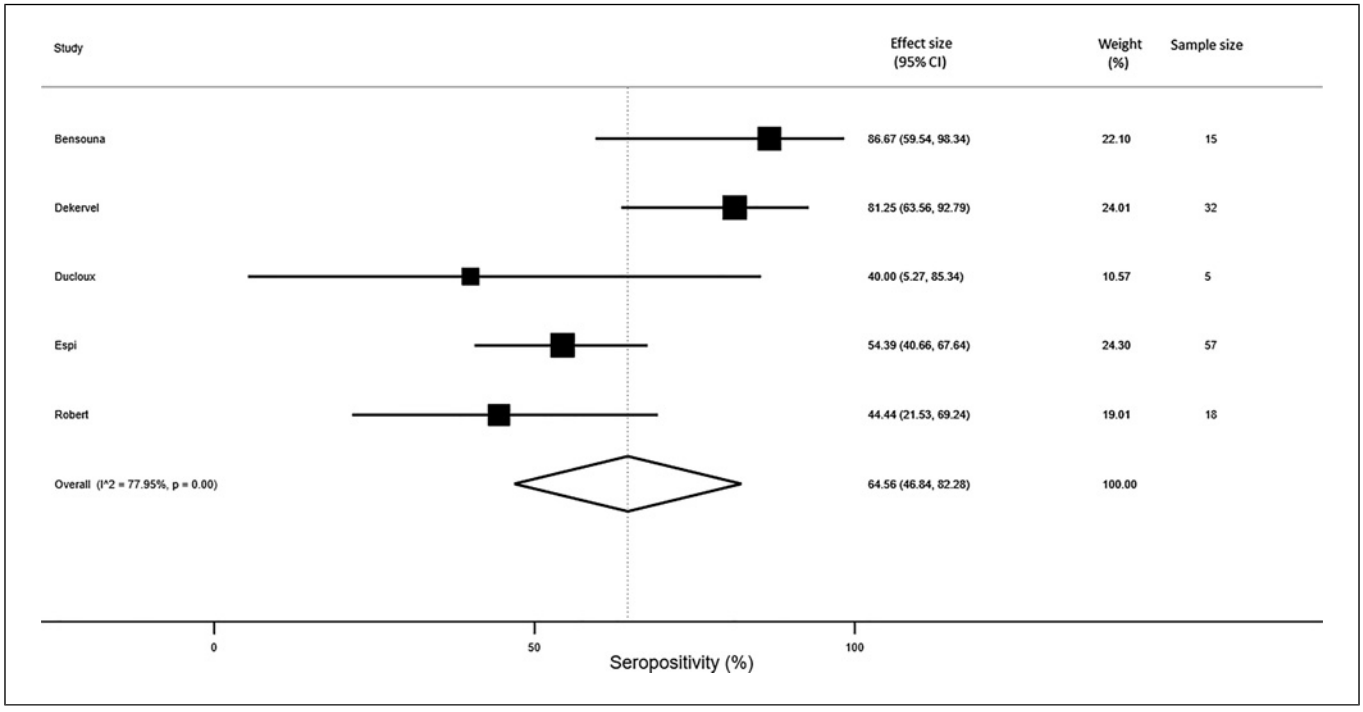

Fig. 6. Immunogenicity after three doses of COVID-19 vaccines in patients receiving chronic dialysis who are non-responders or poor responders after two-dose vaccination.

Table 1. Factors affecting immunogenicity of three-dose COVID-19 vaccination regimen in patients receiving RRT

Factors	Mean±SE	Percentage, %	Coefficient	SEr	Confidence interval	*p* value
Kidney transplant recipients						
Age	60±7.4 years	–	15.8	18.8	−68.1, 36.5	0.449
Transplant vintage	6.6±11.0 years	–	35.6	6.2	15.9, 55.4	0.01
DM	–	26.6	2.3	0.3	−1.5, 6.0	0.082
Steroids	–	73.8	1.3	3.4	−9.6, 12.1	0.732
CNIs	–	86.9	1.2	4.5	−55.8, 58.3	0.83
MMF	–	70.5	2.3	11.1	−45.2, 49.9	0.852
mTORi	–	21.5	27.2	8.1	−7.8, 62.1	0.079
Patients on chronic dialysis						
Age	68.8±16.5 years	–	−5.6	7.7	−38.8, 27.6	0.545
Dialysis vintage	5.7±17.0 years	–	−16.9	9.8	−59.2, 25.4	0.228

CNI, calcineurin inhibitors; DM, diabetes mellitus; MMF, mycophenolate mofetil; mTORi, mammalian target of rapamycin; SE, standard error.

adverse events have been observed. The administration of the third dose of COVID-19 vaccine also did not affect kidney allograft outcomes. Although local and systemic adverse events are quite common, these are usually mild and related to pain over injection sites and malaise.

This study has several limitations. First, the included studies only assess the vaccine immunogenicity by anti-SARS-CoV-2 and one should appreciate that the presence of antibodies does not necessarily correlate with functional humoral immunity required for long-term protection against SARS-CoV-2, though it is currently the best available surrogate marker [54, 55]. Second, important data on cellular immunity and clinical efficacy after the third dose of COVID-19 vaccine were often not reported. Third, it is well recognized that CKD population has a more rapid decline in antibody titers after vaccination compared to the general population [56], and in this study we only evaluated the immune response rate early postvaccination but not the longitudinal changes and durability of anti-SARS-CoV-2. Lastly, data on vaccine efficacy against emerging variants such as Omicron and Delta variants is lacking. Notwithstanding, this study is a comprehensive systematic review of studies on the immunogenicity and safety of the third dose of COVID-19 vaccine in patients on RRT and thus provides important evidence to substantiate the need for three-dose vaccination in kidney transplant and dialysis patients.

Conclusion

The third dose of COVID-19 vaccine in patients on RRT is associated with reduced immunogenicity, especially in KTRs. In KTRs, each year increase in transplant vintage was associated with 35.6% increase in anti-SARS-CoV-2 seropositivity. There are no adverse events associated with third dose of COVID-19 vaccine in KTRs. Further studies are needed to determine the optimal vaccination strategies in this vulnerable population.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors declare no conflicts of interest.

Funding Sources

There is no funding for this study. Desmond Yat-Hin Yap received research donations from the Wai Im Charitable Foundation and the Chan Sui Kau Family Benefits and Charitable Foundation. Desmond Yat-Hin Yap, Sydney Chi Wai Tang, and Tak Mao Chan received research funding support from the Mr. and Mrs. Tam Wing Fun Edmund Renal Research Fund. Tak Mao Chan received research funding support from the Wai Hung Charitable Foundation and Mr. S. Ho.

Author Contributions

Becky Mingyao Ma, Desmond Yat-Hin Yap, and Tak Mao Chan conceptualized the study. Becky Mingyao Ma and Anthony Raymond Tam were responsible for data curation and formal

analysis. Kam Wa Chan was responsible for the methodology. Becky Mingyao Ma wrote the original draft. Desmond Yat-Hin Yap, Tak Mao Chan, Sydney Chi Wai Tang, and Ivan Fan Ngai Hung reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 World Health Organization. Coronavirus (COVID-19) dashboard. Available from: http://covid19.who.int/ (accessed May 12, 2023).
2 Mahalingasivam V, Su G, Iwagami M, Davids MR, Wetmore JB, Nitsch D. COVID-19 and kidney disease: insights from epidemiology to inform clinical practice. Nat Rev Nephrol. 2022;18(8):485–98.
3 Udomkarnjananun S, Kerr SJ, Townamchai N, Susantitaphong P, Tulvatana W, Praditpornsilpa K, 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(1):20073.
4 Jager KJ, Kramer A, Chesnaye NC, Couchoud C, Sánchez-Álvarez JE, Garneata L, et al. Results from the ERA-EDTA Registry indicate a high mortality due to COVID-19 in dialysis patients and kidney transplant recipients across Europe. Kidney Int. 2020;98(6):1540–8.
5 Fishbane S, Hirsch JS, Nair V. Special considerations for Paxlovid treatment among transplant recipients with SARS-CoV-2 infection. Am J Kidney Dis. 2022;79(4):480–2.
6 Khoury J, Najjar-Debbiny R, Hanna A, Jabbour A, Abu Ahmad Y, Saffuri A, et al. COVID-19 vaccine - long term immune decline and breakthrough infections. Vaccine. 2021;39(48):6984–9.
7 Ma BM, Yap DYH, Yip TPS, Hung IFN, Tang SCW, Chan TM. Vaccination in patients with chronic kidney disease-Review of current recommendations and recent advances. Nephrology. 2021;26(1):5–11.
8 Ma BM, Tam AR, Chan KW, Ma MKM, Hung IFN, Yap DYH, et al. Immunogenicity and safety of COVID-19 vaccines in patients receiving renal replacement therapy: a systematic review and meta-analysis. Front Med. 2022;9:827859.
9 Chinnadurai R, Wu HHL, Cox E, Moore J, Clough T, Lamerton E, et al. Humoral response in hemodialysis patients following COVID-19 vaccination and breakthrough infections during Delta and Omicron variant predominance. Vaccines. 2022;10(4):498.
10 Rodríguez-Espinosa D, Montagud-Marrahi E, Cacho J, Arana C, Taurizano N, Hermida E, et al. Incidence of severe breakthrough SARS-CoV-2 infections in vaccinated kidney transplant and haemodialysis patients. J Nephrol. 2022;35(3):769–78.
11 Benotmane I, Gautier G, Perrin P, Olagne J, Cognard N, Fafi-Kremer S, et al. Antibody response after a third dose of the mRNA-1273 SARS-CoV-2 vaccine in kidney transplant recipients with minimal serologic response to 2 doses. JAMA. 2021;326(11):1063–5.
12 Bensouna I, Caudwell V, Kubab S, Acquaviva S, Pardon A, Vittoz N, et al. SARS-CoV-2 antibody response after a third dose of the BNT162b2 vaccine in patients receiving maintenance hemodialysis or peritoneal dialysis. Am J Kidney Dis. 2022;79(2):185–92.e1.
13 Bertrand D, Hamzaoui M, Lemée V, Lamulle J, Laurent C, Etienne I, et al. Antibody and T-cell response to a third dose of SARS-CoV-2 mRNA BNT162b2 vaccine in kidney transplant recipients. Kidney Int. 2021;100(6):1337–40.
14 Chavarot N, Morel A, Leruez-Ville M, Vilain E, Divard G, Burger C, et al. Weak antibody response to three doses of mRNA vaccine in kidney transplant recipients treated with belatacept. Am J Transpl. 2021;21(12):4043–51.
15 Del Bello A, Abravanel F, Marion O, Couat C, Esposito L, Lavayssière L, et al. Efficiency of a boost with a third dose of anti-SARS-CoV-2 messenger RNA-based vaccines in solid organ transplant recipients. Am J Transpl. 2022;22(1):322–3.
16 Dekervel M, Henry N, Torreggiani M, Pouteau LM, Imiela JP, Mellaza C, et al. Humoral response to a third injection of BNT162b2 vaccine in patients on maintenance haemodialysis. Clin Kidney J. 2021;14(11):2349–55.
17 Espi M, Charmetant X, Barba T, Mathieu C, Pelletier C, Koppe L, et al. A prospective observational study for justification, safety, and efficacy of a third dose of mRNA vaccine in patients receiving maintenance hemodialysis. Kidney Int. 2022;101(2):390–402.
18 Hall VG, Ferreira VH, Ku T, Ierullo M, Majchrzak-Kita B, Chaparro C, et al. Randomized trial of a third dose of mRNA-1273 vaccine in transplant recipients. N Engl J Med. 2021;385(13):1244–6.
19 Kamar N, Abravanel F, Marion O, Esposito L, Hebral AL, Médrano C, et al. Anti-SARS-CoV-2 spike protein and neutralizing antibodies at 1 and 3 months after three doses of SARS-CoV-2 vaccine in a large cohort of solid organ transplant patients. Am J Transpl. 2022;22(5):1467–74.
20 Karaba AH, Zhu X, Liang T, Wang KH, Rittenhouse AG, Akinde O, et al. A third dose of SARS-CoV-2 vaccine increases neutralizing antibodies against variants of concern in solid organ transplant recipients. medRxiv. 2021:2021.
21 Massa F, Cremoni M, Gérard A, Grabsi H, Rogier L, Blois M, et al. Safety and cross-variant immunogenicity of a three-dose COVID-19 mRNA vaccine regimen in kidney transplant recipients. EBioMedicine. 2021;73:103679.
22 Masset C, Kerleau C, Garandeau C, Ville S, Cantarovich D, Hourmant M, et al. A third injection of the BNT162b2 mRNA COVID-19 vaccine in kidney transplant recipients improves the humoral immune response. Kidney Int. 2021;100:1132–5.
23 Reindl-Schwaighofer R, Heinzel A, Mayrdorfer M, Jabbour R, Hofbauer TM, Merrelaar A, et al. Comparison of SARS-CoV-2 antibody response 4 weeks after homologous vs heterologous third vaccine dose in kidney transplant recipients: a randomized clinical trial. JAMA Intern Med. 2022;182(2):165–71.
24 Schrezenmeier E, Rincon-Arevalo H, Stefanski AL, Potekhin A, Staub-Hohenbleicher H, Choi M, et al. B and T Cell responses after a third dose of SARS-CoV-2 vaccine in kidney transplant recipients. J Am Soc Nephrol. 2021;32(12):3027–33.
25 Tylicki L, Debska-slizien A, Muchlado M, Ślizień Z, Gołębiewska J, Dąbrowska M, et al. Boosting humoral Immunity from mRNA COVID-19 vaccines in kidney transplant recipients. Vaccines. 2021;10(1):56.
26 Werbel WA, Boyarsky BJ, Ou MT, Massie AB, Tobian AAR, Garonzik-Wang JM, et al. Safety and immunogenicity of a third dose of SARS-CoV-2 vaccine in solid organ transplant recipients: a case series. Ann Int Med. 2021;174(9):1330–2.
27 Westhoff TH, Seibert FS, Anft M, Blazquez-Navarro A, Skrzypczyk S, Zgoura P, et al. A third vaccine dose substantially improves humoral and cellular SARS-CoV-2 immunity in renal transplant recipients with primary humoral nonresponse. Kidney Int. 2021;100(5):1135–6.
28 Marlet J, Gatault P, Maakaroun Z, Longuet H, Stefic K, Handala L, et al. Antibody responses after a third dose of COVID-19 vaccine in kidney transplant recipients and patients treated for chronic lymphocytic leukemia. Vaccines. 2021;9(10):1055.

29 Robert T, Lano G, Giot M, Fourié T, de Lamballeri X, Jehel O, et al. Humoral response after SARS-CoV-2 vaccination in patients undergoing maintenance haemodialysis: loss of immunity, third dose and non-responders. Nephrol Dia Transpl. 2022;37(2):390–2.
30 Ducloux D, Colladant M, Chabannes M, Yannaraki M, Courivaud C. Humoral response after 3 doses of the BNT162b2 mRNA COVID-19 vaccine in patients on hemodialysis. Kidney Int. 2021;100(3):702–4.
31 Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.
32 Ma LL, Wang YY, Yang ZH, Huang D, Weng H, Zeng XT. Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: what are they and which is better? Mil Med Res. 2020;7(1):7.
33 Tau N, Yahav D, Schneider S, Rozen-Zvi B, Abu Sneineh M, Rahamimov R. Severe consequences of COVID-19 infection among vaccinated kidney transplant recipients. Am J Transpl. 2021;21(8):2910–2.
34 Aydillo T, Gonzalez-Reiche AS, Aslam S, van de Guchte A, Khan Z, Obla A, et al. Shedding of viable SARS-CoV-2 after immunosuppressive therapy for cancer. N Engl J Med. 2020;383(26):2586–8.
35 CDC COVID-19 vaccines for moderately to severely immunocompromised people. Available from: http://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html. (accessed May 12 2023).
36 Petrelli F, Luciani A, Borgonovo K, Ghilardi M, Parati MC, Petrò D, et al. Third dose of SARS-CoV-2 vaccine: a systematic review of 30 published studies. J Med Virol. 2022;94(6):2837–44.
37 Halloran PF. Immunosuppressive drugs for kidney transplantation. N Engl J Med. 2004;351(26):2715–29.
38 Roberts MB, Fishman JA. Immunosuppressive agents and infectious risk in transplantation: managing the "net state of immunosuppression. Clin Infect Dis. 2021;73(7):e1302–e1317.
39 Wullschleger S, Loewith R, Hall MN. TOR signaling in growth and metabolism. Cell. 2006;124(3):471–84.
40 Allison AC. Mechanisms of action of mycophenolate mofetil. Lupus. 2005;14(Suppl 1):s2–8.
41 Masset C, Benotmane I, Dantal J, Garandeau C, Gauthier-Vargas G, Cantarovich D, et al. A fourth SARS-CoV-2 mRNA vaccine in strictly seronegative kidney transplant recipients. Kidney Int. 2022;101(4):825–6.
42 Caillard S, Thaunat O, Benotmane I, Masset C, Blancho G. Antibody response to a fourth messenger RNA COVID-19 vaccine dose in kidney transplant recipients: a case series. Ann Intern Med. 2022;175(3):455–6.
43 Jara A, Undurraga EA, Zubizarreta JR, González C, Pizarro A, Acevedo J, et al. Effectiveness of homologous and heterologous booster doses for an inactivated SARS-CoV-2 vaccine: a large-scale prospective cohort study. Lancet Glob Health. 2022;10(6):e798–806.
44 Atmar RL, Lyke KE, Deming ME, Jackson LA, Branche AR, El Sahly HM, et al. Homologous and heterologous Covid-19 booster vaccinations. N Engl J Med. 2022;386(11):1046–57.
45 Masset C, Ville S, Garandeau C, Le Borgne F, Letellier T, Cantarovich D, et al. Observations on improving COVID-19 vaccination responses in kidney transplant recipients: heterologous vaccination and immunosuppression modulation. Kidney Int. 2022;101(3):642–5.
46 Di Fusco M, Lin J, Vaghela S, Lingohr-Smith M, Nguyen JL, Scassellati Sforzolini T, et al. COVID-19 vaccine effectiveness among immunocompromised populations: a targeted literature review of real-world studies. Expert Rev Vaccin. 2022;21(4):435–51.
47 Kho MML, Messchendorp AL, Frölke SC, Imhof C, Koomen VJ, Malahe SRK, et al. Alternative strategies to increase the immunogenicity of COVID-19 vaccines in kidney transplant recipients not responding to two or three doses of an mRNA vaccine (RECOVAC): a randomised clinical trial. Lancet Infect Dis. 2022;27:S1473–3099.
48 Bruminhent J, Setthaudom C, Phornkittikorn P, Chaumdee P, Prasongtanakij S, Srisala S, et al. An additional dose of viral vector COVID-19 vaccine and mRNA COVID-19 vaccine in kidney transplant recipients: a randomized controlled trial (CVIM 4 study). Am J Transpl. 2022;22(11):2651–60.
49 Mrak D, Sieghart D, Simader E, Tobudic S, Radner H, Mandl P, et al. Heterologous vector versus homologous mRNA COVID-19 booster vaccination in non-seroconverted immunosuppressed patients: a randomized controlled trial. Nat Commun. 2022;13(1):5362.
50 Levin MJ, Ustianowski A, De Wit S, Launay O, Avila M, Templeton A, et al. Intramuscular AZD7442 (Tixagevimab–Cilgavimab) for prevention of covid-19. N Engl J Med. 2022;386(23):2188–200.
51 Van Praet J, Reynders M, De Bacquer D, Viaene L, Schoutteten MK, Caluwé R, et al. Predictors and dynamics of the humoral and cellular immune response to SARS-CoV-2 mRNA vaccines in hemodialysis patients: a multicenter observational study. J Am Soc Nephrol. 2021;32:3208–20.
52 Kurts C, Panzer U, Anders HJ, Rees AJ. The immune system and kidney disease: basic concepts and clinical implications. Nat Rev Immunol. 2013;13:738–53.
53 Sanders J-SF, Bemelman FJ, Messchendorp AL, Baan CC, van Baarle D, van Binnendijk R, et al. The RECOVAC immune-response study: the immunogenicity, tolerability, and safety of COVID-19 vaccination in patients with chronic kidney disease, on dialysis, or living with a kidney transplant. Transplantation. 2022;106:821–34.
54 Garcia-Beltran WF, Lam EC, Astudillo MG, Yang D, Miller TE, Feldman J, et al. COVID-19-neutralizing antibodies predict disease severity and survival. Cell. 2021;184:476–88.e11.
55 Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat Med. 2021;27:1205–11.
56 Feng S, Phillips DJ, White T, Sayal H, Aley PK, Bibi S, et al. Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. Nat Med. 2021;27:2032–40.