REVIEW ARTICLE

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Humoral and cellular immune response to severe acute respiratory syndrome coronavirus-2 vaccination in haemodialysis and kidney transplant patients

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Abstract

End-stage renal disease (ESRD) patients are amongst the vulnerable groups and thus prioritized in the Coronavirus disease-2019 vaccination programmes. However, this cohort was excluded from vaccine-trials and yet shares the same vaccination scheme with the general population. Here, we explore trends of immune response-proportions amongst ESRD patients on renal replacement therapy for up to 4 weeks post-vaccination completion with Pfizer/Moderna vaccines. From inception to 10 July 2021, we searched six online-databases for articles reporting humoral and cellular immune response proportions for up to 4 weeks post booster-vaccination. We pooled the responders' proportions by meta-analysis and conducted a meta-regression stratifying outcomes by significant confounders. Twenty-seven eligible studies reported 2789 ESRD patients. 1337, 1452 and 477 were on haemodialysis, received kidney transplantation, and healthy controls, respectively. Haemodialysis patients' proportions of humoral and cellular immune responses varied from 87.29% (80.77–93.81)–88.78% (86.76–90.80) and 62.86% (56.56, 69.17)–85.78% (78.99, 92.57), respectively, between first- and fourth-weeks. Kidney transplant patients' proportions of humoral and cellular immune responses ranged from 2.6% (0.06–13.48)–29.87% (27.68, 32.07) and 5.13% (0.63–17.3)–59.84% (54.57–65.10), respectively, between first- and fourth-weeks. All healthy controls maintained ≥93% proportions of both responses throughout the follow-up. Study design and country of study influenced the pooled response proportions. Conclusively, haemodialysis and kidney transplant patients have lower proportions of humoral and cellular immune responses than healthy controls. However, haemodialysis patients' response proportions improve, reaching near healthy-control levels by the fourth week. Kidney transplant patients' lower responses' proportions also improve but remain significantly lower than healthy controls throughout four-weeks. The "one-size-fits-all" vaccination scheme might be inadequate for kidney transplant patients.

KEYWORDS
clinical immunology, COVID-19, haemodialysis, kidney transplantation, SARS-CoV-2

SUMMARY AT A GLANCE

This meta-regression analysis demonstrated varying humoral and cellular immune responses to mRNA coronavirus vaccination amongst haemodialysis and kidney transplant patients.

1 | INTRODUCTION

Chronic kidney disease (CKD) increases the risk for worsening Coronavirus Disease 2019 (COVID-19).[1] COVID-19 patients with pre-existing autoimmune renal disorders have a higher risk of relapse[2] and mortality.[3] Moreover, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) can cause damage to a healthy kidney through directly infecting renal cells and mediate tubular pathogenesis through dysregulated inflammation and cytokine storm necessitating renal replacement therapy (RRT).[4]

COVID-19 affects between 20% and 25% of end-stage renal disease (ESRD) patients on RRT, causing 16%–32% fatalities.[5] Race/ethnicity (non-Hispanic Black, Hispanic and Asian), age >60 years, obesity and type-2-diabetes increase the risk of adverse outcomes.[6,7] In addition, kidney transplant patients with COVID-19 are 1.28 times more likely to die than matched-haemodialysis patients.[5]

In less than 2 years since the declaration as a pandemic, breakthroughs in the management of COVID-19 have transpired.[8] These include advances in supportive care, pharmacological treatment, therapeutic antibodies from convalescent patients' sera and vaccines.[8] Available vaccines are based on several modes of actions including inactivated virus (i.e., CoronaVac), viral subunit (i.e., NVX-CoV2373), viral-vector (i.e., ChAdOx1 nCoV-19) or messenger ribonucleic-acid (mRNA) vaccines (i.e., BNT162b2/Pfizer vaccine, mRNA-1273/Moderna vaccine).[9] Different vaccines have proven adequate efficacies in relative-risk-reduction (RRR) of severe COVID-19 disease and deaths. Moreover, anti-SARS-CoV-2-Spike antibodies developed through full-dose vaccination have shown to be more effective (including against variants of concern) than those isolated from convalescent patients' sera.[10]

With health authorities extending vaccines provision, it is evident that ESRD patients on RRT, amongst other highly vulnerable groups, need to be prioritized. However, this cohort was largely excluded from the initial vaccine trials.[11] Yet, the current vaccine schemes in this cohort are generalized to that of the general population. Data for this cohort regarding pharmacodynamics and effectiveness of the vaccine in inducing humoral or cellular immunity against SARS-CoV-2 is currently debatable or scarce.[12] In addition, there are concerns that COVID-19 vaccination exacerbates autoimmune renal diseases,[2] and uremia and use of immunosuppressives (i.e., in kidney transplantation) lower immune response, hence low-vaccine efficacy.[11,13] Our present study aims to explore the trends of humoral and cellular immune response proportions amongst ESRD patients on RRT from the first through fourth-week post-completion of vaccination with mRNA vaccines.

2 | MATERIALS AND METHODS

2.1 | Eligibility criteria

We abode by PRISMA guidelines, Supplementary Material S1. We included original research reporting the proportions of humoral or cellular immune response amongst adult patients on haemodialysis or who received kidney transplantation (and healthy controls) between the first and fourth weeks after completion of SARS-CoV-2 vaccination with mRNA vaccines. Only articles published in English or Chinese were eligible for inclusion. We excluded reviews, duplicates, animal studies and pre-prints. We excluded studies reporting patients who received single vaccine dose or kidney transplantation with another organ transplantation. Studies involving the paediatric population or positive SARS-CoV-2 seroconversion before the first vaccination dose were also ineligible.

2.2 | Information sources and search strategy

We searched PubMed, Google Scholar, EMBASE, SCOPUS, Chinese database National Knowledge Infrastructure (CNKI) and the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Registry. The searches were conducted from conception until 10 July 2021. We used advanced search tools in all the databases, firstly utilizing keywords and repeated with MeSH terms (see Supplementary Table S1 for detailed search strategy). We searched for additional sources from screening the reference lists of eligible articles, references of review articles, and google search for published articles using a combination of free texts: immune response, SARS-CoV-2 vaccination, haemodialysis and kidney transplant patients.

2.3 | Study selection process and data collection

We utilized automation- and human-based search to decide on inclusion. The automation tool used filters to exclude animal studies (Filter: Species→Humans) and paediatric patients (Filter: Age→Adult: 19 + years). Human-based decision on eligibility involved six authors (Joel Swai, Ming Gui, Mao Long, Zhu Wei, Zixuan Hu and Shaojun Liu) screening the titles and abstracts of the independently searched results followed by a thorough reading of retrieved full-text reports afterward.

We designed a data collection spreadsheet (see Supplementary Material S2) from Microsoft Excel (MicrosoftExcel® for Microsoft365-MSO[16.0.14131.20296]64-bit) basing on the

principle of Population-Intervention-Comparison-Outcome-Study (i.e., PICOS). Data collection from full-text reports was independently performed by five authors (Joel Swai, Ming Gui, Mao Long, Zhu Wei and Shaojun Liu). In the processes above, the last author sorted the disputed decisions on eligibility.

2.4 | Data items

We had four primary endpoints: (1) Proportion of humoral immunity responders amongst haemodialysis patients after vaccine completion with an mRNA vaccine; (2) the proportion of cellular immunity responders amongst haemodialysis patients after vaccination-completion with an mRNA vaccine; (3) the proportion of humoral immunity responders amongst kidney transplant patients after vaccination completion with an mRNA vaccine; and (4) the proportion of cellular immunity responders amongst kidney transplant patients after vaccination completion with mRNA vaccine. These endpoints were re-recorded at the first, second, third and fourth-week post-vaccination completion.

We recorded authors' names, year of publication, study setting, study design, sample size, demographic data and RRT type used. Data regarding vaccination included the name of vaccine administered, number of doses and their intervals, SARS-CoV-2 serostatus before vaccination, name of the diagnostic test and the definition of the positive immune response. Humoral immune response was defined as the development of detectable titre levels of anti-SARS-CoV-2 immunoglobulin-G (IgG), namely anti-Spike-IgG seroconversion. Cellular immunity response was defined as the development of spike-stimulated antigen-reactive T-helper cells. Our results were compatible with all outcome domains in all the studies retrieved.

2.5 | Study quality appraisal

We utilized the Newcastle-Ottawa scale (see Supplementary Material S3) to assess the bias in each of the included studies. The NOS is designed to use one or two stars (*) to rank the extent of potential bias in the participants' selection, addressing confounders and measuring the outcome. The total number of stars ranks the overall study quality as low, moderate or high.

2.6 | Effect measure and analysis

STATA (StataCorp.2019. Stata Statistical Software: Release 16. College Station, TX:StataCorp LLC) was used for statistical analyses. The effect measure was *proportion*. This was calculated as the number of patients having a positive immune response (humoral and cellular, separately) divided by the sample size of the group tested.

The standard error (*se*), upper and lower confidence intervals (*uci* and *lci*, respectively) of the *proportion* at 95% confidence interval, was generated using the STATA command: *cii proportions n e*, *exact* where *n* is the group's sample size tested, *e* is the number of recorded

positive immune response patients. The proportions were then pooled using a *metan command*:[14] *metan proportion lci uci*. The command generated forest plots, Cochran's Q test and heterogeneity level (I^2). A random-effect model was used. The *metan* command was repeated for each of four endpoints (see Section 2.4 above). Studies reporting the same endpoint were pooled in the same forest plot. The pooled proportions were illustrated in column charts generated from Microsoft Excel (MicrosoftExcel®2019MSO, Version 16.0.14131.20278).

2.7 | Publication bias

We utilized funnel plots to explore publication biases caused by the studies' different sizes (i.e., small-study effect). The plots were generated by *metafunnel command*: *metafunnel ln(proportion) se* whereby *ln(proportion)* is the logit-transformation of the responder's proportions. The plot asymmetries were quantified by Egger's test under the Null-hypothesis that there is no small-study effect. We executed the *metabias command*: *metabias ln(proportion) se, egger* to calculate Egger's test value.

2.8 | Sensitivity analysis

We explored heterogeneity by sensitivity analyses. We performed meta-regression stratifying each outcome by country of study, study design (i.e., cohort or case–control), type of vaccine administered (i.e., BNT162b2, mRNA-1273, or both), and participants' age (i.e., > or ≤60). We used the STATA's command: *metareg ln(proportion) cf*, *wsse(se) eform* whereby *cf* is the confounding factor (i.e., country of study, study-design, vaccine type or participants' age) and *eform* is the exponential form. We used *Knapp-Hartung* as opposed to the *DerSimonian-Laird* method modifying effects in the random-effect model. We generated the linear plots by the STATA's command: *metareg ln(proportion) cf*, *wsse(se) graph*. In outcomes with an insufficient number of studies to perform meta-regression, we conducted descriptive analyses.

2.9 | Certainty assessment

We assessed the certainty for each outcome by using the online version of Grading of Recommendations Assessment, Development and Evaluation (GRADE) named GRADEPro.[15] We based the assessment on the number of studies, study design, risk of bias, inconsistency, indirectness and imprecision. The overall certainty for each pooled proportion was graded as very low, low, moderate and high.

3 | RESULTS

3.1 | Study selection

The search resulted in a total of 1397 records, out of which 1106 were excluded as duplicates, flagged ineligible by automated tools and one was
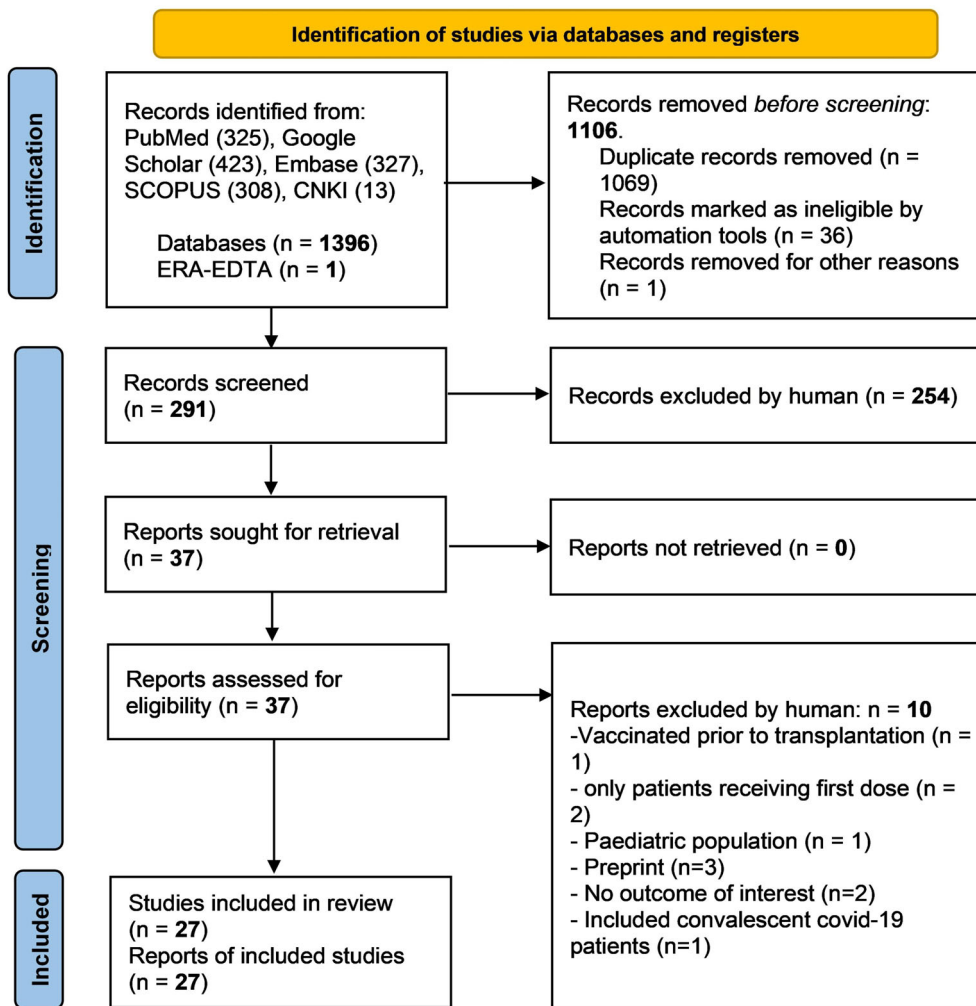
Identification of studies via databases and registers

Identification

Records identified from:
PubMed (325), Google Scholar (423), Embase (327), SCOPUS (308), CNKI (13)

Databases (n = **1396**)
ERA-EDTA (n = **1**)

Records removed *before screening*: **1106**.
Duplicate records removed (n = 1069)
Records marked as ineligible by automation tools (n = 36)
Records removed for other reasons (n = 1)

Screening

Records screened (n = **291**)

Records excluded by human (n = **254**)

Reports sought for retrieval (n = **37**)

Reports not retrieved (n = **0**)

Reports assessed for eligibility (n = **37**)

Reports excluded by human: n = **10**
-Vaccinated prior to transplantation (n = 1)
- only patients receiving first dose (n = 2)
- Paediatric population (n = 1)
- Preprint (n=3)
- No outcome of interest (n=2)
- Included convalescent covid-19 patients (n=1)

Included

Studies included in review (n = **27**)
Reports of included studies (n = **27**)

a registered proposal.[16] We (human-based) excluded 264 studies through screening and eligibility criteria reasons. The latter involved studies reporting vaccinated before kidney transplantation;[17] patients assessed after first dose only;[18,19] paediatric population;[20] preprints;[21] and studies that involved vaccination of covid-19 seroconverted patients.[22,23] We found 27 studies eligible. Figure 1 summarizes the study selection process.

3.2 | Study characteristics

Table 1 summarizes the characteristics of 27 included studies from different countries. Twelve and fifteen studies were case–control and cohort in design, respectively. The studies report 3266 participants; 2789 were cases (1337 on haemodialysis and 1452 kidney transplant), and 477 were healthy controls. Most studies administered two BNT162b2 vaccines at 21 days intervals, unlike three studies[11,24,25] (all in France) administered at 28 days intervals. The latter scheme abides by the French National Health Authority (Haute Autorité de Santé, HAS).[26]

All studies reported patients with negative SARS-CoV-2-19-seroconversion, pre-vaccination, except four[12,13,25,27] that reported both positive and negative separately. However, the proportions were calculated from the seronegative cohort only. All studies reported the

quantity or responders' proportions (i.e., %) of humoral cellular (or both[24,28–31]) immune response at various times post-vaccination, from 1-week,[11,29,31,32] 2-weeks,[11,33–36] 3-weeks[30–32,37,38] and 4-weeks.[11,12,25,28,29,39–42] Other studies reported a follow-up of up to 10 weeks.[31,42] Studies measuring the humoral immune response quantified the anti-SARS-CoV-2 IgG in Arbitrary Units/millilitres, and two reported both IgG and IgA.[29,39]

3.3 | The humoral response amongst haemodialysis patients

Figure 2 summarizes the pooled proportions of humoral immune responders amongst haemodialysis patients at first,[29,31,43] second,[11,36] third[30–32,37,38] and fourth[11,12,25,27–30,39,42,44] weeks post-vaccination completion. The pooled responders' proportions for haemodialysis patients were; 87.29% (80.77, 93.81), 88.98% (83.61, 94.35), 92.67% (89.93, 95.42) and 88.78% (86.76, 90.80) at first, second, third and fourth weeks, respectively. The control group, on the other hand, demonstrated a pooled response proportions of 100% (90.97, 100), 100% (90.80, 109.20), 100% (92.30, 100) and 99.85% (98.55, 101.15) at first, second, third and fourth weeks, respectively (Supplementary Figure S1). Haemodialysis patients demonstrated

TABLE 1 Study characteristics

Author (year); country	Study design; mean/median age (case, control)	Renal replacement therapy; total sample size (cases, controls)	Vaccine administered; number of doses (dosage interval)	Exposure to SARS-CoV-2 before dose-1 vaccination (yes/no); time of assessment post-vaccination	Immune response assessed (humoral/cellular)	Name of diagnostic test and; the cut-off points for a positive test [sensitivity, specificity]	Proportions (%) of responders at different times post-vaccination completion (cases %, controls %)			
							First week	Second week	Third week	Fourth week
Firket et al. (2021);[33] Belgium	Case-control; (51.5 ± 10.5, 49.7 ± 13.8)	KT; 40(10, 10)[b]	BNT162b2; 2 (21 days)	No[b]; 15 days	Humoral	DiaSorin LIAISON® CLIA; NR [NR]	-	0%, 100%	-	-
Dandhu et al. (2021);[11] France	Case-control; KT (64.8 ± 11.5, 51.6 ± 6.8) HD (73.5 ± 12.8, 51.6 ± 6.8)	KT; 81 (74, 7) HD; 85 (78, 7)	BNT162b2; 2 (28 days)	No; 14, 28, 36 and 58 days	Humoral	LIAISON SARS-CoV-2 TrimericS IgG (DiaSorin, Saluggia, Italy); >13 AU per ml [positive agreement: 98.7%; negative agreement: 99.5%]	-	KT: 4.1%, 100% HD: 81%; 100%	-	KT: NR, 100% HD: NA; 100%
Rincon-Arevalo et al. (2021);[39] Germany	Case-control; KT (62.4 [51.25–69.5], 51.0 [34.0–80]) HD (69.0 [81.575–63.0], 51.0 [34.0–80])	KT; 75 (40, 35) HD; 75 (40, 35)	BNT162b2; 2 (21 days)	NR; 3–4 weeks	Humoral	SARS-CoV-2 spike (S) protein ELISA; NR [NR]	-	-	-	KT: 2.5%, 100% HD >70.5%, 100%
Bertrand et al. (2021);[28] France	Cohort (63.5 ± 16.3)	KT; 45 HD; 10 (not all initially available 225, and 75 were assessed)	BNT162b2; 2 (21 days)	No; 4 weeks	Humoral; cellular	ARCHITECT IgG II Quant test (Abbott, USA); >50 AU/ml is positive. [positive agreement, 99.4%; negative agreement, 99.6%] SFC > 3 for CMI, [NR]	-	-	-	KT -Humora: 17.8% -Cellular: 57.8% HD -Humoral:88.9% -Cellular: 100%
Song et al. (2021);[41] USA	Cohort; (most were >65 years)	KT; 7	BNT162b2; 2 (21 days); mRNA-1273; 2 (28 days)	No; 33 days	Humoral	NR; NR [NR]	-	-	-	43%
Rozen-Zvi et al. (2021)[40] Israel	Cohort; (57.51 ± 13.84)	KT; 308	BNT162b2; 2 (21 days)	NR; 4 weeks	Humoral	SARS-CoV-2 IgG II Quant (Abbott©) assay IgG was >50 AU/ml [NR]	-	-	-	36.4%
Korth et al. (2021);[34] Germany	Case-control; (57.7 ± 13.5, 44.4 ± 9.2)	KT; 46 (23, 23)	BNT162b2; 2 (22.0 ± 4.6 days)	No; 2 weeks	Humoral	anti-SARS-CoV-2 IgG CLIA IgG > 13.0, [NR]	-	21.7%, 100%	-	-
Grupper et al. (2021);[35] Israel	Case-control; (58.6 ± 12.7, 52.7 ± 11.5)	KT; 161 (136, 25)	BNT162b2; 2 (21 days)	No; 15 (10–20) days	Humoral	LIAISON SARS-CoV-2 S1/S2 IgG CLIA; >15 AU/ml [NR]	-	37.5%, 100%	-	-

(Continues)

TABLE 1 (Continued)

Author (year); country	Study design; mean/median age (case, control)	Renal replacement therapy; total sample size (cases, controls)	Vaccine administered; number of doses (dosage interval)	Exposure to SARS-CoV-2 before dose-1 vaccination (yes/no); time of assessment post-vaccination	Immune response assessed (humoral/cellular)	Name of diagnostic test and; the cut-off points for a positive test [sensitivity, specificity]	Proportions (%) of responders at different times post-vaccination completion (cases %, controls %)			
							First week	Second week	Third week	Fourth week
Sattler et al. (2021);[29] Germany	Case-control; KT (57.38 ± 14.04, 53.03 ± 17.58) HD (67.39 ± 11.88, 53.03 ± 17.58)	KT; 78 (39, 39) HD; 65 (26; 39)	mRNA-1273; 2 (21 days)	No; day 8 ± 1, and 23 ± 5 days	Humoral; cellular	ELISA-based (Euroimmun, Lübeck, Germany) IgG and IgA; flow cytometry for spike specific CD4, CD8 [NR]	KT: -Humoral **2.6%, 100%** -Cellular (5.13%, NR) HD: -Humoral 84.62%,100% -Cellular (NR, NR)	–	–	KT -Humoral: 8.33%, 92%–100% -Cellular: **92%–100%, 92%–100%** HD -Humoral: **NR, NR** -Cellular: **92%–100%, 92%–100%**
Benotmane et al. (2021);[13] France	Cohort; 58 [51–67.7]	KT; 205	mRNA-1273; 2 (28 days)	No, (Yes-not included in the analysis)[b]; 1 month	Humoral	ARCHITECT IgG II Quant test (Abbott); Titers >50 AU/ml [NR]	–	–	–	47.8%
Ducloux et al. (2021);[27] France	Cohort; NR	HD; 50	BNT162b2; 2–3 (NR)	No, yes[b]. Separately. 28 days after 2nd. (Also 28 days after 3rd)[c]	Humoral	SARS-Cov-2 immunoassay, Abbott®; > 50 UA/ml, [NR]	–	–	–	89%
Broseta et al. (2021);[30] Spain	Cohort; (70.9 ± 14.96)	HD; 205	BNT162b2; 2 (21 days) mRNA-1273; 2 (28 days)	No; 3 weeks	Humoral; cellular	Humoral: Siemens Healthineers Atellica® IM SARS-CoV-2 IgG (sCOVG) assay; ≥1 [Sensitivity: 96.41%, specificity: 99.9%] Cellular: flow cytometry; > events of CD4+ IFN-γ + CD69+, with >2-fold change compared to unstimulated. [NR]	–	–	Humoral 95.4% Cellular 62%	–
Longlune et al. (2021);[25] France	Cohort; (64 ± 14)	HD; 109	BNT162b2; 2–3 (28 days)	No, (yes-not included in the analysis); 28 days after 2nd. (also 28 days 3rd)[c]	Humoral	ELISA-kit (Beijing Wantai Biological Pharmacy Enterprise Co., Ltd., China); >1.1 [NR]	–	–	–	83.07%[d]

TABLE 1 (Continued)

Author (year); country	Study design; mean/median age (case, control)	Renal replacement therapy; total sample size (cases, controls)	Vaccine administered; number of doses (dosage interval)	Exposure to SARS-CoV-2 before dose-1 vaccination (yes/no); time of assessment post-vaccination	Immune response assessed (humoral/cellular)	Name of diagnostic test and; the cut-off points for a positive test [sensitivity, specificity]	Proportions (%) of responders at different times post-vaccination completion (cases %, controls %)			
							First week	Second week	Third week	Fourth week
Goupil et al. (2021),[12] Canada	Case-control; (70 ± 14, 47 ± 12)	HD; 154 (131, 20)[b]	BNT162b2; 2 (3 weeks)	No, (yes;not included in the analysis)[b], 28 days	Humoral	ELISA (Abbott Architect 1200SR; +3 SD above the mean relative light units from COVID-19 negative plasma obtained from 10 volunteers pre-pandemic. [NR]	-	-	-	43%, 95%
Jahn et al. (2021),[36] Germany	Case-control; (54.0 [53.0–57.0], 45.5 [41.2; 54.7])	HD; 88 (72, 16)	BNT162b2; 2 (3–4 weeks)	No; 14 days	Humoral	anti-SARS-CoV-2 IgG CLIA (LIAISON® SARS-CoV-2 TrimericS IgG assay, Diasorin, Saluggia, Italy); ≥13.0 [NR]	-	93%, 100%	-	-
Yanay et al. (2021),[42] Israel	Case-control; (69 [62–78], 50.5 [41–60])	HD; 292 (160, 132)	BNT162b2; 2 [NR]	1-month weeks	Humoral	LIAISON SARS-CoV-2 S1/S2 IgG; DiaSorin); [NR]	-	-	-	90%, 100%
Schrezenmeier et al. (2021),[31] Germany	Case-control; (74 [66.0, 82.0], 80 [75.75–82.25])	HD; 87 (36,44)[b]	BNT162b2; 2 (21 days)	No; ~1, ~3–4 and ~10 weeks	Humoral; cellular	Humoral: anti-SARS-CoV-2-S1 ELISA. (Euroimmun Medizinische Labordiagnostika AG, Lübeck, Germany). [NR] Cellular: Interferon-gamma release assay (IGRA). [NR]	Humoral 55.56%, NR	-	Humoral: (88.9% [at 10 weeks 84.37%], NR) Cellular: (67.7%, 93.3%,)	-
Frantzen et al. (2021),[44] France	Cohort; (76 ± 13)	HD; 244	BNT162b2; 2 (21 days)	No; 1 month	Humoral	Elecsys® Anti SARS-CoV-2 S test; >15 U/ml [NR]	-	-	-	91%
Simon et al. (2021),[38] Austria	Case-control; (67 [34–86], 49 [29–65])	HD; 161 (81,80)	BNT162b2; 2 (21 days)	No; 21 days	Humoral	ElecsysVR Anti-SARS-CoV-2 S on a Cobas e 801; NR [NR]	-	-	73%, NR	-
Speer et al. (2021),[32] Germany	Case-control; (72 [51–82], 67 [54–90])	HD; 68 (22,46)	BNT162b2; 2 (21 days)	No; 21 days	Humoral	SARS-CoV-2 total assay (Siemens, Eschborn, Germany); ≥1 [sensitivity: 89%, specificity 100%]	-	-	82%, 100%	-

(Continues)

TABLE 1 (Continued)

Author (year); country	Study design; mean/median age (case, control)	Renal replacement therapy; total sample size (cases, controls)	Vaccine administered; number of doses (dosage interval)	Exposure to SARS-CoV-2 before dose-1 vaccination (yes/no); time of assessment post-vaccination	Immune response assessed (humoral/cellular)	Name of diagnostic test and; the cut-off points for a positive test [sensitivity, specificity]	Proportions (%) of responders at different times post-vaccination completion (cases %, controls %)			
							First week	Second week	Third week	Fourth week
Chan et al. (2021);[43] USA	Cohort; (70 ± 11)	HD; 41[b]	mRNA-1273; 2 (28 days)	No[b]; 1 week	Humoral	Abbot IgG nucleocapsid assay, anti-N; >1.39 [sensitivity: 96.8%, specificity 99.6%]	95%	-	-	-
Rodriguez-Espinoza et al. (2021);[37] Spain	Cohort; (65.7 ± 16.3)	HD; 32	mRNA-1273; 2 (28 days)	No; 3 weeks	Humoral	Siemens Healthineers Atellica IM SARS-CoV-2 IgG assay; NR [NR]	-	-	97%	-
Husain et al. (2021);[45] USA	Cohort; 66 (42–87)	KT; 25	BNT162b2; 2 (21 days); mRNA-1273 2 (28 days)	No (3 Yes-not included in the analysis); 28 days	Humoral	Anti-spike IgG immunoassay Liaison assay [Dia-Sorin, Saluggia, Italy]; NR [sensitivity: 96.6%, specificity: 100%]	-	-	-	28%
Chavarot et al. (2021);[24] France	Cohort; 64 (53–73)	KT; 101	BNT162b2; 2 (28 days)	No; 32 days	Humoral; cellular	Humoral: SARS-CoV-2 IgG II Quant antibody test (Abbott); [sensitivity: 97%, specificity: >99%] Cellular: (EliSpot) measuring interferon-γ produced by specific SARS-CoV-2 T-cells; S1 reactivity >20 spots [NR]	-	-	-	Humoral: 5.7% Cellular: 30.4%
Cucchiari et al. (2021);[23] Spain	Cohort; (59 ± 52.42)	KT (and Pancreas); 117[a]	mRNA-1273; 2 (4 weeks)	No (31 yes-not included in the analysis); 14 days	Humoral; cellular	Humoral: Luminex Cellular: ELISpot	-	Humoral: 23.1% Cellular: 54.7%	-	-
Ou et al. (2021);[22] USA	Cohort; 58 (45–68)	KT; 400[a]	BNT162b2; 2 (21 days); mRNA-1273 2	No; 1 month	Humoral	Anti-SARS-CoV-2-S1 ELISA (EUROIMMUN, Lübeck, Germany); ≥1.1 arbitrary units. (sensitivity: 87.0%, specificity: 97.5%) Anti-SARS-CoV-2-S1 ELISA (Roche Elecsys, Rotkreuz, Switzerland); ≥0.8 U/ml [Sensitivity: 84.0%, Specificity: 100%]	-	-	-	48%

TABLE 1 (Continued)

Author (year); country	Study design; mean/median age (case, control)	Renal replacement therapy; total sample size (cases, controls)	Vaccine administered; number of doses (dosage interval)	Exposure to SARS-CoV-2 before dose-1 vaccination (yes/no); time of assessment post-vaccination	Immune response assessed (humoral/cellular)	Name of diagnostic test and; the cut-off points for a positive test [sensitivity, specificity]	Proportions (%) of responders at different times post-vaccination completion (cases %, controls %)			
							First week	Second week	Third week	Fourth week
Boyarsky et al. (2021);[46] USA	Cohort; 55.9 (41.3–67.4)	KT (and other); 322[a]	BNT162b2; 2 (21 days); mRNA-1273 2 (28 days)	No; 1 month	Humoral	Roche Elecsys anti-SARS-CoV-2 S enzyme immunoassay, positive; >0.8 U/ml EUROIMMUN enzyme immunoassay: >1.1 arbitrary units	-	-	-	47.8%

Note: None of the studies reported outcomes stratified by the SARS-CoV-2 variant of concern/interest. All kidney transplant patients were on immunosuppressive medication.

Abbreviations: CLIA, chemiluminescent immunoassay; HD, haemodialysis; KT, kidney transplant; NA, exact data not accessed (i.e., present in a figure); NR, not reported; USA–United States of America.

[a]Only patients fitting criteria were included in the current analysis.

[b]Only non-exposed patients are included in the present analysis.

[c]Only patients receiving two doses were included in the present analysis.

[d]The five patients with prior exposure not included.

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lower proportions of responses than healthy controls at each of four time points, Figure 3A.

3.4 | The cellular response amongst haemodialysis patients

Four studies[28–31] reported cellular immune responses amongst haemodialysis patients. The pooled proportions amongst the cases were 62.86% (56.56, 69.17), and 85.78% (78.99, 92.57) at the third and fourth weeks, respectively Figure 4. The controls demonstrated proportions of 93.3% (81.34, 99.32)[31] and 96% (82.68, 99.37)[29] at second and fourth weeks, respectively. The proportions were lower in the haemodialysis patients than in the control group. However, the response in the haemodialysis illustrated a gradual increase with time, Figure 3B.

3.5 | The humoral immune response amongst kidney transplant patients

Fifteen studies reported proportions of humoral immune response amongst kidney transplant patients at first,[29] the second,[11,23,33–35] and fourth[11,13,22,24,28,29,39–41,45,46] weeks post-vaccination completion. The pooled proportions were 2.6% (0.06, 13.48),[29] 15.13% (11.43, 18.83) and 29.87% (27.68, 32.07), respectively at first, second and fourth weeks, Figure 5. On the contrary, the controls demonstrated 100% (90.97, 100) between the first and second week (i.e., 100% [95.34, 104.66]) followed by 98.99% (94.79, 103.19) during the fourth week. The controls attained 100% response during the first week and maintained >98% response throughout the 4 weeks. Kidney transplant patients demonstrated a gradually increasing responses throughout the follow-up. However, the responses were significantly lower than to controls, Figure 3C.
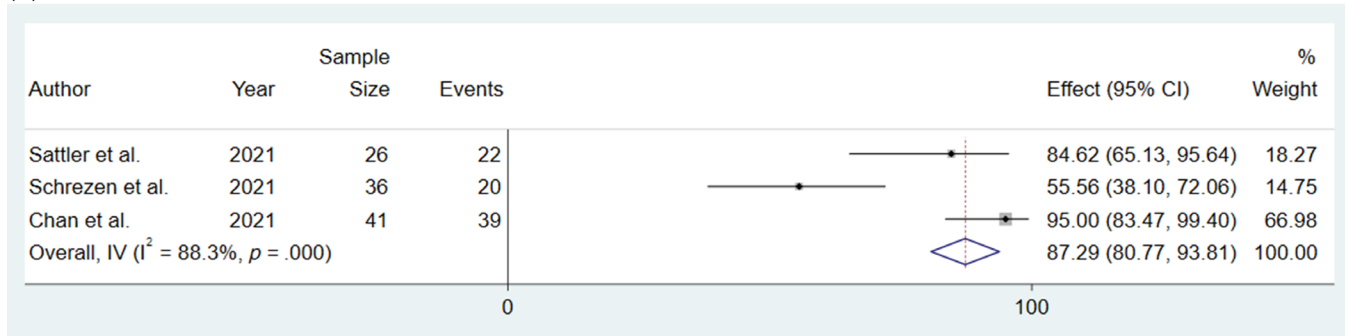
3.6 | The cellular immune response amongst kidney transplant patients

Four studies[23,24,28,29] reported this outcome. Kidney transplant patients demonstrated responses of 5.13% (0.63, 17.3),[29] 54.70% (45.36, 64.04) and 59.84% (54.57, 65.10) (Figure 5) during the first, second and fourth weeks, respectively. One study[29] reported the control group's proportion of 96% (82.68, 99.37) at the fourth-week post-vaccination completion. Cellular immunity amongst kidney transplants increased with time but remained significantly lower than the control counterpart, Figure 3D.
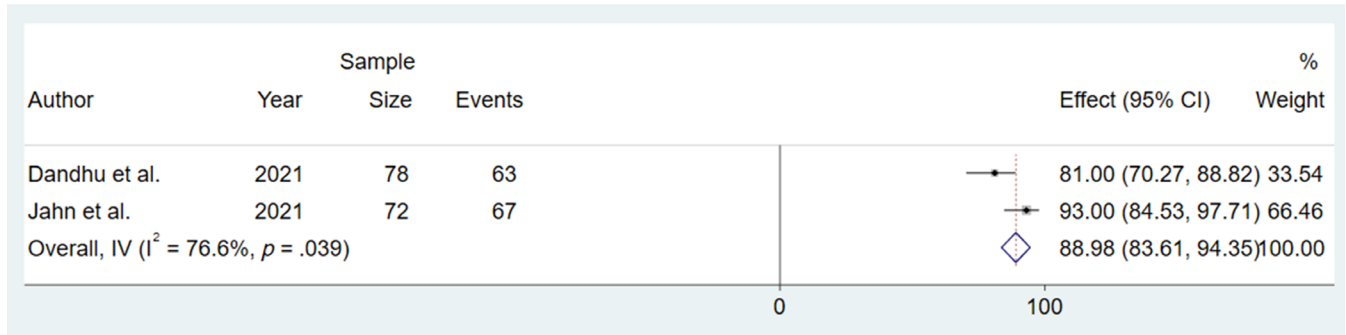
3.7 | Study quality

We reported the cohort studies and case–control study appraisals separately in Supplementary Table S2 and S3, respectively. All (100%) studies were of high quality at variable values above 80%. This finding is attributed to the diagnostic tools' high accuracy (i.e., sensitivity ≥89% and specificity ≥99%). Only three (23%) case-control studies[29,31,33] matched the

(A)

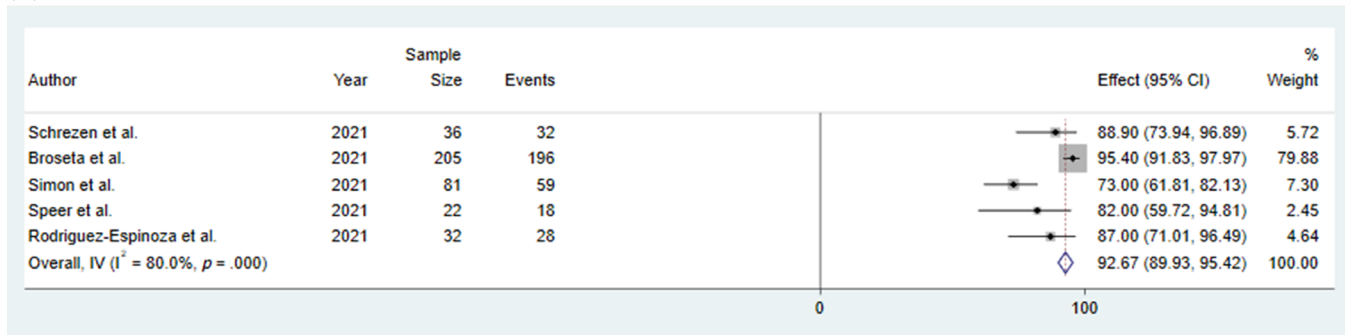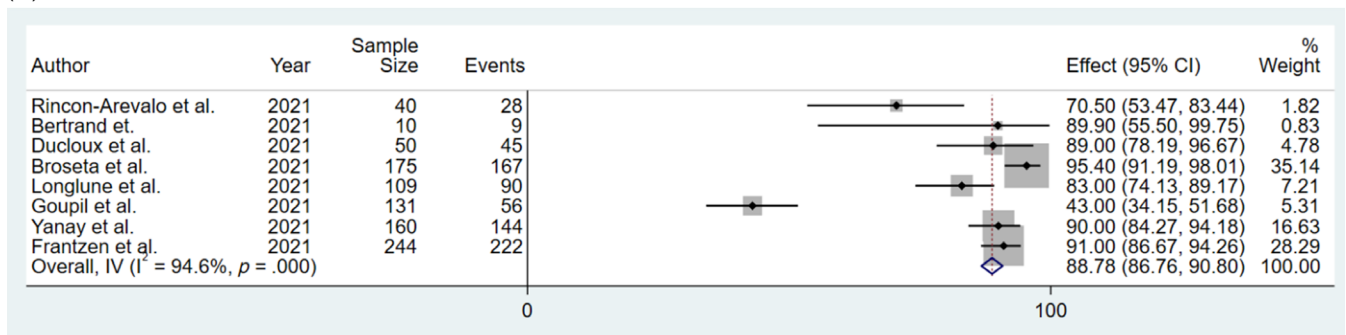| Author	Year	Sample Size	Events	Effect (95% CI)	% Weight
Sattler et al.	2021	26	22	84.62 (65.13, 95.64)	18.27
Schrezen et al.	2021	36	20	55.56 (38.10, 72.06)	14.75
Chan et al.	2021	41	39	95.00 (83.47, 99.40)	66.98
Overall, IV (I^2 = 88.3%, p = .000)				87.29 (80.77, 93.81)	100.00

0   100

(B)

Author	Year	Sample Size	Events	Effect (95% CI)	% Weight
Dandhu et al.	2021	78	63	81.00 (70.27, 88.82)	33.54
Jahn et al.	2021	72	67	93.00 (84.53, 97.71)	66.46
Overall, IV (I^2 = 76.6%, p = .039)				88.98 (83.61, 94.35)	100.00

0   100

(C)

Author	Year	Sample Size	Events	Effect (95% CI)	% Weight
Schrezen et al.	2021	36	32	88.90 (73.94, 96.89)	5.72
Broseta et al.	2021	205	196	95.40 (91.83, 97.97)	79.88
Simon et al.	2021	81	59	73.00 (61.81, 82.13)	7.30
Speer et al.	2021	22	18	82.00 (59.72, 94.81)	2.45
Rodriguez-Espinoza et al.	2021	32	28	87.00 (71.01, 96.49)	4.64
Overall, IV (I^2 = 80.0%, p = .000)				92.67 (89.93, 95.42)	100.00

0   100

(D)

Author	Year	Sample Size	Events	Effect (95% CI)	% Weight
Rincon-Arevalo et al.	2021	40	28	70.50 (53.47, 83.44)	1.82
Bertrand et.	2021	10	9	89.90 (55.50, 99.75)	0.83
Ducloux et al.	2021	50	45	89.00 (78.19, 96.67)	4.78
Broseta et al.	2021	175	167	95.40 (91.19, 98.01)	35.14
Longlune et al.	2021	109	90	83.00 (74.13, 89.17)	7.21
Goupil et al.	2021	131	56	43.00 (34.15, 51.68)	5.31
Yanay et al.	2021	160	144	90.00 (84.27, 94.18)	16.63
Frantzen et al.	2021	244	222	91.00 (86.67, 94.26)	28.29
Overall, IV (I^2 = 94.6%, p = .000)				88.78 (86.76, 90.80)	100.00

0   100

FIGURE 2   Pooled proportions of humoral immune responders amongst haemodialysis patients at (A) first, (B) second, (C) third and (D) fourth-week post-vaccination completion

participants by confounders (e.g., age); however, most used unmatched controls (i.e., affecting comparability). Most studies (>95%) sampled participants from a single-centre, thus contributing to selection bias. In addition, none of the studies reported having calculated the minimum sample size required, thus resulting in small sample-sized studies[33,45] that poorly represent the population assessed.

3.8 | Publication bias

Supplementary Figure S2 summarizes the funnel plots exploring publication biases. We illustrated funnel plots for haemodialysis patients at 1–4 weeks, controls at the fourth week, and cellular immunity at the third and fourth weeks. We also reported
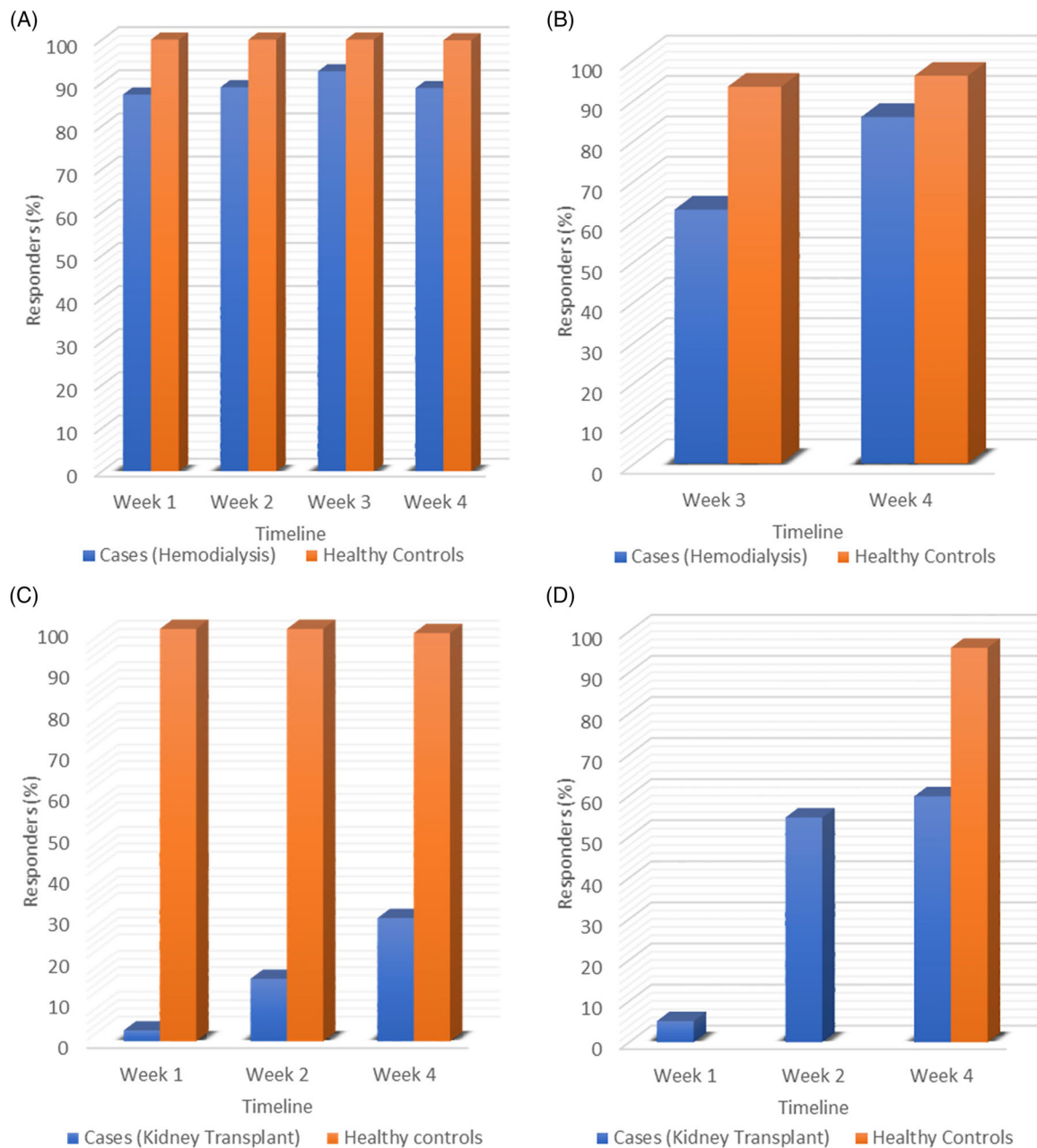
FIGURE 3 Trends of immune responses for participants from the first through fourth weeks post-vaccination completion. The trend of proportions of (A) humoral immunity and (B) cellular immune responders amongst the haemodialysis patients and healthy controls. Trends of proportions of (C) humoral immunity and (D) cellular immunity responders' proportions amongst kidney transplant patients compared to healthy controls. We did not find data for the third week of humoral. We did not find cellular response data for the first (controls), second and third weeks

funnel plots of kidney transplant patients at the second and fourth weeks and the controls at the fourth week. Funnel plots for other outcomes could not be developed because of insufficient studies or all reporting the same effect measure. Egger's tests for all explored outcomes demonstrated p-values greater than 0.05 signifying no small study effect (i.e., publication bias). Therefore, our study was not significantly influenced by publication biases.

3.9 | Sensitivity analysis

We stratified the analyses by country of study, study design, vaccine type and participant's age. We reported regression plots for findings for humoral immune responses for haemodialysis and kidney transplant patients during the fourth week. In other outcomes, meta-regression was inapplicable because of an insufficient number of studies.

(A)
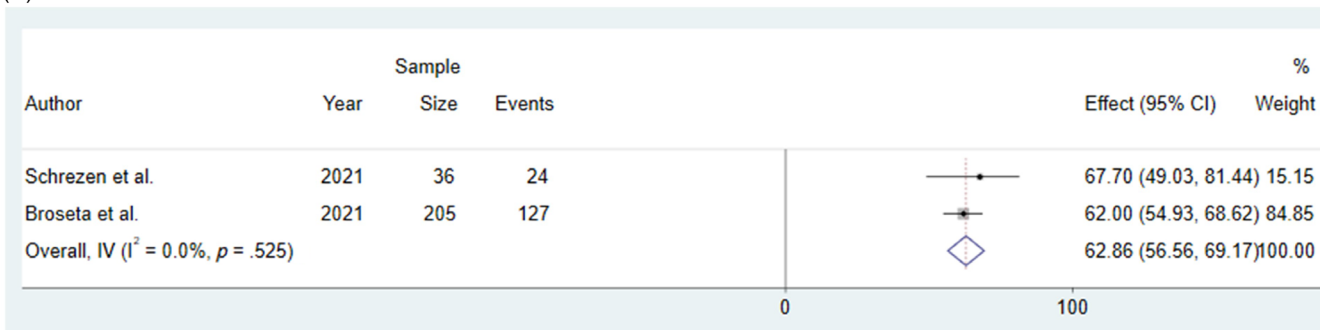
(B)
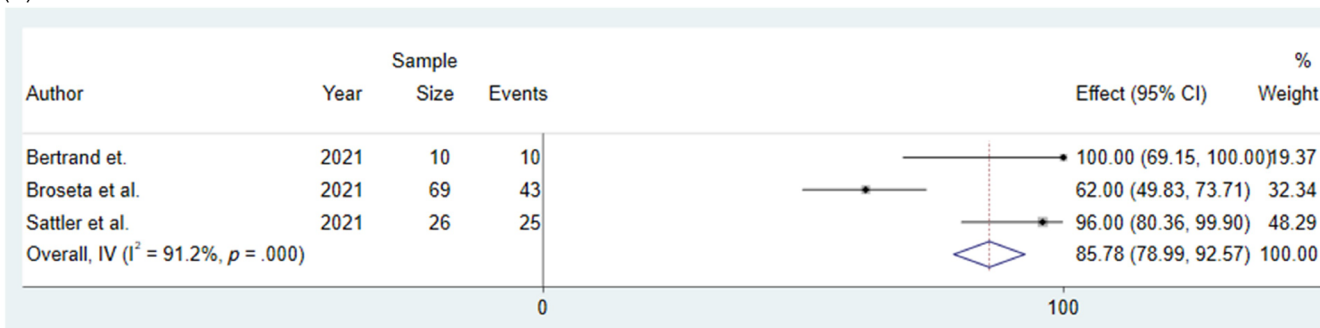
FIGURE 4 Pooled proportions of cellular immune responders amongst haemodialysis patients at (A) third and (B) fourth-week post-vaccination completion. Of note, we did not find a study reporting this outcome in the first and second weeks

Neither country of study (Beta = 0.93 [0.82–1.07], t = −1.28, p-value = .25) nor vaccine type (Beta = 1.11 [0.78–1.59], t = −0.72, p-value = .50), had statistically significant influence on the humoral response amongst haemodialysis patients, Figure 6A,C, respectively. However, cohort studies had significantly higher humoral response proportions than case control-studies (Beta = 0.47 [0.24–0.93], t = −2.69, p-value = .036), Figure 6B. Regarding age, all studies reported patients above 60 years (i.e., none <60). The linear plot (amongst >60 years patients) demonstrated a trend of decreasing responses with age; however, the finding did not reach statistical significance (Beta = 0.78 [0.60–1.01], t = −2.31, p-value = .06). Meta-regression figure for the latter was not created because all studies reported one side (>60).

Kidney transplant patients' humoral responses were statistically significantly influenced by the country of study and study design. Studies from USA (and Israel) had higher responses relative to Germany (and France), Beta = 0.61 [0.11–1.11], t = 2.91, p-value = .0023 (Figure 6D).

Cohort studies demonstrated statistically significantly higher pooled humoral responses amongst kidney transplant patients than case–control studies, Beta = 4.74 [1.04–21.53], t = 2.43, p-value = .0045 (Figure 6E). In the contrary, vaccine type (Beta = 1.85 [0.72–4.77], t = 1.54, p-value = .168) and age (Beta = 0.62 [0.12–3.30], t = −0.67, p-value = .523) did not have statistically significant influence over pooled humoral immune response proportions. The latter two are illustrated by Figure 6F, G, respectively.

We also conducted a sensitivity analysis by pooling response-proportions by potential confounders, Figure 7. See Supplementary Table S4 for the exact numeric values of this analysis.

3.10 | Level of evidence

Supplementary Tables S5–S10 summarizes the certainty levels of all our outcomes. Most (93%) of our outcomes were graded as moderate, and none (0%) as very low or high. This finding is attributed to the risk of selection bias. All studies used small sample sizes, none reported to have calculated minimum sample size beforehand, all were single-centred, and none was reported from Africa or Australia and Oceania hence less representation of the global population. Moreover, most demonstrated high heterogeneity, thus inconsistent findings. However, on the other hand, our outcomes had no publication biases (see Section 3.8 above), and all studies used reliable methods in identifying immune responders (i.e., outcomes).
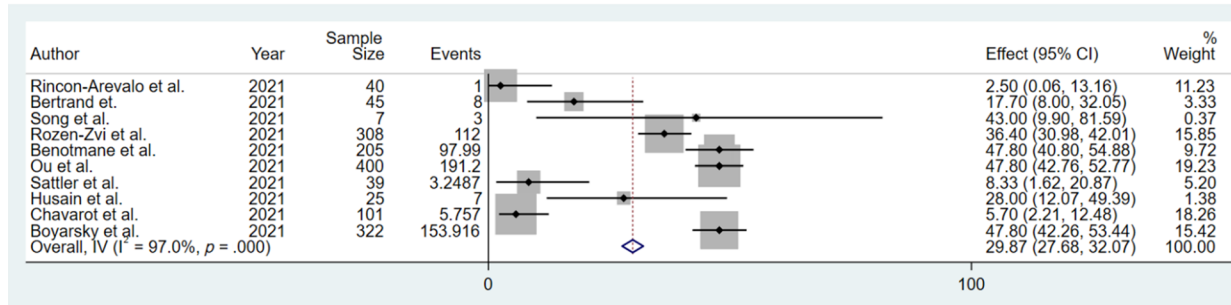
3.11 | Discussion

We explored the humoral and cellular immune response amongst ESRD patients on RRT for up to fourth-week post-completion of vaccination with an mRNA vaccine. From our findings, >88% of haemodialysis patients could mount humoral immunity as early as the first through fourth week post-vaccination. Despite a gradual
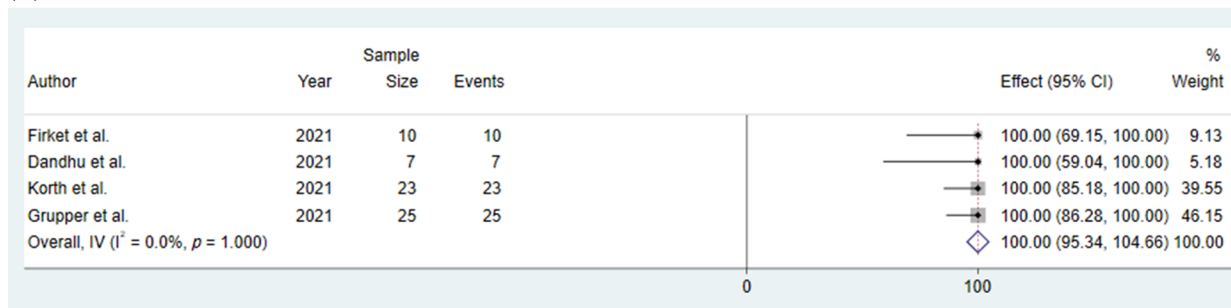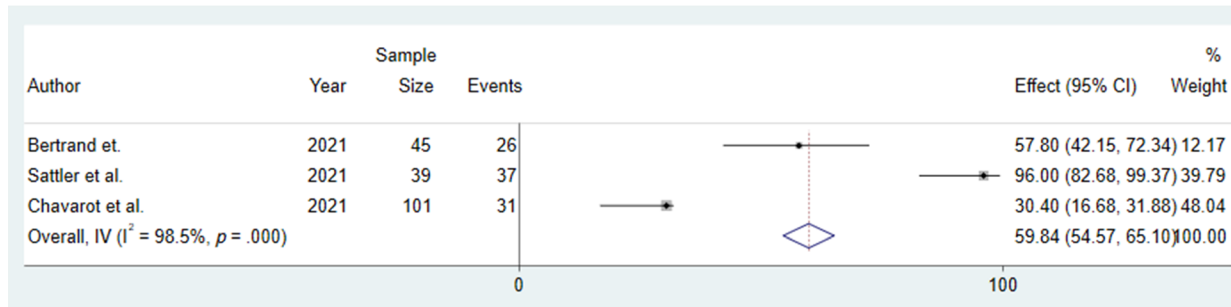
(A)
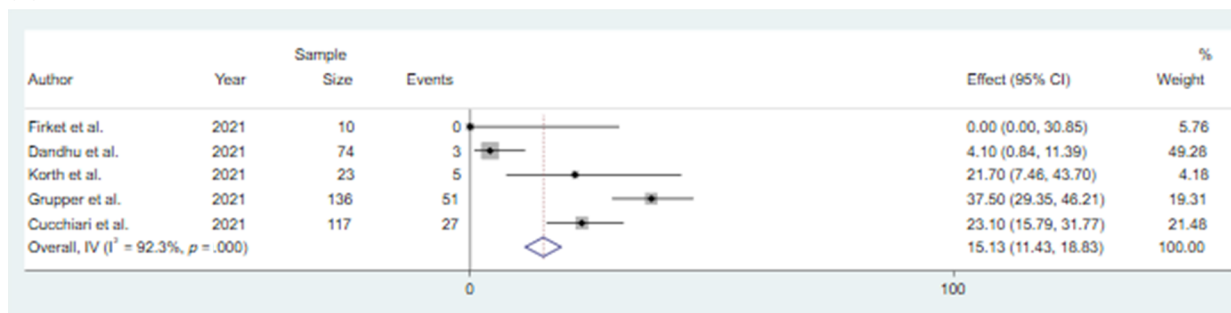
(B)

(C)

(D)

FIGURE 5 Pooled proportions of humoral immune responders amongst kidney transplant patients at (A) second and (B) fourth-week post-vaccination completion. Controls are illustrated by (C) in the second week. Of note is (D) that summarizes cellular response amongst kidney transplant patients at the fourth week

increase in responders' proportions from first through the third week, the control group maintained ≥99% proportion throughout the 4 weeks (Figure 3A). The lower proportions have previously been reported at first,[29] the second,[36] third[32] and fourth weeks[42] post-vaccination. However, these studies used significantly younger controls. For instance, Sattler et al.[27] used cases and controls with mean ages of 67.39 ± 11.88, and 53.03 ± 17.58 years,

respectively. Jahn et al.[35] found equal responses after matching the groups by age in their sensitivity analysis. Our meta-regression analysis could not confirm this finding because all pooled studies reporting this specific outcome had mean participants' age of >60. However, the linear regression in the >60 group demonstrated a non-significant trend (Beta = 0.78 [0.60–1.01], t = −2.31, p-value = .06) of lower response proportions with increasing age.
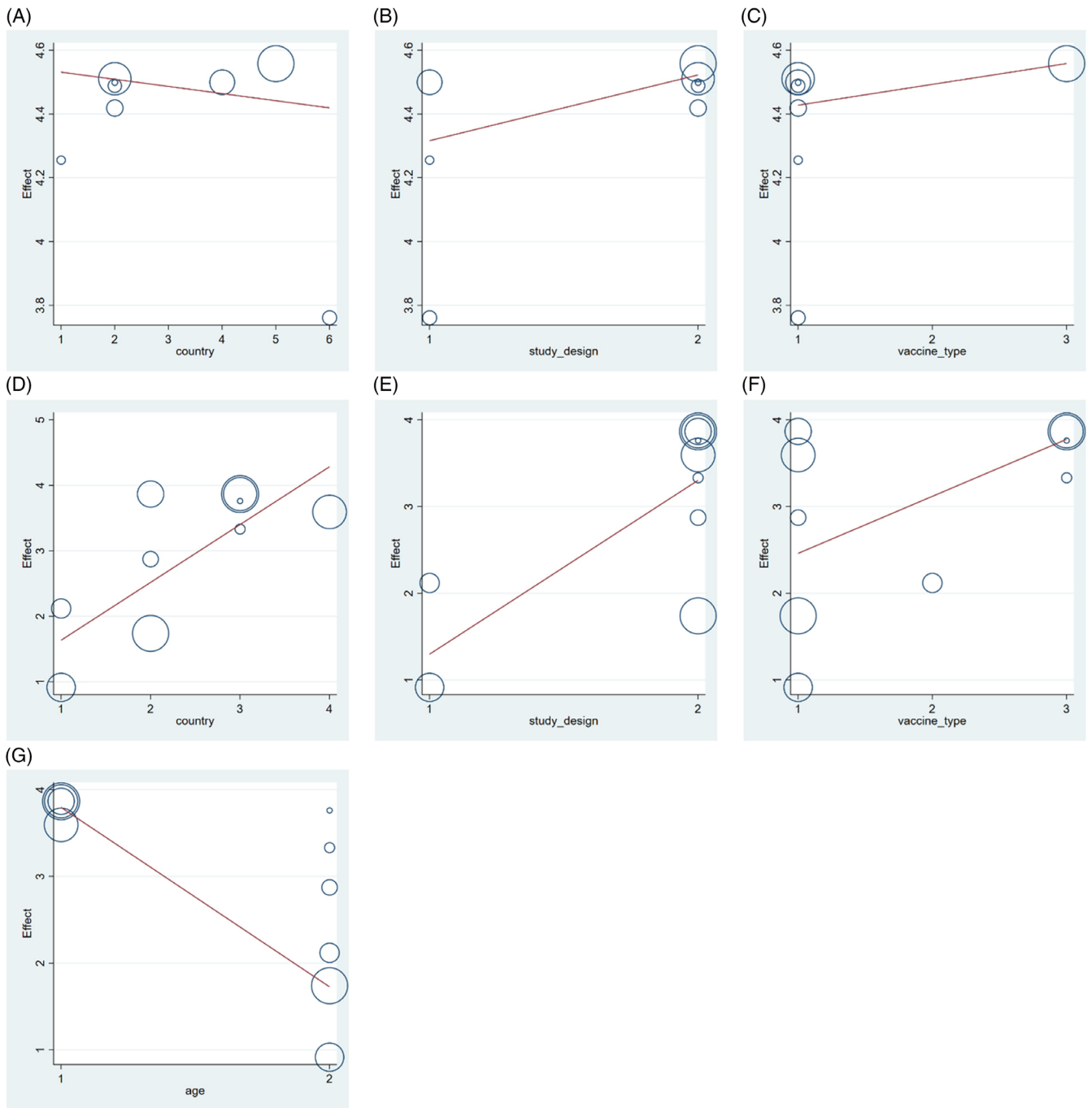
FIGURE 6 Meta-regression linear plots for proportions of humoral responses responders by the end of follow-up. Of note, we did not conduct meta-regression for cellular responses because of an insufficient number of studies. Y-axis labels. Effect: Logit transformation of the responders'. X-axis labels: (A) 1-Germany, 2-France, 3-USA, 4-Israel; 5-Spain, 6-Canada. (B) 1-Case-control study, 2-Cohort study. (C) 1-Pfizer vaccine, 2-Moderna vaccine, 3-Pfizer and Moderna vaccines (both). (D) 1-Germany, 2-France, 3-USA, 4-Israel. (E) 1-Case-control study, 2-Cohort study. (F) 1-Pfizer vaccine, 2-Moderna vaccine, (3) Pfizer and Moderna vaccines (both). (G) 1- ≤60 years, 2- >60 years

Therefore, we attribute the lower humoral immune proportions in the haemodialysis to the effect of uremia due to ESRD dampening humoral immunity.[11] Other reasons may include low lymphocyte count,[47] immunosuppressive therapy,[25] comorbidities (i.e., diabetes, HIV) and possibly malnutrition.[48] Interestingly, the lower humoral response was transiently delayed and resolved with longer follow-up reaching robust and protective levels[31] by the fourth week.

From our meta-regression analysis, cohort studies reporting haemodialysis patients had significantly (p-value = .036) higher humoral response proportions than case-control studies, Figure 7C. The finding may be attributed to comparability bias in
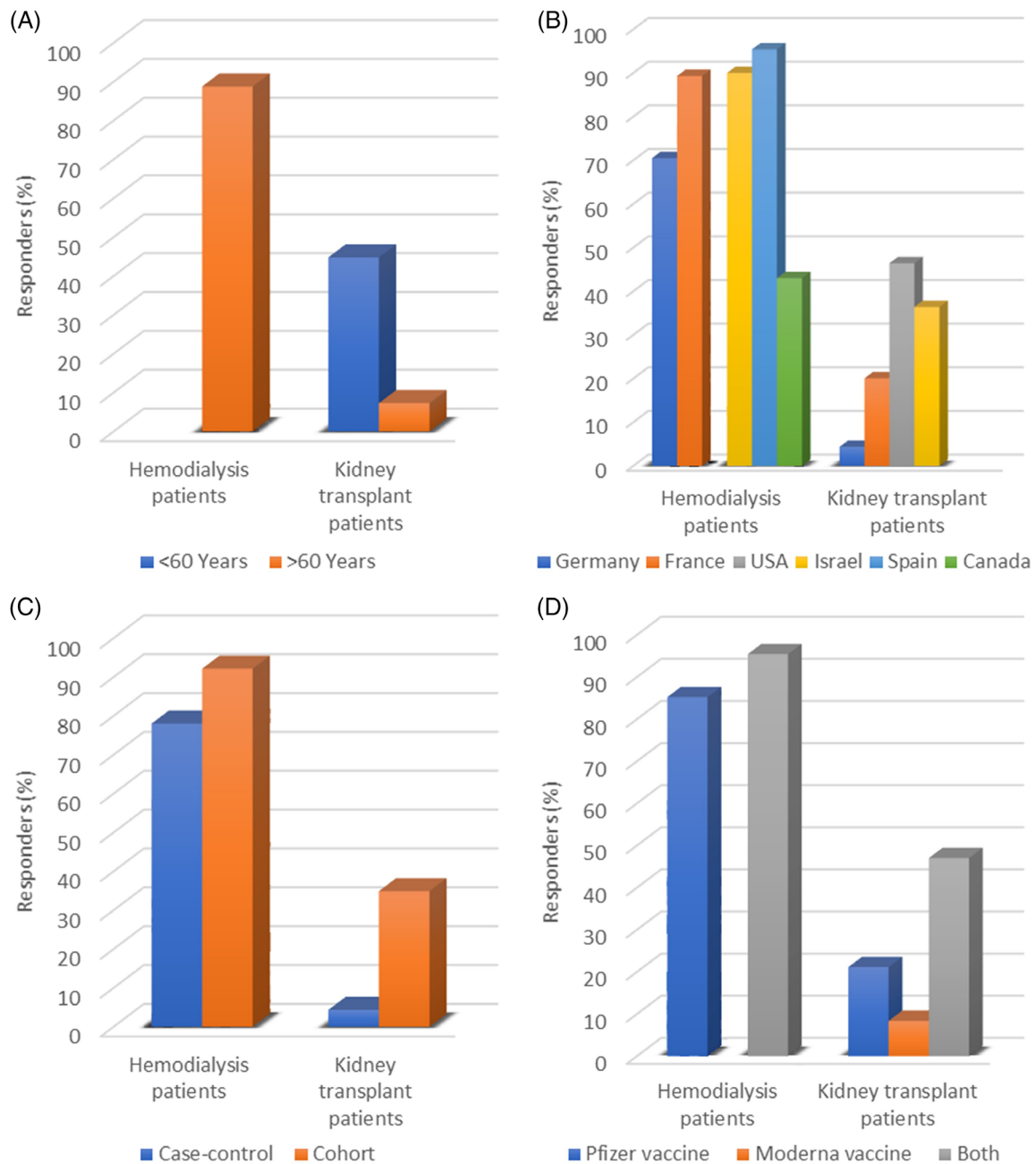
FIGURE 7　Column charts illustrating stratification of humoral immune response proportions by potential confounding factors

most case-control studies (see Section 3.7); and larger sample size in the cohort studies relative to the case-control reporting this outcome.

Cellular immune response proportions were lower in the haemodialysis patients (62%–85%) than healthy controls (93%–96%) throughout third- and fourth-weeks post-vaccination completion, Figure 3B. Moreover, the cellular response in haemodialysis was lower than one observed in humoral immunity (88%–92%) during the same period. Broseta et al.[30] reported a non-significant correlation between the humoral and cellular immune responses or between a positive cellular response and higher levels of anti-Spike-Receptor-Binding-Domain-IgG. Lower cellular immune response in haemodialysis

patients is supported by Schrezenmeier et al.[31] in an age-matched study. Reduced plasmablasts and memory B-cells observed amongst haemodialysis patients explain this finding.[31,39] Due to a limited number of studies reporting this finding, meta-regression was inapplicable in our present analysis.

Regarding kidney transplantation, humoral immunity response proportions were significantly low, with a gradual increase peaking at 29.87% in the fourth-week post-vaccination completion. This contrasts the control group that maintained >98% throughout from as early as the first-week post-vaccination, Figure 3C. This finding coincides with most previous literature[11,33–35] and is attributed to immunosuppressant

therapy, comorbidity (i.e., diabetes), high-dose corticosteroids and older age.[22,23] However, old age is disputed by Dandhu et al.,[11] who studied younger kidney transplant patients with a fair renal function (mean eGFR = 44.5 ± 18.5 ml/min) and still recorded a diminished humoral response of 4.3% 5 weeks post-vaccination completion.

From our meta-regression analysis (for kidney transplant patients), studies from the USA and Israel reported significantly higher humoral responses relative to Germany and France, p-value = .0023, Figure 7B. Variations in the vaccine dosage intervals might explain this finding. USA and Israel administered BNT162b2 vaccine at 21 days interval; contrary to 28 days in France[11,25] and variable (2–3 weeks) in Germany.[36] We call upon robust original studies exploring this hypothesis. In addition, cohort studies demonstrated higher humoral responses than case-control studies (p-value = .0045) for the same reason explained earlier, Figure 7C. Interestingly, studies administering both vaccines (not to the same patient) had a non-significant (p-value = .168) highest response, followed by Pfizer then Moderna, Figure 7D.

Cellular immune responders amongst kidney transplant patients increased from 5% to about 59.84% between first and fourth weeks, respectively, Figure 3D. We found only one study reporting controls in this outcome at the fourth week (96%). However, at this point, the cellular immune response for healthy controls is well established as high (>90%).[29] The lower cellular response is significantly attributed to immunosuppressive therapy, as explained earlier. Interestingly, the cellular response amongst kidney transplant patients is higher by the fourth week (59.84%) than that of the humoral counterpart, 29.87%. This finding might mean immunosuppression affects humoral immunity more than cellular immunity; thus, the latter might confer some, though not adequate, protection in this cohort.

3.12 | Practical implications and recommendations

We provide evidence that the current "one-size-fits-all" vaccination programme leaves kidney transplant patients vulnerable and needs to be individualized. Therefore, we call upon robust clinical trials in this vulnerable cohort. The individualized vaccination plan might consider: Vaccinating before transplantation (if possible);[19] giving more than two doses;[18,25,27] or developing a scheme that combines different vaccine platforms to improve vaccines immunogenicity.[34] However, we should continue promoting safety measures by maintaining physical distancing, avoiding crowds, quarantining and wearing facemasks before and after vaccination.

3.13 | Limitations

We excluded pre-prints as they have not been certified by peer-review; however, significant evidence might be available in the pre-prints. Moreover, we did not find studies reporting our outcome stratified by the SARS-CoV-2 variants of concern as their altered immunogenicity also affects immune response mounting.[49] We used IgG response to assess humoral immunity; however, IgA also protects against respiratory infections.[50] Also, different immune response measurement-kits have different sensitivities (i.e., 89%–97%) and specificities (i.e., 99%–100%).[51] Moreover, studies were conducted in different settings, meaning different healthcare standards, local guidelines and burdens exerted on healthcare facilities due to the COVID-19 pandemic.[52]

3.14 | Conclusions

Haemodialysis and kidney transplant patients have lower humoral and cellular immune responses than healthy controls. However, haemodialysis patients' responses improve, reaching near healthy-control levels by the fourth week post-vaccination completion. Kidney transplant patients' lower responses also improve but remain significantly lower than healthy controls throughout 4-weeks. The "one-size-fits-all" mRNA vaccination scheme may be inadequate for kidney transplant patients.

CONFLICTS OF INTEREST
The author declares that there is no conflict of interest.

AUTHOR CONTRIBUTIONS
Study designing: Joel Swai, Zhu Wei and Ming Gui; *data search*: Joel Swai, Ming Gui, Mao Long, Zhu Wei, Zixuan Hu and Shaojun Liu; *data extraction*: Joel Swai, Ming Gui, Mao Long, Zhu Wei and Shaojun Liu; *data quality appraisal, analysis, and interpretation*: Joel Swai, Ming Gui, Zhu Wei and Shaojun Liu; *manuscript drafting*: Joel Swai; *manuscript critical intellectual content revision*: Joel Swai, Ming Gui, Mao Long, Zhu Wei and Zixuan Hu. All authors read and approved the final version of the manuscript.

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