PLOS ONE

RESEARCH ARTICLE

Outcomes of vaccinations against respiratory diseases in patients with end-stage renal disease undergoing hemodialysis: A systematic review and meta-analysis

Metalia Puspitasari[1☯]*, Prenali D. Sattwika[1,2☯], Dzerlina S. Rahari[2,3☯], Wynne Wijaya[1☯], Auliana R. P. Hidayat[1☯], Nyoman Kertia[1‡], Bambang Purwanto[4‡], Jarir At Thobari[2,5‡]

1 Department of Internal Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta, Indonesia, **2** Clinical Epidemiology and Biostatistics Unit, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta, Indonesia, **3** Department of Epidemiology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Thailand, **4** Department of Internal Medicine, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia, **5** Department of Pharmacology and Therapy, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

☯ These authors contributed equally to this work.
‡ NK, BP and JAT also contributed equally to this work.
* metaliapuspitasari@ugm.ac.id

Check for updates

OPEN ACCESS

Citation: Puspitasari M, Sattwika PD, Rahari DS, Wijaya W, Hidayat ARP, Kertia N, et al. (2023) Outcomes of vaccinations against respiratory diseases in patients with end-stage renal disease undergoing hemodialysis: A systematic review and meta-analysis. PLoS ONE 18(2): e0281160. https://doi.org/10.1371/journal.pone.0281160

Editor: Etsuro Ito, Waseda University: Waseda Daigaku, JAPAN

Received: October 6, 2022

Accepted: January 16, 2023

Published: February 9, 2023

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: https://doi.org/10.1371/journal.pone.0281160

Copyright: © 2023 Puspitasari et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: Data of extraction table is accessible on Open Science Framework

Abstract

Due to the nature of the disease, end-stage renal disease (ESRD) patients suffer from dysfunction of the adaptive immune system, which leads to a poorer response to vaccination. Accordingly, it is crucial to evaluate the efficacy and safety of management strategies, including vaccinations, which could potentially reduce the risk of respiratory diseases, such as pneumonia, influenza, or COVID-19, and its associated outcomes. We searched PubMed, CENTRAL, ScienceDirect, Scopus, ProQuest, and Google Scholar databases using designated MeSH keywords. The risk of bias was assessed using ROBINS-I. The quality of evidence was assessed using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach. Relative risk (RR) and 95% confidence interval (CI) were calculated. Heterogeneity was investigated using forest plots and I^2 statistics. This systematic review included a total of 48 studies, with 13 studies of influenza (H1N1 and H3N2) vaccination and 35 studies of COVID-19 vaccination. H1N1 vaccination in ESRD patients undergoing hemodialysis induced lower seroconversion rates (RR 0.62, 95% CI: 0.56–0.68, p <0.00001) and lower seroprotection rates (RR 0.76, 95% CI: 0.70–0.83, p <0.00001) compared to controls. H3N2 vaccination in ESRD patients undergoing hemodialysis yielded lower seroconversion rates (RR 0.76, 95% CI: 0.68–0.85, p <0.00001) and lower seroprotection rates (RR 0.84, 95% CI: 0.77–0.90, p <0.00001) compared to controls. Twenty-nine studies demonstrate significantly lower antibody levels in ESRD patients undergoing hemodialysis compared to the controls following COVID-19 vaccination. This review presents evidence of lower seroconversion and seroprotection rates after vaccination against viral respiratory diseases in patients with ESRD undergoing hemodialysis. Since hemodialysis patients are more susceptible to infection and severe disease

(OSF) portal through this link: https://osf.io/es2ma/ .

Funding: The author(s) received no specific funding for this work.

Competing interests: The authors have declared that no competing interests exist.

progression, a weakened yet substantial serological response can be considered adequate to recommend vaccination against respiratory diseases in this population. Vaccination dose, schedule, or strategy adjustments should be considered in stable ESRD patients on maintenance hemodialysis.

Trial registration: Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021255983, identifier: CRD42021255983.

1. Introduction

According to the International Society of Nephrology's (ISN) 2019 Global Kidney Health Atlas (GKHA), from 79 countries worldwide, the average number of new end-stage renal disease (ESRD) diagnoses was 144 individuals per million general population. In this population, hemodialysis is the most common technique of predominant renal replacement therapy (RRT) [1]. ESRD patients requiring dialysis are identified as high-risk patients for the severe form of respiratory infections, including pneumonia, influenza, and coronavirus disease 2019 (COVID-19), due to their frequent contact with health care providers and other patients, high burden of comorbid conditions, and altered immune responses [2–5]. Approximately 20% of infections in ESRD patients are attributable to pulmonary causes. The mortality rate of respiratory infections in dialysis patients is 14 to 16-fold higher than in the general population [6].

The high incidence, morbidity, and mortality rate of respiratory infections in ESRD patients have rendered vaccination a vital measure to prevent life-threatening complications. However, ESRD patients mount lower responses to vaccination than healthy individuals due to dysfunction of the adaptive immune system [5, 7, 8]. Furthermore, end-stage renal disease patients have been largely excluded from vaccine trials for safety reasons. Therefore, more convincing evidence regarding the efficacy and safety of vaccinations against respiratory infections is required. This systematic review and meta-analysis aimed to evaluate and summarize the available evidence on the efficacy and safety of vaccination against respiratory infections in ESRD patients undergoing hemodialysis and its associated outcomes to help guide clinical practice and vaccination recommendations.

2. Materials and methods

2.1 Protocol registration

The protocol of this systematic review has been registered and accepted in PROSPERO with the registration number CRD42021255983 available at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021255983 (S1 Protocol).

2.2 Search strategy and eligibility criteria

We searched PubMed, The Cochrane Central Register of Controlled Trials (CENTRAL), ScienceDirect, Scopus, ProQuest, and Google Scholar for interventional (non-randomized or randomized controlled trials [RCTs]) and observational studies from inception until 20 October 2022. Electronic searches were complemented by manually searching all reference lists of identified studies and reviews for additional studies. We used the MeSH-related keywords such as "end-stage renal disease" AND "hemodialysis" AND ("pneumococcal vaccines" OR "influenza vaccines" OR "COVID-19 vaccines"), as well as their common synonyms. Restrictions involved non-English language and animal studies. The complete search strategy is shown in S1 Appendix.

One reviewer conducted the initial searches. After removing duplicates, three reviewers first scanned all remaining articles by title and abstract. Then, two independent reviewers read the full text of potentially eligible items and decided on which studies to include. Discrepancies were resolved by discussion.

Studies had to meet the following inclusion criteria: (i) original report on the efficacy and safety within six weeks after vaccination against respiratory diseases (pneumococcal, influenza, and COVID-19 vaccines) in adult patients with ESRD undergoing hemodialysis, and (ii) control participants had to be clinically healthy populations who received vaccination against respiratory diseases. We excluded studies in which participants with ESRD in the intervention arm underwent peritoneal dialysis or renal transplant.

2.3 Data extraction

Four authors performed data extraction independently using a standardized data extraction form [9]. The following information was extracted from eligible studies: first author, year of publication, study registration, setting, study design, inclusion and exclusion criteria, participant numbers and characteristics, vaccine type, dose, timing and route of administration, outcome definition, and outcome proportion in each arm for dichotomous data or mean and standard deviation (SD) for continuous data. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were applied to the search strategy (S1 Checklist) [10]. The complete data extraction table is accessible on the Open Science Framework (OSF) portal via this link: https://osf.io/es2ma/?view_only=87b0e57246704617aa094219a60ba73b.

2.4 Risk of bias and quality of evidence assessment

The risk of bias was independently assessed by two authors using a tool for assessing the risk of bias in non-randomized studies of interventions (ROBINS-I) [11]. The tool views each study as an attempt to emulate a hypothetical pragmatic randomized trial and covers seven distinct domains through which bias might be introduced. The judgments within each domain are carried forward to an overall risk of bias judgment across domains for the assessed outcome. The categories for risk of bias judgments are "Low risk", "Moderate risk", "Serious risk", and "Critical risk" of bias. The "No information" category should be used only when insufficient data are reported to permit a judgment. Discrepancies were resolved by discussion. Funnel plots were constructed to check for publication bias in studies included in meta-analyses.

The quality (certainty) of evidence was assessed using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) framework. The quality of the overall evidence was rated as one of four levels: very low, low, moderate, and high, based on the assessment of the domains for risk of bias, imprecision, inconsistency, indirectness, and publication bias [12].

2.5 Data synthesis and statistical analysis

We examined dichotomous outcomes and expressed results as risk ratio (RR) with a 95% confidence interval (CI). From the included studies, we used the data of seroconversion rate, seroprotection rate, and adverse events rate for meta-analysis. Whenever available, we extracted the data of antibody titer. The analysis was separated between each type of vaccine group. Statistical analysis and generation of forest plots were conducted using Review Manager (RevMan) 5.4 software, with $p<0.05$ deemed statistically significant.

The variability across studies due to heterogeneity was investigated using forest plots and I^2 statistics, with I^2 values of 0% to 40%, 30% to 60%, 50% to 90%, and 75% to 100%

corresponding to not important, moderate, substantial and considerable levels of heterogeneity, respectively [9].

3. Results

3.1 Characteristics of included studies

During the initial search, we identified 1080 records from electronic databases, 58 records from Google Scholar, and four additional records from manual searching. After further screening, we included 48 eligible studies (Fig 1). The included studies mostly have cohort design [13–53], five studies are of case-control design [30, 54–57], two studies are of cross-sectional design [58, 59], and 1 study is an open-label clinical trial [60].

Among thirteen studies, eleven provide data on the H1N1 influenza vaccine [15, 21, 30, 32, 42, 49, 50, 55, 57, 58, 60], and 11 studies on the H3N2 influenza vaccine [15, 21, 26, 42, 49, 50,

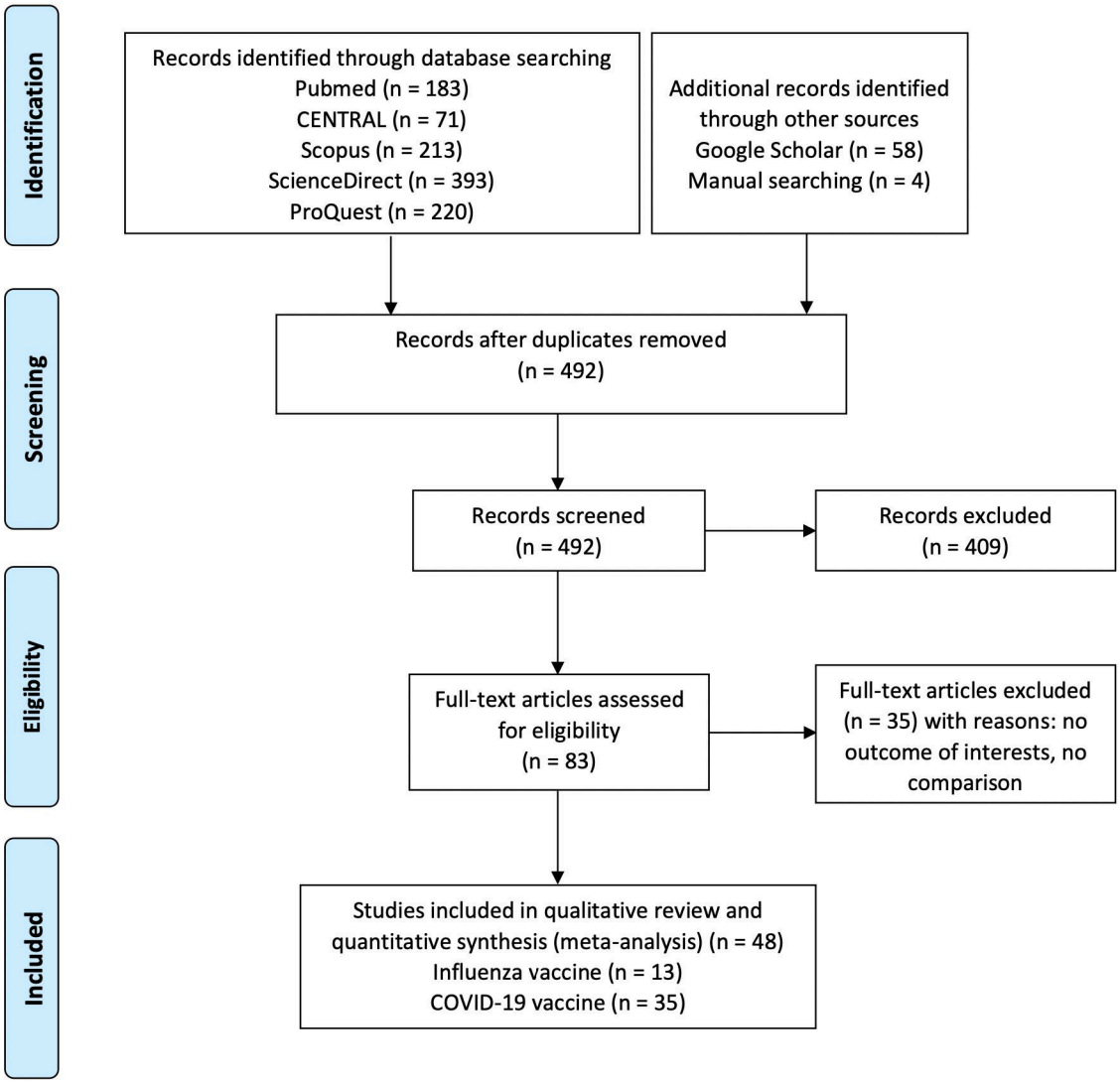


Fig 1. PRISMA flow diagram for included studies [10].

https://doi.org/10.1371/journal.pone.0281160.g001

55–58, 60]. Most of them used hemagglutination-inhibiting (HI) assay to measure seroconversion and seroprotection. Meanwhile, thirty-five studies on COVID-19 vaccines [13, 16–20, 24, 25, 27–29, 31, 33–41, 43–48, 51–54, 59] used various vaccine platforms (including mRNA-based, inactivated, viral vector, and heterologous vaccines) and various units of measurement for IgG levels and neutralizing antibodies (NAbs) percentage (%) of inhibition. We could not find any studies on pneumococcal vaccines. The outcome of seroconversion and seroprotection rates were assessed for all studies. Table 1 summarizes the characteristics of included studies.

3.2 Risk of bias assessment

The risk of bias assessment in each individual study is summarized in Fig 2. We rated the overall risk of bias on the outcome of seroconversion and seroprotection rates to be high risk of bias in two studies and unclear risk of bias in six of thirteen observational studies investigating influenza vaccinations in patients with ESRD undergoing hemodialysis. These risks of bias arise from each domain. Two studies by Versluis in 1985 and 1988 [50, 57] was considered to have high risks of bias due to selection bias in sequence generation and selective reporting (reporting bias). From thirty-five included observational studies of COVID-19 vaccinations for patients with ESRD undergoing hemodialysis, twenty-one studies showed an unclear risk of bias due to bias in sequence generation (selection bias) [13, 16, 22–24, 34, 40, 41, 48, 52], blinding of participants and personnel (performance bias) [29, 35, 36, 41, 47], blinding of outcome assessment (performance bias) [33], incomplete outcome data (attrition bias) [13, 20, 54], or selective reporting (reporting bias) [17, 51, 59]. Funnel plots to assess publication bias in studies included for meta-analyses were also constructed and displayed in S2 Appendix.

3.3 Outcome

This section discusses the outcomes of vaccination in patients with ESRD undergoing hemodialysis consisting of efficacy and adverse events outcomes in included studies.

3.3.1 H1N1 vaccine. For the H1N1 vaccine, vaccination in ESRD patients undergoing hemodialysis showed lower seroconversion and seroprotection rates compared to controls. Ten of the included studies reported the outcome of seroconversion rate. H1N1 vaccination in patients with ESRD undergoing hemodialysis induced lower seroconversion rates (Fig 3A, with 10 studies, 1191 participants: RR 0.62, 95% CI: 0.56–0.68, $p<0.00001$) with substantial heterogeneity ($I^2 = 81\%$). One study by Labriola in 2011 utilized a seroneutralization assay to measure antibody level and reported a significantly lower seroconversion rate in HD patients (64,2%) compared to controls (93,8%) (p = 0.002) [30]. Seroprotection rate was lower in ESRD patients receiving H1N1 vaccines compared to controls (Fig 3B, with 7 studies, 1001 participants: RR 0.76, 95% CI: 0.70–0.83, p<0.00001) with considerable heterogeneity ($I^2 = 96\%$). There was only one study reporting adverse events following vaccinations of H1N1 with 2 of 53 patients with ESRD experiencing moderate local pain at the site of injection with no adverse events observed in the control group [30].

3.3.2 H3N2 vaccine. H3N2 vaccination in patients with ESRD undergoing hemodialysis produced lower rates of seroconversion compared to controls (Fig 4A, with 10 studies, 1012 participants: RR 0.76, 95% CI: 0.68–0.85, $p < 0.00001$) with moderate heterogeneity ($I^2 = 43\%$) and lower rates of seroprotection (Fig 4B, with 6 studies, 754 participants: RR 0.84, 95% CI: 0.77–0.90, $p < 0.00001$) with considerable heterogeneity ($I^2 = 85\%$). A study by Nikoskelainen in 1982 determined the antibody responses with single radial hemolysis (SRH) technique and demonstrated a higher seroconversion rate in HD patients (92%) compared to controls (88%) [56]. In terms of adverse events, ESRD patients undergoing hemodialysis experienced lower

Table 1. Characteristics of included studies.

No	Author, year	Setting	Study design	Study population	Number of participants	Comparison	Vaccination	Outcomes	Additional Remarks
Influenza Vaccines									
1	Antonen 2003	Finland	Cohort	Hemodialysis patients	Exposure: 23 Comparison: 26	Military conscript	Influenza vaccine (H3N2)	Seroprotection	Platform of vaccine: inactivated trivalent vaccine Method to measure antibody response (unit): haemagglutination-inhibiting (HI) antibodies (%), pre and 5 weeks after vaccination
2	Beyer 1987	Netherlands	Cohort	Hemodialysis patients	H3N2 Exposure: 73 Comparison: 20 H1N1 Exposure: 91 Comparison: 25	Healthy controls	Influenza vaccine (H3N2, H1N1)	Seroconversion, seroprotection	Platform of vaccine: inactivated trivalent vaccine Method to measure antibody response (unit): haemagglutination-inhibiting (HI) antibodies (%), pre and 4 weeks after vaccination
3	Eiselt 2016	Czech Republic	Cohort	Hemodialysis patients	H3N2 Exposure: 133 Comparison: 40 H1N1 Exposure: 133 Comparison: 40	Healthy Controls	Influenza vaccine (H3N2, H1N1)	Seroconversion, seroprotection	Platform of vaccine: inactivated trivalent vaccine Method to measure antibody response (unit): haemagglutination-inhibiting (HI) antibodies (%), pre and 4 weeks after vaccination
4	Hodges 1979	USA	Cohort	Hemodialysis patients	Exposure: 13 Comparison: 41	Healthy controls	Influenza vaccine (H3N2)	Seroconversion	Platform of vaccine: inactivated bivalent split-virus Method to measure antibody response (unit): haemagglutination-inhibiting (HI) antibodies (%), before and after vaccination
5	Krairittichai 2013	Thailand	Cross-sectional	Hemodialysis patients	H3N2 Exposure: 22 Comparison: 6 H1N1 Exposure: 23 Comparison: 20	Healthy controls	Influenza vaccine (H3N2, H1N1)	Seroconversion, seroprotection	Platform of vaccine: inactivated trivalent vaccine Method to measure antibody response (unit): haemagglutination-inhibiting (HI) antibodies (%), before and 6 weeks after vaccination
6	Labriola 2011	Belgium	Case-control	Hemodialysis patients	Exposure: 53 Comparison: 32	Healthy controls	Influenza vaccine (H1N1)	Seroconversion, adverse effects	Platform of vaccine: monovalent adjuvanted influenza A/California/2009 (H1N1) vaccine Method to measure antibody response (unit): seroneutralization (SN) assay (%) day 0 and 30

(*Continued*)

Table 1. (Continued)

No	Author, year	Setting	Study design	Study population	Number of participants	Comparison	Vaccination	Outcomes	Additional Remarks
7	Lertdumrongluk 2011	Thailand	Cohort	Hemodialysis patients	Exposure: 44 Comparison: 149	Healthy controls	Influenza H1N1 vaccine	HI antibody titer, seroconversion	Platform of vaccine: a single dose of non-adjuvanted 2009 influenza A (H1N1) vaccine (Paneza®) Method to measure antibody response (unit): Hemagglutination inhibition (HI) assays (GMT), before, 4 weeks, and 24 weeks after vaccination
8	Mastalerz-Migas 2015	Poland	Case-control	Hemodialysis patients	H3N2 Exposure: 71 Comparison: 63 H1N1 Exposure: 71 Comparison: 63	Healthy controls	Influenza vaccine (H3N2, H1N1)	Seroconversion, seroprotection	Platform of vaccine: inactivated trivalent vaccine Method to measure antibody response (unit): haemagglutination-inhibiting (HI) antibodies (%), before and after vaccination
9	Nikoskelainen 1982	Finlandia	Case-control	Hemodialysis patients	Exposure: 12 Comparison: 40	Healthy controls	Influenza vaccine (H3N2)	Seroconversion	Platform of vaccine: inactivated trivalent vaccine Method to measure antibody response (unit): single radial hemolysis (SRH) technique
10	Song 2006	South Korea	Cohort	Hemodialysis patients	Exposure: 50 Comparison: 50	Healthy controls	Influenza vaccine (H3N2, H1N1)	HI antibody titer, seroresponse, seroprotection	Platform of vaccine: a single dose of trivalent inactivated split vaccine (Inflexin®) (H1N1, H3N2, B/Hongkong) Method to measure antibody response (unit): hemagglutination-inhibiting (HI) antibodies (%), 4 weeks after vaccination
11	Versluis 1985	Netherlands	Cohort	Hemodialysis patients	H3N2 Exposure: 10 Comparison: 4 H1N1 Exposure: 10 Comparison: 6	Healthy controls	Influenza vaccine (H3N2, H1N1)	Seroconversion	Platform of vaccine: whole virus vaccine Method to measure antibody response (unit): haemagglutination-inhibiting (HI) antibodies (%) at day 0, 30, and 60
12	Versluis 1988	Netherlands	Case-control	Hemodialysis patients	H3N2 Exposure: 101 Comparison: 30 H1N1 Exposure: 101 Comparison: 30	Healthy controls	Influenza vaccine (H3N2, H1N1)	Seroconversion	Platform of vaccine: inactivated trivalent vaccine Method to measure antibody response (unit): haemagglutination-inhibiting (HI) antibodies (%), pre and 4 weeks after vaccination

(*Continued*)

Table 1. (Continued)

No	Author, year	Setting	Study design	Study population	Number of participants	Comparison	Vaccination	Outcomes	Additional Remarks
13	Vogtlander 2004	Netherlands	Cohort	Hemodialysis patients	Exposure: 44 Comparison: 19	Hospital staff	Influenza vaccine (H3N2, H1N1)	HI antibody titer, seroconversion, seroprotection	Platform of vaccine: Method to measure antibody response (unit): SARS-CoV-2 IgG II Quant assay (AU/mL), 5 weeks after second dose
COVID-19 Vaccines									
14	Ahmed 2022	Egypt	Cohort	Hemodialysis patients	Exposure: 44 Comparison: 22	Non-renal patients	Inactivated or mRNA SARS-CoV-2 vaccines	IgG level and adverse events	Platform of vaccine: Sinopharm Method to measure antibody response (unit): SARS-CoV-2 IgG ELISA assay (AU/ml) at 30 days after second dose
15	Bai 2022	Pakistan	Cross-sectional	Hemodialysis patients	Exposure: 50 Comparison: 31	Healthy individuals	Inactivated or mRNA SARS-CoV-2 vaccines	IgG level	Platform of vaccine: BBIBP-CorV produced by Sinopharm Beijing or CoronaVac® Method to measure antibody response (unit): Cobas® Elecsys Anti-SARS-CoV-2 S Immunoassay (Roche Diagnostics, Basel, Switzerland) (U/ml), at baseline, 20 days after the first dose, and 3 weeks after the second dose
16	Boongird 2021a	Thailand	Cohort	Hemodialysis patients	Exposure: 60 Comparison: 30	Healthy controls	CoronaVac vaccine	IgG level, seroconversion	Platform of vaccine: two doses of CoronaVac vaccine Method to measure antibody response (unit): semiquantitative SARS-CoV-2 IgG assay (Abbott Diagnostics) at 2 weeks after second dose
17	Boongird 2022b	Thailand	Cohort	Hemodialysis patients	Exposure: 31 Comparison: 30	Healthy control	Inactivated whole-virus SARS-CoV-2 vaccine	IgG levels, NAbs % inhibition	Platform of vaccine: two doses of CoronaVac® Method to measure antibody response (unit): SARS-CoV-2 IgG II Quant; Abbott Diagnostics (AU/ml) and sVNT (Euroimmun kits), at baseline, 4 weeks after the first dose, and 2 weeks after the second dose

(*Continued*)

Table 1. (Continued)

No	Author, year	Setting	Study design	Study population	Number of participants	Comparison	Vaccination	Outcomes	Additional Remarks
18	Bruminhent 2022	Thailand	Cohort	Hemodialysis patients	Exposure: 31 Comparison: 16	Healthy controls	CoronaVac vaccine	IgG level, NAbs % inhibition, Seroconversion	Platform of vaccine: two doses of CoronaVac vaccine Method to measure antibody response (unit): Abbott SARS-CoV-2 IgG II Quantification assay (Abbott Diagnostics, USA) (BAU/mL) and SARS-CoV-2 NeutraLISA surrogate neutralization assay (Euroimmun) (%) at 2 weeks after second dose
19	Danthu 2021	France	Cohort	Hemodialysis patients	Exposure: 78 Comparison: 7	Healthy controls	Pfizer BNT162b2 vaccine	IgG level, seroconversion	Platform of vaccine: two doses of CoronaVac vaccine Method to measure antibody response (unit): the LIAISON SARS-CoV-2 TrimericS IgG (DiaSorin, Saluggia, Italy) (AU/mL) and Abbott Alinity SARS-CoV-2 IgG, Chicago, IL, USA (%) at 0, 14, 28, 36, and 58 days after the first dose (8 days after second dose)
20	Dheir 2022	Turkey	Cohort	Hemodialysis patient	Exposure: 50 Comparison: 41	Healthy group	CoronaVac vaccine	IgG level	Platform of vaccine: two doses of inactivated vaccine CoronaVac Method to measure antibody response (unit): SARS-CoV-2 IgG II Quant; Abbott Diagnostics (AU/ml) at 28 days, 3 and 6 months
21	Fu 2022	Taiwan	Cohort	Hemodialysis patients	Exposure: 385 Comparison: 66	Healthcare workers	ChAdOx1 nCoV-19 vaccines	IgG level, seroconversion	Platform of vaccine: two doses of ChAdOx1 nCoV-19 vaccines Method to measure antibody response (unit): Elecsys® Anti-SARS-CoV-2-S immunoassay (U/mL), 4 weeks after second dose
22	Fucci 2022	Italy	Cohort	Hemodialysis patients	Exposure: 155 Comparison: 77	Healthy control	COVID-19 mRNA vaccination	IgG level, Seroconversion	Platform of vaccine: two doses of BNT162b2 vaccines Method to measure antibody response (unit): COVID-19 QuantiGEM SARS-CoV-2 IgG ELISA Kit CE-IVD (ng/mL), 33–45 days after the first dose (12–24 days after the second dose)

(*Continued*)

Table 1. (Continued)

No	Author, year	Setting	Study design	Study population	Number of participants	Comparison	Vaccination	Outcomes	Additional Remarks
23	Grupper 2021	Israel	Cohort	Hemodialysis patients	Exposure: 56 Comparison: 95	Health care workers	Pfizer BNT162b2 vaccine	IgG level	Platform of vaccine: BNT162B2 Method to measure antibody response (unit): a chemiluminescent microparticle immunoassay (SARS-CoV-2 IgG II Quant assay on an ARCHITECT analyzer; Abbott) (AU/ml) 4 weeks after second dose
24	Haase 2022	Germany	Cohort	Hemodialysis patients	Exposure: 137 Comparison: 24	Immunocompetent medical personnel	ChAdOx1-S-nCoV-19 and BNT162B2	IgG level	Platform of vaccine: ChAdOx1-S-nCoV-19 and BNT162B2 Method to measure antibody response (unit): The SARS-CoV-2-IgG-II-Quant-assay is an automated CMIA (BAU/ml) 6 weeks after second dose
25	Jahn 2021	Germany	Cohort	Hemodialysis patients	Exposure: 72 Comparison: 16	Healthcare workers	Pfizer BNT162b2 vaccine	IgG level, Seroconversion rate	Platform of vaccine: two doses of mRNA-based BNT162b2 vaccines Method to measure antibody response (unit): anti-SARS-CoV-2 IgG CLIA LIAISON® SARS-CoV-2 TrimericS IgG assay (AU/ml), two weeks after second dose
26	Kim 2022	South Korea	Cohort	Hemodialysis patients	Exposure: 100 Comparison: 100	Hospital workers	HD: ChAdOx1/ BNT162b2 Control: ChAdOx1/ ChAdOx1	IgG level, seroconversion	Platform of vaccine: two doses of SARS-CoV-2 vaccines (ChAdOx1/ BNT162b2) Method to measure antibody response (unit): ARCHITECT IgG II Quant test (Abbott Laboratories) (AU/ml), two months after second dose
27	Kolb 2021	Germany	Cohort	Hemodialysis patients	Exposure: 32 Comparison: 78	Healthy control	BNT162b2 or mRNA-1273 vaccine	IgG level, seroconversion	Platform of vaccine: two doses of mRNA-based SARS-CoV-2 vaccines (BNT162b2 or mRNA-1273) Method to measure antibody response (unit): Anti-SARS-CoV-2 QuantiVac ELISA (Euroimmun) (BAU/ml), 14 days after second dose

(*Continued*)

Table 1. (Continued)

No	Author, year	Setting	Study design	Study population	Number of participants	Comparison	Vaccination	Outcomes	Additional Remarks
28	Labriola 2021	Belgium	Cohort	Hemodialysis patients	Exposure: 24 Comparison: 33	Non-dialyzed nursing home resident	BNT162b2	IgG level, seroconversion	Platform of vaccine: two doses of BNT162b2 vaccines Method to measure antibody response (unit): electrochemiluminescent assays from Elecsys (U/ml), 28 days after first dose (7 days after second dose)
29	Lesny 2021	Germany	Cohort	Hemodialysis patient	Exposure: 23 Comparison: 18	Hemodialysis patient with prior COVID-19 infection	First mRNA- or vector-based SARS-CoV-2 vaccination	IgG level	Platform of vaccine: first mRNA- or vector-based SARS-CoV-2 vaccination Method to measure antibody response (unit): The SARS-CoV-2 IgG II Quant assay is an automated CMIA (AU/ml) 2 weeks after first dose
30	Matsunami 2021	Japan	Cohort	Hemodialysis patients	Exposure: 78 Comparison: 38	Healthy controls	Pfizer BNT162b2 vaccine	IgG level	Platform of vaccine: BNT162B2 Method to measure antibody response (unit): system Elecsys® Anti-SARS-CoV-2 S RUO (Roche Diagnostics, Basel, Switzer-land) (U/ml) 2–8 weeks after second dose
31	Murt 2021	Turkey	Cohort	Hemodialysis patients	Exposure: 85 Comparison: 103	Healthy controls	inactivated or mRNA SARS-CoV-2 vaccines	IgG level	Platform of vaccine: CoronaVac® or BNT162b2 Method to measure antibody response (unit): Abbott SARS-CoV-2 IgG II Quant (Chicago, USA) (AU/ml), 21–28 days after the second dose
32	Panizo 2022	Spain	Cohort	Hemodialysis patients	Exposure: 52 Comparison: 18	Healthy control	mRNA-1273 or BNT162b2 vaccine	IgG level, seroconversion	Platform of vaccine: two doses of mRNA vaccines (mRNA-1273 or BNT162b2) Method to measure antibody response (unit): Roche Elecsys® Anti-SARS-CoV-2 S (U/ml), 15 days and 3 months after second dose
33	Park 2022	South Korea	Cohort	Hemodialysis patients	Exposure: 33 Comparison: 55	Healthy controls	ChAdOx1/ ChAdOx1 or ChAdOx1/ BNT162b2 (for HD patients)	IgG level, NAbs % inhibition, seroconversion	Platform of vaccine: two doses of ChAdOx1 or mix-and-match ChAdOx1/ BNT162b2 (only for HD patients) Method to measure antibody response (unit): Roche Elecsys® Anti-SARS-CoV-2 S (U/ml) and cPass™ SARS-CoV-2 Neutralization Antibody Detection Kit, 56 days after first dose (28 days after second dose)

(*Continued*)

Table 1. (Continued)

No	Author, year	Setting	Study design	Study population	Number of participants	Comparison	Vaccination	Outcomes	Additional Remarks
34	Piotrowska 2022	Poland	Cohort	Hemodialysis patients	Exposure: 35 Comparison: 34	Healthy controls	Pfizer BNT162b2 vaccine	Anti-S IgG level, seroconversion rate	Platform of vaccine: two doses of BNT162b2 vaccines Method to measure antibody response (unit): DiaSorin LIAISON®SARS-CoV-2 S1/S2 IgG (AU/ml), 21 days after the first dose and 14–21 days after the second dose
35	Piscitani 2022	Italy	Case-control	Hemodialysis patients	Exposure: 21 Comparison: 16	Healthy controls	Pfizer BNT162b2 vaccine	IgG level	Platform of vaccine: BNT162b2 Method to measure antibody response (unit): fluorescence polarization immunoassay (FPIA) (Roche®) (IU/ml), after second dose
36	Scharpe 2009	Belgium	Open-label study	Hemodialysis patients	H1N1 Exposure: 201 Comparison: 41 H1N1 Exposure: 201 Comparison: 41	Healthy controls	Influenza vaccine (H3N2, H1N1)	Seroprotection, seroconversion, adverse event	Platform of vaccine: inactivated trivalent vaccine Method to measure antibody response (unit): haemagglutination-inhibiting (HI) antibodies (%), before and 1 month after vaccination
37	Schrezenmeier 2021	Germany	Cohort	Hemodialysis patients	Exposure: 36 Comparison: 44	Healthy controls	Tozinameran (BNT162b2 BioNTech/ Pfizer)	Seroconversion, Anti-SARS-CoV-2 antibody titers	Platform of vaccine: BNT162b2 BioNTech/ Pfizer Method to measure antibody response (unit): anti-SARSCoV-2-S1 IgG/IgA ELISA (Euroimmun, Lübeck, Germany) (IU/ml), week 1 and week 3–4
38	Simon 2021	Austria	Cohort	Hemodialysis patients	Exposure: 81 Comparison: 80	Healthy controls	COVID-19 mRNA vaccination	Anti-SARS-CoV-2 antibody titers, adverse event	Platform of vaccine: mRNA vaccine BNT162b2 Method to measure antibody response (unit): Elecsys® Anti-SARS-CoV-2 test (U/ml), 21 days after second dose
39	Smith 2022	United Kingdom	Cohort	Hemodialysis patients	Exposure: 260 Comparison: 144	Healthy controls	ChAdOx1 BNT162b2	IgG level, seroconversion	Platform of vaccine: mRNA vaccine BNT162b2 Method to measure antibody response (unit): Elecsys® Anti-SARS-CoV-2 test (MFI titer), 4–6 weeks after complete vaccination

(*Continued*)

Table 1. (Continued)

No	Author, year	Setting	Study design	Study population	Number of participants	Comparison	Vaccination	Outcomes	Additional Remarks
40	Speer 2021a	Germany	Cohort	Hemodialysis patients	Exposure: 124 Comparison: 20	Healthy controls	BNT162b2	Anti-S1 IgG level, NAbs % inhibition, seroconversion	Platform of vaccine: two doses of BNT162b2 vaccines. Method to measure antibody response (unit): SARS-CoV-2 Total Assay (Siemens) (semiquantitative index) and SARS-CoV-2 surrogate virus neutralizing assay (Medac) (%), at 20 (18–23) days for HD and 19 (19–23) days for control after second dose
41	Speer 2021b	Germany	Cohort	Hemodialysis patients	Exposure: 22 Comparison: 46	Healthy controls	BNT162b2	Anti-S1 IgG level, NAbs % inhibition, seroconversion	Platform of vaccine: two doses of BNT162b2 vaccines. Method to measure antibody response (unit): SARS-CoV-2 Total Assay (Siemens) (semiquantitative index) and SARS-CoV-2 surrogate virus neutralizing assay (Medac) (%), 20 days after second dose
42	Speer 2021c	Germany	Cohort	Hemodialysis patients	Exposure: 30 Comparison: 18	Healthy controls	BNT162b2	Anti-S1 IgG level, NAbs % inhibition, seroconversion	Platform of vaccine: two doses of BNT162b2 vaccines. Method to measure antibody response (unit): SARS-CoV-2 Total Assay (Siemens) (semiquantitative index) and SARS-CoV-2 surrogate virus neutralizing assay (Medac) (%), 21 days after second dose
43	Strengert 2021	Germany	Cohort	Hemodialysis patients	Exposure: 81 Comparison: 34	Healthcare workers	BNT162b2	IgG level, NAbs % inhibition, seroconversion	Platform of vaccine: two doses of BNT162b2 vaccines. Method to measure antibody response (unit): multiplex immunoassay MULTICOV-AB (MFI) and anti-SARS-CoV-2-QuantiVac-ELISA IgG (Euroimmun), at 21 days after second dose

(*Continued*)

Table 1. (Continued)

No	Author, year	Setting	Study design	Study population	Number of participants	Comparison	Vaccination	Outcomes	Additional Remarks
44	Tillmann 2021	Germany	Cohort	Hemodialysis patients	Exposure: 95 Comparison: 60	Healthy staff	BNT162b2	Neutralizing antibodies % inhibition, seroconversion	Platform of vaccine: two doses of BNT162b2 or ChAdOx1 vaccines. Method to measure antibody response (unit): GenScript SARS-CoV-2 Surrogate Virus Neutralization Test Kit (%), 4–5 weeks after second dose
45	Van Praet 2021	Belgium	Cohort	Hemodialysis patients	Exposure: 543 Comparison: 75	Healthy individuals	BNT162b2 or mRNA-1273	IgG level, seroconversion	Platform of vaccine: two doses of BNT162b2 or mRNA-1273 vaccines. Method to measure antibody response (unit): SARS-CoV-2 IgG II Quant assay (AU/mL), 5 weeks after second dose
46	Wang 2022	Taiwan	Cohort	Hemodialysis patients	Exposure: 204 Comparison: 34	Healthcare workers	ChAdOx1	Anti-RBD IgG level, seroconversion, adverse events	Platform of vaccine: two doses of ChAdOx1 vaccines Method to measure antibody response (unit): Abbott AdviseDx SARS-CoV-2 IgG II assay (AU/mL), T1, four to six weeks after the first dose of vaccine, (efforts were made to try to coordinate with routine blood tests to reduce the negative effects of the extra blood draw); T2, one week before the second dose (to establish baseline concentration); and T3, four to six weeks after the second dose (to assess the antibody response after both injections of the vaccine were complete)
47	Yau 2021	Canada	Cohort	Hemodialysis patients	Exposure: 142 Comparison: 35	Healthcare workers	BNT162b2	IgG level (anti spike, anti-RBD, anti-NP), seroconversion	Platform of vaccine: two doses of BNT162b2 vaccines Method to measure antibody response (unit): automated enzyme-linked immunosorbent assay platform, baseline and weekly until 14 days after second vaccine dose

(*Continued*)

Table 1. (Continued)

No	Author, year	Setting	Study design	Study population	Number of participants	Comparison	Vaccination	Outcomes	Additional Remarks
48	Zhao 2022	Japan	Cohort	Hemodialysis patients	Exposure: 65 Comparison: 500	Residents	BNT162b2	Anti-S1 IgG level, NAbs % inhibition, seroconversion	Platform of vaccine: two doses of BNT162b2 vaccines Method to measure antibody response (unit): the CLIA assay with iFlash 3000 (YHLO Biotech, Shenzhen, China) and iFlash-2019-nCoV series (YHLO Biotech, Shenzhen, China) at 105 days (range 70–112) for dialysis group and 117 days (range 15–170) for control group after second dose

https://doi.org/10.1371/journal.pone.0281160.t001

adverse events rated compared to the control group (HD: 22% vs control: 56%, $p = 0.003$) [60]. ESRD patients developed fewer local symptoms and had fewer symptoms of generalized myalgia and headache.

3.3.3 COVID-19 vaccine. Thirty-five studies investigated the antibody responses after COVID-19 vaccination in ESRD patietns undergoing hemodialysis compared to healthy controls. These studies used various vaccine platforms (including mRNA, inactivated, viral vector and heterologous vaccines) as well as different units of measurements. Table 2 summarizes the comparison of IgG levels between HD and control groups following COVID-19 vaccination obtained from the 30 studies [16–20, 22–25, 27–29, 31, 33–36, 38–40, 43, 44, 46–48, 51, 53, 54, 59]. Overall, twenty-nine studies demonstrated lower IgG levels after COVID-19 vaccination in HD patients compared to healthy controls, whereas only one study by Panizo showed a contrary finding [36].

A study by Haase in 2022 reported higher spike IgG levels in HD patients receiving heterologous vaccination with ChAd/BNT (1744 [267–2840] BAU/mL) compared to HD patients receiving homologous vaccination with BNT/BNT (361 [120–936] BAU/mL), ChAd/ChAd (100 [41–346] BAU/mL), and healthy controls (650 [217–1402] BAU/mL). However, the study did not differentiate the spike IgG levels between different vaccine platforms combinations in the control group [25]. Lesny 2021 showed a lower mean IgG level in HD patients (1.6 [0–14.5] AU/mL) compared to controls (73.1 [16.1–1324.5] AU/mL) after only the first dose of vaccination. This study also reported a lower ACE 2 receptor binding inhibition capacity in HD patients (5.0% [3.1–10.4]) compared to healthy controls (10.5% [6.0–40.9]) [33].

ESRD patients undergoing hemodialysis presented with a lower number of adverse events compared to the control group (Fig 5, with 5 studies, 677 participants: RR 0.34, 95% CI: 0.27–0.42, $p < 0.00001$) with substantial heterogeneity ($I^2 = 88\%$) [13, 20, 25, 40, 51].

4. Discussion

4.1 H1N1 vaccine

In this present study, the intensity of immune response to vaccinations for viral respiratory diseases such as influenza (H1N1 and H3N2) and COVID-19 was inferior in patients with ESRD undergoing hemodialysis compared to healthy subjects. Serological conversion

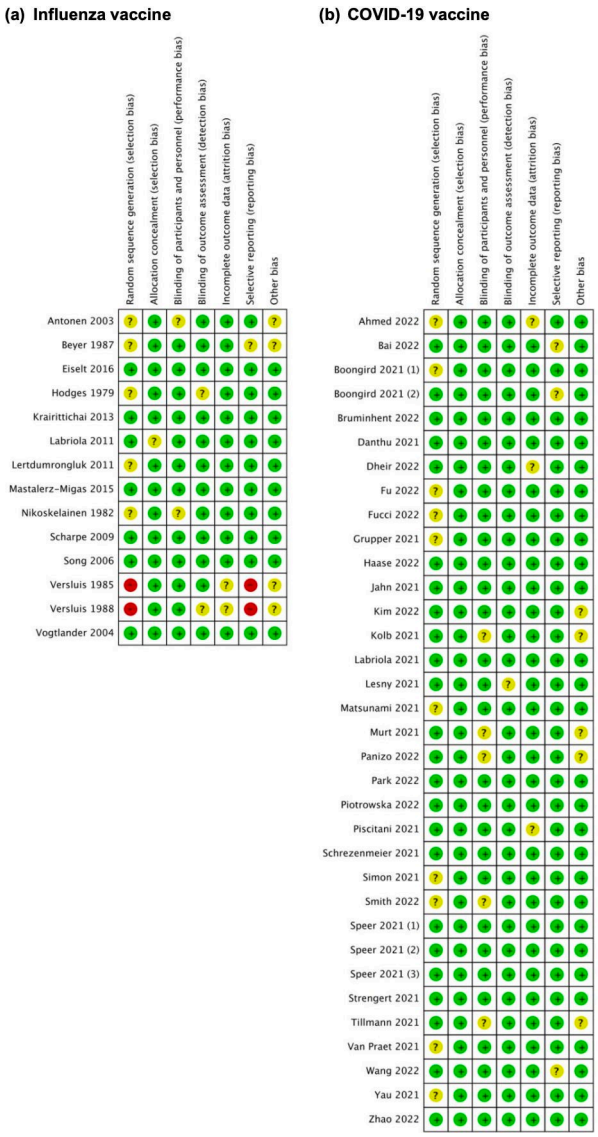


Fig 2. Assessment risk of bias in non-randomized studies of interventions. (a) Influenza vaccine and (b) COVID-19 vaccine studies (green: low risk, yellow: moderate risk, red: serious risk, black: critical risk).

https://doi.org/10.1371/journal.pone.0281160.g002

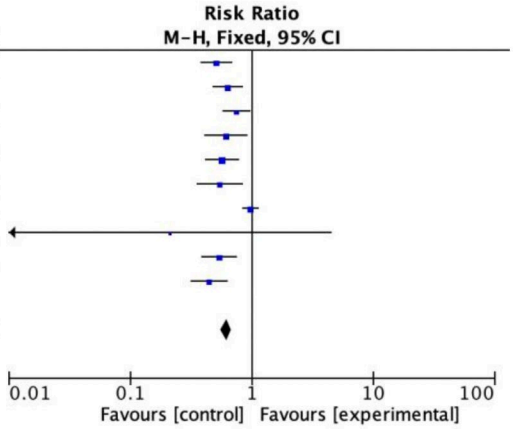
following influenza vaccinations was determined as the outcome measure of efficacy due to the unavailability of hemagglutination-inhibiting antibody titers in most included studies. Ten heterogenous studies were used to generate pooled estimates of seroconversion rate after H1N1 vaccination in patients with ESRD receiving hemodialysis and healthy controls. Except for two studies by Versluis in 1985 and Song in 2006, all investigations found a significant reduction in seroconversion rate in patients with ESRD on hemodialysis compared to healthy controls. The pooled estimates showed a 38% decrease in seroconversion rate in patients with ESRD undergoing hemodialysis. This result is consistent with previous literature reviews in which patients with CKD and ESRD experience significant dysregulation in the adaptive immunity, including T cells and B cells, which impairs vaccine response. The B cells changes in patients with CKD/ESRD include a decrease in the number of B cells, B-cell activating factor, B-cell lymphoma 2 (Bcl-2), and an increase in apoptosis. All of these changes result in the

(a) Seroconversion rate

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Beyer 1987	39	91	21	25	10.3%	0.51 [0.38, 0.68]
Eiselt 2016	59	133	28	40	13.5%	0.63 [0.48, 0.84]
Krairittichai 2013	17	23	20	20	6.9%	0.75 [0.58, 0.96]
Lertdumrongluk 2011	17	44	94	149	13.4%	0.61 [0.41, 0.91]
Mastalerz-Migas 2015	30	71	47	63	15.6%	0.57 [0.42, 0.77]
Scharpe 2009	48	201	18	41	9.4%	0.54 [0.36, 0.83]
Song 2006	40	45	32	35	11.3%	0.97 [0.84, 1.12]
Versluis 1985	0	10	1	6	0.6%	0.21 [0.01, 4.51]
Versluis 1988	40	101	22	30	10.6%	0.54 [0.39, 0.75]
Vogtlander 2004	19	44	19	19	8.5%	0.44 [0.32, 0.63]
Total (95% CI)		**763**		**428**	**100.0%**	**0.62 [0.56, 0.68]**
Total events	309		302			

Heterogeneity: $Chi^2 = 47.11$, df = 9 ($P < 0.00001$); $I^2 = 81\%$

Test for overall effect: $Z = 9.03$ ($P < 0.00001$)



(b) Seroprotection rate

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Beyer 1987	23	91	21	25	11.0%	0.30 [0.20, 0.45]
Eiselt 2016	106	133	38	40	19.5%	0.84 [0.75, 0.94]
Lertdumrongluk 2011	22	44	100	149	15.2%	0.74 [0.54, 1.02]
Mastalerz-Migas 2015	30	71	47	63	16.6%	0.57 [0.42, 0.77]
Scharpe 2009	163	201	29	41	16.1%	1.15 [0.93, 1.41]
Song 2006	45	45	35	35	13.3%	1.00 [0.95, 1.05]
Vogtlander 2004	20	44	18	19	8.4%	0.48 [0.34, 0.67]
Total (95% CI)		**629**		**372**	**100.0%**	**0.76 [0.70, 0.83]**
Total events	409		288			

Heterogeneity: $Chi^2 = 168.35$, df = 6 ($P < 0.00001$); $I^2 = 96\%$

Test for overall effect: $Z = 6.10$ ($P < 0.00001$)

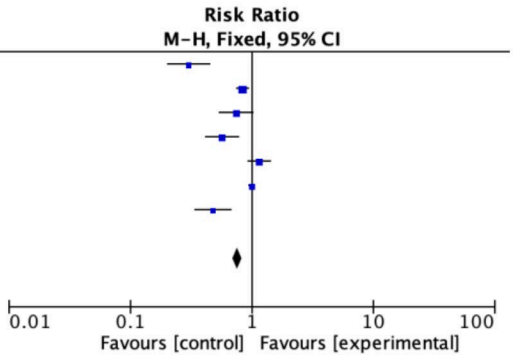


Fig 3. Forest plot of studies reporting. (a) seroconversion rate and (b) seroprotection rate after H1N1 vaccination in patients with ESRD undergoing hemodialysis.

https://doi.org/10.1371/journal.pone.0281160.g003

depletion of serological response [5]. The insignificant results of Versluis in 1985 could be related to the small sample size [50]. However, the power of this study (weighted at 0.6%) is insufficient to alter the outcome of our analysis. The limitation of the study by Song in 2006 was that a previous vaccination history was not considered and there was a considerable number of dropouts—which might affect the seroconversion rate [42].

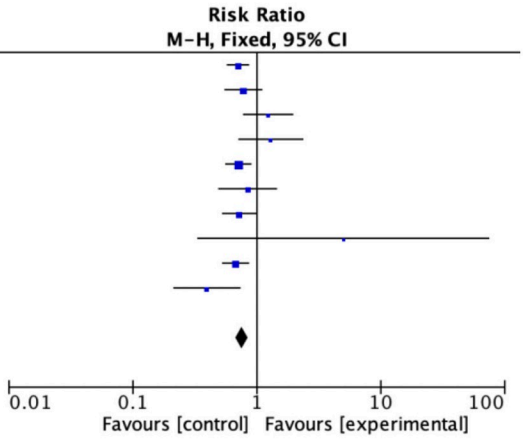
Pooled estimates of seroprotection rate after H1N1 vaccination were derived from seven studies with considerable heterogeneity ($I^2 = 96\%$). Five of the seven studies showed a significant reduction in seroprotection rate in patients with ESRD on hemodialysis compared to healthy controls, which is consistent with a previous literature review of adaptive immune dysfunction in patients with CKD/ESRD [5]. The study by Scharpe in 2009 demonstrated an insignificantly higher seroprotection rate in hemodialysis patients compared to healthy controls, both in subjects with and without baseline seroprotection before vaccination. We assume that this is attributable to (1) a higher seroprotection rate in hemodialysis patients due to more frequent immunizations the previous year and (2) the role of recent dialysis procedural improvements and therapeutic drug advancements [60]. However, only further studies with a larger number of patients will be able to confirm or refute this hypothesis. As mentioned before, the study by Song in 2006 had several limitations that might have affected the outcomes [42].

(a) Seroconversion rate

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Beyer 1987	49	73	19	20	12.3%	0.71 [0.58, 0.85]
Eiselt 2016	57	133	22	40	13.9%	0.78 [0.55, 1.10]
Hodges 1979	9	13	23	41	4.6%	1.23 [0.79, 1.94]
Krairittichai 2013	19	22	4	6	2.6%	1.30 [0.72, 2.34]
Mastalerz-Migas 2015	41	71	51	63	22.3%	0.71 [0.57, 0.90]
Scharpe 2009	50	201	12	41	8.2%	0.85 [0.50, 1.45]
Song 2006	26	45	28	35	13.0%	0.72 [0.54, 0.97]
Versluis 1985	5	10	0	4	0.3%	5.00 [0.34, 74.04]
Versluis 1988	57	101	25	30	15.9%	0.68 [0.54, 0.86]
Vogtlander 2004	11	44	12	19	6.9%	0.40 [0.21, 0.73]
Total (95% CI)		**713**		**299**	**100.0%**	**0.76 [0.68, 0.85]**
Total events	324		196			

Heterogeneity: $Chi^2 = 15.75$, df = 9 (P = 0.07); $I^2 = 43\%$

Test for overall effect: Z = 4.84 (P < 0.00001)



(b) Seroprotection rate

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Antonen 2003	8	23	20	26	7.6%	0.45 [0.25, 0.82]
Beyer 1987	48	73	17	20	10.8%	0.77 [0.60, 0.99]
Eiselt 2016	124	133	40	40	25.2%	0.94 [0.89, 1.00]
Mastalerz-Migas 2015	41	71	54	63	23.2%	0.67 [0.54, 0.84]
Scharpe 2009	175	201	34	41	22.9%	1.05 [0.90, 1.22]
Vogtlander 2004	34	44	18	19	10.2%	0.82 [0.67, 0.99]
Total (95% CI)		**545**		**209**	**100.0%**	**0.84 [0.77, 0.90]**
Total events	430		183			

Heterogeneity: $Chi^2 = 33.21$, df = 5 (P < 0.00001); $I^2 = 85\%$

Test for overall effect: Z = 4.53 (P < 0.00001)

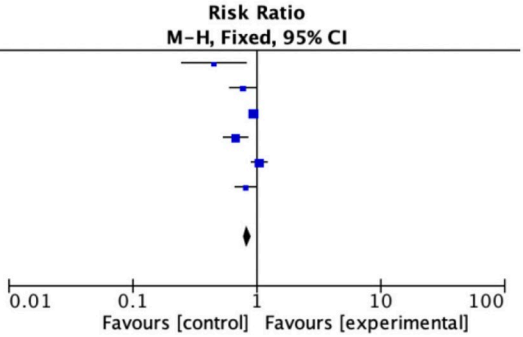


Fig 4. Forest plot of studies reporting. (a) seroconversion rate and (b) seroprotection rate (below) after H3N2 vaccination in patients with ESRD undergoing hemodialysis.

https://doi.org/10.1371/journal.pone.0281160.g004

We found only one study that measured the adverse events after H1N1 influenza vaccination as an outcome. Labriola in 2011 reported that 2 out of 53 hemodialysis patients presented with moderate local pain at the site of injection. No other side effects associated with the vaccination were observed in hemodialysis patients. However, the number of hemodialysis patients included in the study was small. The results were limited in generalizability due to a larger Caucasian population in the study group. In addition, the intensity and types of local adverse reactions were not characterized [30]. As a result, further studies with larger sample sizes and more diverse subjects are required to evaluate adverse events following H1N1 vaccination in hemodialysis patients.

4.2 H3N2 vaccine

Pooled estimates of seroconversion rate after H3N2 vaccination in patients with ESRD undergoing hemodialysis were derived from 10 studies with moderate heterogeneity. Our findings showed a 24% decrease in seroconversion rate in hemodialysis patients, indicating impaired serological response compared to healthy subjects, which is consistent with a recent literature review [5]. In six of the ten studies, the seroconversion rates of hemodialysis patients were shown to be significantly lower than healthy controls.

Table 2. Comparison of IgG levels between HD and control group after COVID-19 vaccination extracted from 30 studies [16–20, 22–25, 27–29, 31, 33–36, 38–40, 43, 44, 46–48, 51, 53, 54, 59].

No	Author	Unit of IgG level	Time to measurement after vaccination	Baseline data				Follow up data			
				HD group		Control group		HD group		Control group	
				N	Mean (SD) or median (IQR)	N	Mean (SD) or median (IQR)	N	Mean (SD) or median (IQR)	N	Mean (SD) or median (IQR)
mRNA vaccines											
1	Danthu 2021	AU/mL	14d 36d	NA NA	NA NA	NA NA	NA NA	75 75	4 (1.85–12.2) 6.6 (2.1–19.0)	7 7	59 (26.5–216.5) 1082 (735–1662)
2	Fucci 2022	ng/mL	22-32d	NA	NA	NA	NA	155	1116 (307.5–9366)	77	4882623 (1177973–5000000)
3	Grupper 2021	AU/mL	30d	NA	NA	NA	NA	56	2900 (1128–5651)	95	7401 (3687–15471)
4	Jahn 2021	AU/mL	HD 17d (15–18) Control 13d (13–13)	NA	NA	NA	NA	72	366.5 (89.6–606)	16	800 (520.0–800)
5	Kolb 2021	AU/mL	HD 14d (13–15) Control 17d	NA	NA	NA	NA	32	503 (481)	78	1922 (2485)
6	Labriola 2021	U/mL	7d	NA	NA	NA	NA	24	25 (5–250)	33	199 (9–250)
7	Matsunami 2021	U/mL	2-8wk	NA	NA	NA	NA	78	200.5 (116.2–376.5)	38	447 (308.2–1067)
8	Panizo 2022	BAU/mL	15d	48	0 (0–2500)	14	(0–114)	50	mRNA-1273: 1146 (0–2500) BNT162b2: 381 (0.90–2500)	16	mRNA-1273: 641 (0–2500) BNT162b2: 517 (0.90–2500)
9	Piotrowska	BAU/mL	14-21d	NA	NA	NA	NA	35	926 (460–1908)	34	2080 (1827–4342)
10	Piscitani 2021	IU/mL	30d	NA	NA	NA	NA	21	492.39 (713.09)	15	1901.20 (287.33)
11	Schrezenmeier	IU/mL	4wk	NA	NA	NA	NA	36	74.29 (56.43–86.90)	44	90.91 (77.42–97.05)
12	Simon 2021	U/mL	3wk	NA	NA	NA	NA	81	171 (477.7)	80	2500 (943.5)
13	Speer 2021a	NA	HD 20d (18–23) Control 19d (19–23)	NA	NA	NA	NA	124	7 (2.8–24.3)	20	134.9 (28.3–283.6)
14	Speer 2021b	NA	18-22d	NA	NA	NA	NA	17	6 (1–11)	46	81 (45–150)
15	Strengert 2021	RU/mL	21d	NA	NA	NA	NA	81	272.3	34	456.8
16	Van Praet 2021 (BNT162b2)	AU/mL	4 or 5w	322	4	37	3	322	393	37	877
	Van Praet 2021 (mRNA-1273)	AU/mL	4 or 5w	221	4	38	3	221	1757	38	2600
17	Zhao 2022	AU/mL	Dialysis: 105d (range 70–112) Control 117d (range 15–170)	NA	NA	NA	NA	65	168.35 (4.48–1074.29)	500	286.66 (4.72–3556.17)
Viral vector vaccines											
18	Fu 2022	U/mL	4w	385	23.1 (7.3–56.6)	NA	NA	385	602 (307.5–1623)	66	662.5 (391.25–109.25)
19	Wang 2022	AU/mL	4-6w	NA	NA	NA	NA	204	138 (138–140)	34	924 (580.6–1741.5)
Inactivated vaccines											
20	Bai 2022	AU/mL	20d after 1st	NA	NA	NA	NA	50	143.4 (117.8)	31	156.3 (113.8)
			3w after 2nd dose	NA	NA	NA	NA	50	180.6 (105.8)	31	186.7 (97.9)
21	Boongird 2021a	AU/mL	2w	NA	NA	NA	NA	60	590 (219–1427)	30	1767 (312–7870)
22	Boongird 2021b	AU/mL	2w	NA	NA	NA	NA	30	500 (72–2785)	30	1785 (785–3785)
23	Bruminhent 2022	BAU/mL	2w	NA	NA	NA	NA	31	85.3 (33–412.1)	16	250.9 (90.9–612.2)
24	Dheir 2022	AU/mL	28d	NA	NA	NA	NA	50	27.4 (7.8–161.5)	41	74.9 (24.6–270.1)
25	Murt 2021	AU/mL	21-28d	NA	NA	NA	NA	85	408.9 (433.5)	103	685.9 (436.9)

(*Continued*)

Table 2. (Continued)

No	Author	Unit of IgG level	Time to measurement after vaccination	Baseline data				Follow up data			
				HD group		Control group		HD group		Control group	
				N	Mean (SD) or median (IQR)	N	Mean (SD) or median (IQR)	N	Mean (SD) or median (IQR)	N	Mean (SD) or median (IQR)
mRNA or viral vector vaccines											
26	Lesny 2021	AU/mL	2w after 1st dose	23	0.0 (0.0–0.8)	NA	NA	23	1.6 (0–14.5)	14	73.1 (16.1–1324.5)
27	Kim 2022	AU/mL	2m	NA	NA	NA	NA	100	82.1 (34.5–176.6)	100	197.1 (124–346)
28	Park 2022	U/mL	7d	25	0.4 (0)	55	0.4 (0)	25	523.9 (672.9)	55	1192 (881.7)
29	Tillmann 2021	AU/mL	4-5w	NA	NA	NA	NA	95	78 (35)	60	92 (20)
mRNA or viral vector or heterologous vaccines											
30	Haase 2022	BAU/mL	6w	NA	BNT/BNT 0 (0.0–0.3) ChAd/ChAd 0.1 (0.0–0.3) ChAd/BNT 0 (0–0.4)	NA	NA	100	BNT/BNT 361 (120–936) ChAd/ChAd 100 (41–346) ChAd/BNT 1744 (276–2840)	24	650 (217–1402)

https://doi.org/10.1371/journal.pone.0281160.t002

Scharpe et al. reported a lower seroconversion rate, but with an insignificant difference, in hemodialysis patients compared to healthy controls, indicating a similar immune response to healthy subjects. In addition, the seroconversion rate is independently related to the baseline seroprotection rate. It is detailed that the baseline seroprotective rate is affected by the frequencies of past immunizations and higher ferritin levels. This study, however, is underpowered to detect a significant difference in immune responses between healthy subjects and hemodialysis patients, with a post hoc power analysis finding that indicated an unrealistically large number of patients would be necessary to achieve an 80% power [60].

Three studies reported an insignificantly higher seroconversion rate in patients with ESRD undergoing hemodialysis than in healthy individuals [26, 50, 58]. However, all three studies are also underpowered (each weighted at 4.6%, 2.6%, and 0.3%) to affect the pooled estimates due to the small number of participants. In addition, one study by Hodges in 1979 still utilized a bivalent split-virus vaccine containing A/New Jersey/76 and A/Victoria/75 instead of a trivalent influenza vaccine [26].

Six studies with considerable heterogeneity were analyzed to generate pooled estimates of the seroprotection rate after H3N2 vaccination in patients with ESRD undergoing hemodialysis. Our study demonstrated a significant decrease of 16% in seroprotection rate in hemodialysis patients compared to healthy subjects. Four of the six studies reported a significantly lower seroprotection rate in patients with ESRD undergoing hemodialysis compared to healthy

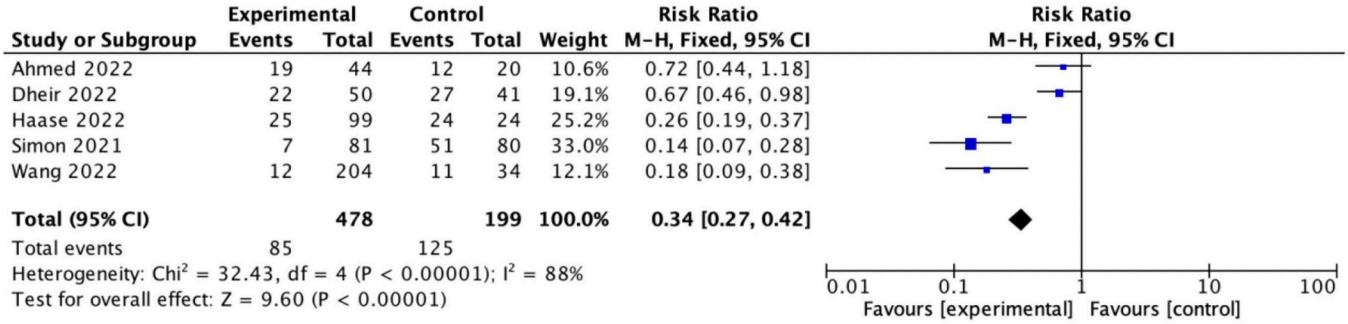


Fig 5. Forest plot of studies reporting adverse events after COVID-19 vaccination in patients with ESRD undergoing hemodialysis.

https://doi.org/10.1371/journal.pone.0281160.g005

subjects. Furthermore, Eiselt et al. also found a lower seroprotection rate in patients with ESRD undergoing hemodialysis, although the difference was not statistically significant. Nevertheless, Scharpé et al. reported a slightly higher seroprotection rate in hemodialysis patients. Similar to the response to H1N1 influenza vaccination, the higher seroprotection rate might be caused by a higher baseline seroprotection rate in hemodialysis patients due to more frequent immunizations the previous year and the impact of recent advancements in dialysis technology and therapeutic drugs [60].

We found only one study by Scharpé in 2009, which evaluated the safety of H3N2 influenza vaccinations as an outcome. In this study, neither hemodialysis patients nor healthy subjects experienced adverse side effects. Compared to healthy controls, the number of mild adverse events was considerably lower in hemodialysis patients. Hemodialysis patients demonstrated fewer local symptoms, fewer generalized myalgia, and fewer headache symptoms [60]. This finding indicates a more potent immune reaction in healthy subjects compared to hemodialysis patients.

4.3 COVID-19 vaccine

Since COVID-19 is a novel disease and numerous different vaccine platforms are currently used, studies investigating immune responses after COVID-19 vaccinations in the HD population also utilize various methods and units of measurement and different vaccine platforms and combinations. Of the included 35 studies investigating COVID-19 vaccination in this systematic review, 30 studies provided data on SARS-CoV-2 IgG antibody response following vaccination (Table 2). Most studies demonstrated lower antibody response in HD patients compared to healthy controls after COVID-19 vaccination, except for one study (i.e., Panizo 2022).

This finding suggests that dialysis patients have a poorer overall antibody response than healthy subjects. As a result, dialysis patients are less likely to be able to neutralize the SARS--CoV-2 virus even after two homologous vaccine doses, no matter the vaccine platform. Thus, vulnerable populations such as hemodialysis patients are more susceptible to infection and severe disease progression [61]. Meanwhile, an interesting finding by Haase et al. 2022 demonstrated higher spike IgG levels in HD patients receiving heterologous vaccination with ChAd/BNT compared to HD patients receiving homologous vaccination with BNT/BNT, ChAd/ChAd, and healthy controls. However, the study did not differentiate the spike IgG levels between different vaccine platforms combinations in the control group. With these findings, a prompt consideration for vaccination dose or schedule adjustment and the administration of heterologous vaccines in ESRD patients on maintenance hemodialysis should be made as done with different vaccines in the past [62].

Meanwhile, a study by Panizo et al. revealed the opposite result. This study demonstrated a higher median anti-RBD IgG level among HD patients (1146 [0–2500] BAU/mL) compared to controls (641 [0–2500] BAU/mL) 15 days after completion of the vaccination schedule with the mRNA-1273 vaccine. This finding might be caused by the larger proportion of seropositive HD patients (12.5%) compared to controls (7%) before vaccination. The participants who were seropositive at baseline might have had a recent COVID-19 infection before vaccination. However, antibody measurement three months after the vaccination showed a waning of antibody levels and a reversal between the two groups (HD: 388 [0–2500] BAU/mL vs. Control: 477 [5.9–2500] BAU/mL). The more pronounced decline in HD patients suggests accelerated kinetics of antibody waning in this population [36].

Even though the gold standard to measure the neutralizing capacity of patients' serum antibodies is a plaque reduction neutralization test [63], the anti-SARS-CoV-2 S antibody has been

shown to have a high correlation with a direct virus neutralization test and a surrogate neutralization assay [64]. Therefore, the anti-SARS-CoV-2 antibody can be used as a surrogate marker for vaccine-induced immunity.

This review demonstrated that, generally, patients with ESRD undergoing hemodialysis have a blunted early serological response to SARS-CoV-2 vaccination. The dynamics of humoral immune response to different SARS-CoV-2 vaccines in this population may be affected by several factors, such as the use of immunosuppressive medications, dialysis vintage, and previous history of COVID-19 vaccination. A multivariate analysis from a prospective cohort study conducted by Van Praet et al. revealed that COVID-19 experience, immunosuppressive drugs use, and dialysis vintage represent independent predictors of humoral immune responses (Van Praet 2021). However, not all included studies in this review provided the data on immunosuppressive drugs and dialysis vintage (extracted data available in https://osf.io/es2ma/?view_only=87b0e57246704617aa094219a60ba73b).

Pooled estimates of the adverse events rate after COVID-19 vaccination were derived from five studies with substantial heterogeneity (I^2 = 88%). Four studies showed a significantly lower number of adverse events in ESRD patients undergoing hemodialysis compared to healthy controls. The pooled estimates in our study demonstrated a 66% lower percentage of adverse events rate in ESRD patients undergoing hemodialysis. This result represents a more potent and noticeable immune reaction in cellular and humoral arms in healthy individuals. The correlation of adverse events with the amount of immunosuppression and whether the number of AEs can indirectly predict response to vaccination are potential research topics to be explored in the future. Further studies are needed to determine the potential causal relationship between adverse events and immune response in patients with ESRD on hemodialysis.

To our knowledge, this review is the first to investigate vaccination against respiratory diseases in ESRD patients undergoing hemodialysis. The overall quality of evidence for seroconversion and seroprotection rate after both H1N1 and H3N2 vaccination and the adverse events rates in COVID-19 vaccination was assessed using the GRADE framework (S1 Table).

There are several limitations of our study. In the absence of RCT data, serological conversion represents the most appropriate surrogate for efficacy despite not being a true measure. Antibody titer data were extracted. However, due to heterogeneous measurement methods, pooled analyses could not be performed. Secondly, due to a lack of available data, our discussion on vaccine safety was limited. In addition, data on immunosuppressive medications, the onset of dialysis, the glomerular filtration rate, and other predictors potentially influencing the immunogenicity outcomes were also inadequate.

5. Conclusions

Our systematic review demonstrates evidence of lower seroconversion and seroprotection rates after vaccinations against viral respiratory diseases in ESRD patients undergoing hemodialysis. We consistently found a lower incidence of minor adverse events and no reported serious adverse events in hemodialysis patients after vaccination. Considering that hemodialysis patients are more susceptible to infection and severe disease progression, a weakened yet substantial serological response can be considered adequate for the recommendation of vaccination against respiratory diseases vaccination in this population. Vaccination dose, schedule, or strategy adjustments should be considered in ESRD patients undergoing hemodialysis.

Supporting information

S1 Checklist. PRISMA 2009 checklist.
(PDF)

S1 Protocol. Protocol of systematic review.
(PDF)

S1 Appendix. Database searching strategy.
(PDF)

S2 Appendix. Funnel plots of studies included in the meta-analyses.
(PDF)

S1 Table. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria for studies included in the meta-analyses.
(PDF)

Acknowledgments

Authors express gratitude to the staff of Klinik Bahasa in the Office of Research and Publication, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia for the English language and grammar editing of the manuscript.

Author Contributions

Conceptualization: Metalia Puspitasari, Prenali D. Sattwika.

Data curation: Metalia Puspitasari, Prenali D. Sattwika, Dzerlina S. Rahari, Wynne Wijaya, Auliana R. P. Hidayat.

Formal analysis: Metalia Puspitasari, Prenali D. Sattwika, Dzerlina S. Rahari, Wynne Wijaya.

Funding acquisition: Metalia Puspitasari.

Investigation: Metalia Puspitasari, Prenali D. Sattwika, Dzerlina S. Rahari, Wynne Wijaya, Auliana R. P. Hidayat.

Methodology: Metalia Puspitasari, Prenali D. Sattwika, Dzerlina S. Rahari, Wynne Wijaya, Auliana R. P. Hidayat.

Project administration: Metalia Puspitasari, Dzerlina S. Rahari, Wynne Wijaya, Auliana R. P. Hidayat.

Resources: Metalia Puspitasari, Prenali D. Sattwika, Dzerlina S. Rahari, Wynne Wijaya, Auliana R. P. Hidayat.

Software: Metalia Puspitasari, Prenali D. Sattwika, Dzerlina S. Rahari, Wynne Wijaya, Auliana R. P. Hidayat.

Supervision: Nyoman Kertia, Bambang Purwanto, Jarir At Thobari.

Validation: Metalia Puspitasari, Prenali D. Sattwika, Nyoman Kertia, Bambang Purwanto, Jarir At Thobari.

Writing – original draft: Metalia Puspitasari, Dzerlina S. Rahari, Wynne Wijaya, Auliana R. P. Hidayat.

Writing – review & editing: Metalia Puspitasari, Prenali D. Sattwika, Dzerlina S. Rahari, Wynne Wijaya, Auliana R. P. Hidayat.

References

1. Thurlow JS, Joshi M, Yan G, Norris KC, Agodoa LY, Yuan CM, et al. Global epidemiology of end-stage kidney disease and disparities in kidney replacement therapy. Am J Nephrol. 2021; 52: 98–107. https://doi.org/10.1159/000514550 PMID: 33752206
2. Guo H, Liu J, Collins AJ, Foley RN. Pneumonia in incident dialysis patients—The United States Renal Data System. Nephrol Dial Transplant. 2008; 23: 680–686. https://doi.org/10.1093/ndt/gfm474 PMID: 18029368
3. Cho J-H, Do J-Y, Kim S-H, Kim J-Y, Seo J-J, Choi J-Y, et al. Impact of Dialysis Modality on the Incidence of 2009 Pandemic H1N1 Influenza in End-Stage Renal Disease Patients. 2011; 31: 347–350. https://doi.org/10.3747/pdi.2010.00158 PMID: 21555416
4. Naicker S, Yang CW, Hwang SJ, Liu BC, Chen JH, Jha V. The Novel Coronavirus 2019 epidemic and kidneys. Kidney Int. 2020; 97: 824–828. https://doi.org/10.1016/j.kint.2020.03.001 PMID: 32204907
5. Syed-Ahmed M, Narayanan M. Immune Dysfunction and Risk of Infection in Chronic Kidney Disease. Adv Chronic Kidney Dis. 2019; 26: 8–15. https://doi.org/10.1053/j.ackd.2019.01.004 PMID: 30876622
6. Sarnak MJ, Jaber BL. Pulmonary infectious mortality among patients with end-stage renal disease. Chest. 2001; 120: 1883–1887. https://doi.org/10.1378/chest.120.6.1883 PMID: 11742917
7. Kato S, Chmielewski M, Honda H, Pecoits-Filho R, Matsuo S, Yuzawa Y, et al. Aspects of immune dysfunction in end-stage renal disease. Clin J Am Soc Nephrol. 2008; 3: 1526–1533. https://doi.org/10.2215/CJN.00950208 PMID: 18701615
8. Eleftheriadis T, Antoniadi G, Liakopoulos V, Kartsios C, Stefanidis I. Disturbances of acquired immunity in hemodialysis patients. Semin Dial. 2007; 20: 440–451. https://doi.org/10.1111/j.1525-139X.2007.00283.x PMID: 17897251
9. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane handbook for systematic reviews of interventions. John Wiley & Sons; 2019.
10. Moher D, Liberati A, Tetzlaff J, Altman DG. Academia and Clinic Annals of Internal Medicine Preferred Reporting Items for Systematic Reviews and Meta-Analyses: Ann Intern Med. 2009; 151: 264–269.
11. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016; 355: 4–10. https://doi.org/10.1136/bmj.i4919 PMID: 27733354
12. Guyatt GH. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. 2008;336. https://doi.org/10.1136/bmj.39489.470347.AD PMID: 18436948
13. Ahmed MF, Ahmed AO, Ahmed AM, El-Hameed ARA. Assessment of Immune Response to the COVID-19 Vaccination in Egyptian Patients Undergoing Maintenance Hemodialysis. Egypt J Hosp Med. 2022; 88: 3457–3463. https://doi.org/10.21608/EJHM.2022.248784
14. Antonen JA, Pyhälä R, Hannula PM, Ala-Houhala IO, Santanen R, Ikonen N, et al. Influenza vaccination of dialysis patients: Cross-reactivity of induced haemagglutination-inhibiting antibodies to H3N2 subtype antigenic variants is comparable with the response of naturally infected young healthy adults. Nephrol Dial Transplant. 2003; 18: 777–781. https://doi.org/10.1093/ndt/gfg012 PMID: 12637648
15. Beyer WEP, Versluis DJ, Kramer P, Diderich PPMN, Weimar W, Masurel N. Trivalent influenza vaccine in patients on haemodialysis: Impaired seroresponse with differences for A-H3N2 and A-H1N1 vaccine components. Vaccine. 1987; 5: 43–48. https://doi.org/10.1016/0264-410x(87)90008-9 PMID: 3577356
16. Boongird S, Chuengsaman P, Setthaudom C, Nongnuch A, Assanatham M, Phanprasert S, et al. Short-Term Immunogenicity Profiles and Predictors for Suboptimal Immune Responses in Patients with End-Stage Kidney Disease Immunized with Inactivated SARS-CoV-2 Vaccine. Infect Dis Ther. 2021; 11: 351–365. https://doi.org/10.1007/s40121-021-00574-9 PMID: 34859359
17. Boongird S, Chuengsaman P, Phanprasert S, Kitpermkiat R, Assanatham M, Nongnuch A, et al. Anti–SARS-CoV-2 spike protein S1 receptor-binding domain antibody after vaccination with inactivated whole-virus SARS-CoV-2 in end-stage kidney disease patients: an initial report. Kidney Int. 2021; 100: 1136–1138. https://doi.org/10.1016/j.kint.2021.08.007 PMID: 34419552
18. Bruminhent J, Setthaudom C, Kitpermkiat R, Kiertiburanakul S, Malathum K, Assanatham M, et al. Immunogenicity of ChAdOx1 nCoV-19 vaccine after a two-dose inactivated SARS-CoV-2 vaccination of dialysis patients and kidney transplant recipients. Sci Rep. 2022; 12: 1–9.
19. Danthu C, Hantz S, Dahlem A, Duval M, Ba B, Guibbert M, 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: 2153–2158. https://doi.org/10.1681/ASN.2021040490 PMID: 34135083
20. Dheir H, Tocoglu A, Toptan H, Pinar M, Demirci T, Koroglu M, et al. Short and mid-term SARS-CoV-2 antibody response after inactivated COVID-19 vaccine in hemodialysis and kidney transplant patients. J Med Virol. 2022; 94: 3176–3183. https://doi.org/10.1002/jmv.27714 PMID: 35277975

21. Eiselt J, Kielberger L, Rajdl D, Racek J, Pazdiora P, Malánová L. Previous vaccination and age are more important predictors of immune response to influenza vaccine than inflammation and iron status in dialysis patients. Kidney Blood Press Res. 2016; 41: 139–147. https://doi.org/10.1159/000443416 PMID: 26914585

22. Fu C, Tsai K, Kuo W, Wu C, Yu C, You H. The Waxing, Waning, and Predictors of Humoral Responses to Vector-Based SARS-CoV-2 Vaccine in Hemodialysis Patients. 2022; 1–15. https://doi.org/10.3390/vaccines10091537 PMID: 36146615

23. Fucci A, Giacobbe S, Guerriero I, Suzumoto Y, D'Andrea EL, Scrima M, et al. The DiaCoVAb study in South Italy: immune response to Sars-CoV-2 vaccination in dialysis patients. Kidney Blood Press Res. 2022. https://doi.org/10.1159/000524034 PMID: 35318291

24. Grupper A, Sharon N, Finn T, Cohen R, Israel M, Agbaria A, et al. Humoral response to the Pfizer BNT162b2 vaccine in patients undergoing maintenance hemodialysis. Clin J Am Soc Nephrol. 2021; 16: 1037–1042. https://doi.org/10.2215/CJN.03500321 PMID: 33824157

25. Haase M, Lesny P, Anderson M, Cloherty G, Stec M, Haase-Fielitz A, et al. Humoral immunogenicity and tolerability of heterologous ChAd/BNT compared with homologous BNT/BNT and ChAd/ChAd SARS-CoV-2 vaccination in hemodialysis patients: A multicenter prospective observational study. J Nephrol. 2022; 35: 1467–1478. https://doi.org/10.1007/s40620-022-01247-7 PMID: 35084719

26. Hodges GR, Davis JW, Lewis HD Jr, Whittier FC Jr, Siegel CD, Chin TD, et al. Response to influenza A vaccine among high-risk patients. South Med J. 1979; 72: 29–32. https://doi.org/10.1097/00007611-197901000-00010 PMID: 366766

27. Jahn M, Korth J, Dorsch O, Anastasiou OE, Sorge-Hädicke B, Tyczynski B, et al. Humoral response to SARS-CoV-2-vaccination with BNT162b2 (Pfizer-BioNTech) in patients on hemodialysis. Vaccines. 2021; 9: 360. https://doi.org/10.3390/vaccines9040360 PMID: 33918085

28. Kim DK, Jung SW, Moon J-Y, Jeong KH, Hwang HS, Kim JS, et al. Severe Acute Respiratory Syndrome Coronavirus 2 Antibody Response After Heterologous Immunizations With ChAdOx1/BNT162b2 in End-Stage Renal Disease Patients on Hemodialysis. Front Immunol. 2022;13. https://doi.org/10.3389/fimmu.2022.894700 PMID: 35734170

29. Kolb T, Fischer S, Müller L, Lübke N, Hillebrandt J, Andrée M, et al. Impaired immune response to SARS-CoV-2 vaccination in dialysis patients and in kidney transplant recipients. Kidney360. 2021; 2: 1491. https://doi.org/10.34067/KID.0003512021 PMID: 35373105

30. Labriola L, Hombrouck A, Maréchal C, Van Gucht S, Brochier B, Thomas I, et al. Immunogenicity of an adjuvanted 2009 pandemic influenza A (H1N1) vaccine in haemodialysed patients. Nephrol Dial Transplant. 2011; 26: 1424–1428. https://doi.org/10.1093/ndt/gfq782 PMID: 21273236

31. Labriola L, Scohy A, Van Regemorter E, Robert A, Clerbaux G, Gillerot G, et al. Immunogenicity of BNT162b2 SARS-CoV-2 vaccine in a multicenter cohort of nursing home residents receiving maintenance hemodialysis. Am J Kidney Dis. 2021; 78: 766–768. https://doi.org/10.1053/j.ajkd.2021.07.004 PMID: 34364905

32. Lertdumrongluk P, Changsirikulchai S, Limkunakul C. Safety and immunogenicity of a 2009 influenza A (H1N1) vaccine in hemodialysis patients. Vaccine. 2012; 30: 1108–1114. https://doi.org/10.1016/j.vaccine.2011.12.023 PMID: 22178515

33. Lesny P, Anderson M, Cloherty G, Stec M, Haase-Fielitz A, Haarhaus M, et al. Immunogenicity of a first dose of mRNA-or vector-based SARS-CoV-2 vaccination in dialysis patients: a multicenter prospective observational pilot study. J Nephrol. 2021; 34: 975–983. https://doi.org/10.1007/s40620-021-01076-0 PMID: 34050904

34. Matsunami M, Suzuki T, Terao T, Kuji H, Matsue K. Immune response to SARS-CoV-2 vaccination among renal replacement therapy patients with CKD: a single-center study. Clin Exp Nephrol. 2022; 26: 305–307. https://doi.org/10.1007/s10157-021-02156-y PMID: 34746991

35. Murt A, Altiparmak MR, Yadigar SS, Yalin SF, Ozbey D, Yildiz Z, et al. Antibody Responses to the SARS-CoV-2 Vaccines in Hemodialysis Patients: Is inactivated vaccine effective? Ther Apher Dial. 2021; 769–774. https://doi.org/10.1111/1744-9987.13752 PMID: 34741418

36. Panizo N, Albert E, Giménez-Civera E, Puchades MJ, D'Marco L, Gandía-Salmerón L, et al. Dynamics of SARS-CoV-2-Spike-reactive antibody and T-cell responses in chronic kidney disease patients within 3 months after COVID-19 full vaccination. Clin Kidney J. 2022; 15: 1562–1573. https://doi.org/10.1093/ckj/sfac093 PMID: 35880064

37. Park J-S, Minn D, Hong S, Jeong S, Kim S, Lee CH, et al. Immunogenicity of COVID-19 Vaccination in Patients With End-Stage Renal Disease Undergoing Maintenance Hemodialysis: The Efficacy of a Mix-and-Match Strategy. J Korean Med Sci. 2022;37. https://doi.org/10.3346/jkms.2022.37.e180 PMID: 35698835

38. Piotrowska M, Zieliński M, Tylicki L, Biedunkiewicz B, Kubanek A, Ślizień Z, et al. Local and Systemic Immunity Are Impaired in End-Stage-Renal-Disease Patients Treated With Hemodialysis, Peritoneal

Dialysis and Kidney Transplant Recipients Immunized With BNT162b2 Pfizer-BioNTech SARS-CoV-2 Vaccine. Front Immunol. 2022;13. https://doi.org/10.3389/fimmu.2022.832924 PMID: 35935974

39. Schrezenmeier E, Bergfeld L, Hillus D, Lippert J-DD, Weber U, Tober-Lau P, et al. Immunogenicity of COVID-19 tozinameran vaccination in patients on chronic dialysis. Front Immunol. 2021; 12: 690698. https://doi.org/10.3389/fimmu.2021.690698 PMID: 34276681

40. Simon B, Rubey H, Treipl A, Gromann M, Hemedi B, Zehetmayer S, et al. Hemodialysis patients show a highly diminished antibody response after COVID-19 mRNA vaccination compared to healthy controls. MedRxiv. 2021; 36: 1709–1716.

41. Smith RM, Cooper DJ, Doffinger R, Stacey H, Al-Mohammad A, Goodfellow I, et al. SARS-COV-2 vaccine responses in renal patient populations. BMC Nephrol. 2022;23. https://doi.org/10.1186/s12882-022-02792-w PMID: 35641961

42. Song JY, Cheong HJ, Ha SH, Kee SY, Jeong HW, Kim WJ. Active Influenza Immunization in Hemodialysis Patients: Comparison between Single-Dose and Booster Vaccination. Am J Nephrol. 2006; 26: 206–211. https://doi.org/10.1159/000093306 PMID: 16699258

43. Speer C, Schaier M, Nusshag C, Töllner M, Buylaert M, Kälble F, et al. Longitudinal humoral responses after covid-19 vaccination in peritoneal and hemodialysis patients over twelve weeks. Vaccines. 2021;9. https://doi.org/10.3390/vaccines9101130 PMID: 34696238

44. Speer C, Göth D, Benning L, Buylaert M, Schaier M, Grenz J, et al. Early humoral responses of hemodialysis patients after COVID-19 vaccination with BNT162b2. Clin J Am Soc Nephrol. 2021; 16: 1073–1082. https://doi.org/10.2215/CJN.03700321 PMID: 34031181

45. Speer C, Benning L, Töllner M, Nusshag C, Kälble F, Reichel P, et al. Neutralizing antibody response against variants of concern after vaccination of dialysis patients with BNT162b2. Kidney Int. 2021; 100: 700–702. https://doi.org/10.1016/j.kint.2021.07.002 PMID: 34265359

46. Strengert M, Becker M, Ramos GM, Dulovic A, Gruber J, Juengling J, et al. Cellular and humoral immunogenicity of a SARS-CoV-2 mRNA vaccine in patients on haemodialysis. EBioMedicine. 2021; 70: 103524. https://doi.org/10.1016/j.ebiom.2021.103524 PMID: 34391096

47. Tillmann F, Figiel L, Ricken J, Still H, Korte C, Plassmann G, et al. Evolution of SARS-CoV-2-Neutralizing Antibodies after Two Standard Dose Vaccinations, Risk Factors for Non-Response and Effect of a Third Dose Booster Vaccination in Non-Responders on Hemodialysis: A Prospective Multi-Centre Cohort Study. 2021. https://doi.org/10.3390/jcm10215113 PMID: 34768631

48. 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: 3208–3220. https://doi.org/10.1681/ASN.2021070908 PMID: 34588184

49. Vogtländer NPJ, Brown A, Valentijn RM, Rimmelzwaan GF, Osterhaus ADME. Impaired response rates, but satisfying protection rates to influenza vaccination in dialysis patients. 2004; 22: 2199–2201. https://doi.org/10.1016/j.vaccine.2003.11.046 PMID: 15149777

50. Versluis DJ, Beyer WEP, Masurel N, Weimar W. Influenza vaccination in dialysis and transplant patients. Antiviral Res. 1985; 5: 289–292. https://doi.org/10.1016/s0166-3542(85)80040-1 PMID: 3909959

51. Wang H, Wu J, Chang M, Wu H, Ho L, Chi P, et al. Antibody Response and Adverse Events of AZD1222 COVID-19 Vaccination in Patients Undergoing Dialysis: A Prospective Cohort Study. Vaccines. 2022; 10: 1460. https://doi.org/10.3390/vaccines10091460 PMID: 36146538

52. Yau K, Abe KT, Naimark D, Oliver MJ, Perl J, Leis JA, et al. Evaluation of the SARS-CoV-2 Antibody Response to the BNT162b2 Vaccine in Patients Undergoing Hemodialysis. JAMA Netw Open. 2021; 4: e2123622–e2123622. https://doi.org/10.1001/jamanetworkopen.2021.23622 PMID: 34473256

53. Zhao T, Nishi-Uchi T, Omata F, Takita M, Kawashima M, Nishikawa Y, et al. Humoral response to SARS-CoV-2 vaccination in haemodialysis patients and a matched cohort. BMJ Open. 2022; 12: 1–7. https://doi.org/10.1136/bmjopen-2022-065741 PMID: 36351730

54. Piscitani L, Del Pinto R, Basili A, Tunno M, Ferri C. Humoral Immune Response to COVID-19 Vaccination in Hemodialysis Patients: A Retrospective, Observational Case–Control Pilot Study. High Blood Press Cardiovasc Prev. 2022; 29: 163–167. https://doi.org/10.1007/s40292-021-00502-5 PMID: 34978702

55. Mastalerz-Migas A, Bujnowska-Fedak M, Brydak LB. Immune efficacy of first and repeat trivalent influenza vaccine in healthy subjects and hemodialysis patients. Adv Exp Med Biol. 2015; 836: 47–54. https://doi.org/10.1007/5584_2014_36 PMID: 25248348

56. Nikoskelainen J, Väänänen P, Forsström J, Kasanen A. Influenza vaccination in patients with chronic renal failure. Scand J Infect Dis. 1982; 14: 245–251. https://doi.org/10.3109/inf.1982.14.issue-4.01 PMID: 7163777

57. Versluis DJ, Beyer WEP, Masurel N, Diderich PPNM, Kramer P, Weimar W. Intact humoral immune response in patients on continuous ambulatory peritoneal dialysis. Nephron. 1988; 49: 16–19. https://doi.org/10.1159/000184979 PMID: 3380215

58. Krairittichai U, Chittaganpitch M. Efficacy of the trivalent influenza vaccination in Thai patients with hemodialysis or kidney transplant compared with healthy volunteers. J Med Assoc Thailand = Chotmaihet Thangphaet. 2013; 96: S1–7. PMID: 23682516

59. Bai S, Dhrolia M, Qureshi H, Qureshi R, Nasir K, Ahmad A. Comparison of COVID-19 Inactivated Virus Vaccine Immunogenicity Between Healthy Individuals and Patients on Hemodialysis: A Single-Center Study From Pakistan. 2022;14. https://doi.org/10.7759/cureus.24153 PMID: 35582560

60. Scharpé J, Peetermans WE, Vanwalleghem J, Maes B, Bammens B, Claes K, et al. Immunogenicity of a standard trivalent influenza vaccine in patients on long-term hemodialysis: an open-label trial. Am J kidney Dis. 2009; 54: 77–85. https://doi.org/10.1053/j.ajkd.2008.11.032 PMID: 19339089

61. Francis A, Baigent C, Ikizler TA, Cockwell P, Jha V. The urgent need to vaccinate dialysis patients against severe acute respiratory syndrome coronavirus 2: a call to action. Kidney Int. 2021; 99: 791–793. https://doi.org/10.1016/j.kint.2021.02.003 PMID: 33582109

62. Centers for Disease Control and Prevention. CDC Updated Vaccine Guideline for Dialysis and Chronic Kidney Disease Patients. Centers for Disease Control and Prevention; 2021.

63. Muruato AE, Fontes-Garfias CR, Ren P, Garcia-Blanco MA, Menachery VD, Xie X, et al. A high-throughput neutralizing antibody assay for COVID-19 diagnosis and vaccine evaluation. Nat Commun. 2020; 11: 1–6.

64. Tan CW, Chia WN, Qin X, Liu P, Chen MI-C, Tiu C, et al. A SARS-CoV-2 surrogate virus neutralization test based on antibody-mediated blockage of ACE2–spike protein–protein interaction. Nat Biotechnol. 2020; 38: 1073–1078. https://doi.org/10.1038/s41587-020-0631-z PMID: 32704169