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Letter to the Editor

The effect of SARS-CoV-2 double vaccination on the outcomes of hemodialysis patients with COVID-19: A meta-analysis

Dear Editor,

We read with great interest the article by Marra et al.[1] who described the effectiveness of COVID-19 vaccines in immunocompromised patients. They showed that patients with solid organ transplant, malignant diseases and inflammatory rheumatic diseases had lower vaccine effectiveness compared to the controls. Hemodialysis patients are another group of immunocompromised patients. They have impaired innate and adaptive immune responses and have a higher baseline mortality and severity risk following COVID-19 infection compared to the general population.[2] The uremic state in hemodialysis patients is associated with a persistent inflammatory state and functional defects in immune cell populations, correlating to premature immunological aging.[3,4]

Patients on hemodialysis are also at greater risk of infection with COVID-19 due to comorbidities, regular invasive procedures, and inability to isolate during treatment.[4] While vaccination is one of the most effective ways to protect against severity of COVID-19, hemodialysis patients have a reduced immune response resulting in a lower seroconversion rate and lower antibody titers.[5,6] Several studies have associated a higher antibody titer with improved prognosis from COVID-19 infection, suggesting that higher antibody titers have a protective effect.[7] Therefore, whether low antibody titers in hemodialysis patients can effectively improve the severity and mortality of COVID-19 in this population needs to be further investigated.

To the best of our knowledge, there is no prior meta-analysis describing the outcomes of hemodialysis patients infected with COVID-19 after SARS-CoV-2 double vaccination. We perform here the first meta-analysis in the literature to investigate the effects of SARS-CoV-2 double vaccination on severity and mortality in hemodialysis patients with COVID-19.

Scopus, PubMed, Embase, Cochrane Library databases, and medRxiv were all searched electronically between December 1, 2019, and August 13, 2022. No limits on the publication, language, or year were imposed. The following medical subject Heading Terms (MeSH) and key words were used: ((coronavirus disease 2019 OR COVID-19 OR SARS-CoV-2) AND (vaccine OR vaccination OR immunization OR immunization)) AND (ESRD OR ESKD OR dialysis OR haemodialysis OR hemodialysis).

The followings were the inclusion criteria: (1) patients with confirmed COVID-19; (2) Comparison of clinical outcomes between hemodialysis patients who received two-dose vaccination with those unvaccinated was reported. Following studies were excluded (1) reviews, case reports, commentary letters, conference proceedings, abstracts, and editorials; and (2) duplicated publications. We also extracted data on baseline characteristics of included studies and participants, including first author's name, year of publication, country of origin, study design, age, gender, number of participants, types of vaccines, and outcomes of interest (mortality and need for oxygen supplementation).

The statistical analysis was performed using statistical software STATA (Stata Corporation, University of Texas, TX, USA). Dichotomous data were analyzed by using the odds ratio (OR) computed using the Mantel Haenszel method (fixed or random models). Heterogeneity was assessed using the Cochran Q-statistic and I^2 tests. A P value of < 0.05 is considered to be statistically significant. The protocol for this meta-analysis is registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42022355331).

Our search strategy identified a total of 6 studies.[8–13] involving 6244 adult patients with COVID-19, including 3744 in the unvaccinated group and 1921 in the two-dose vaccination group, were included in this meta-analysis. Baseline patient demographics and disease characteristics are summarized in Table 1. Three studies were from Europe, two from Japan and one from Chile. Three studies were prospective observational study. Some studies reported both unadjusted and adjusted results in terms of mortality and need for oxygen supplementation. Most studies used BNT162b2 vaccine. All studies were published in between 2021 and 2022 with different sample patient sizes that ranged from 26 to 1323 hemodialysis patients.

The meta-analysis of unadjusted results showed that hemodialysis patients after second-dose vaccination was associated with a decrease in mortality (OR = 0.35, 95%CI: 0.15 to 0.81, $P = 0.014$; $I^2 = 87.8\%$) (Fig. 1A) and need for oxygen supplementation (OR = 0.38, 95%CI: 0.22 to 0.67, $P = 0.001$; I^2=81.2%) (Fig. 1B) compared to unvaccinated patients with hemodialysis. Moreover, the meta-analysis of adjusted results indicated that second-dose vaccination group was also associated with lower risk of mortality (OR = 0.43, 95%CI: 0.20 to 0.93, $P = 0.031$; I^2=81.6%) (Fig. 1C) and need for oxygen supplementation (OR = 0.36, 95%CI: 0.15 to 0.87, $P = 0.023$; $I^2 = 79.1\%$) (Fig. 1D) compared to unvaccinated patients with hemodialysis.

In this study, we find that SARS-CoV-2 double vaccination in hemodialysis patients is associated with a significant reduction of overall mortality as well as need for oxygen supplementation.

While patients on hemodialysis having been demonstrated as having a weaker immune response to vaccination compared to the general population, the reduced morbidity and mortality of hemodialysis patients with COVID-19 following SARS-CoV-2 vaccination is likely due to the effective antibody response that is still mounted.[4] The production of neutralizing antibodies to SARS-CoV-2, while still lower than the response mounted by a healthy control, serve a sufficient protective role in reducing the severity of disease and likelihood of overall mortality.[5,6]

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Table 1
Characteristics of included studies.

Study	Country	Second-dose Age[a]	Male (%)	Unvaccinated Age[a]	Male (%)	Study design	Sample size	Types of vaccines
Ashby[8] 2022 a	United Kingdom	60 (50–72)	251 (58)	55 (44–64)	100 (50)	Observational Cohort Study	1126	BNT162b2 or mRNA-1273
Ashby[9] 2022 b	United Kingdom	63 (52–73)	117 (62)	61 (53–72)	622 (59)	Observational Cohort Study	1323	BNT162b2 or AZD1222
Espi[10] 2021	France	74.0 ± 13.5	79 (62)	68.5 ± 15.2	639 (57)	Prospective observational study	1247	BNT162b2
Kikuchi[11] 2022	Japan	NR	61 (66)	NR	819 (70)	Prospective observational study	1260	BNT162b2
Toda[12] 2022	Japan	68.3	8 (73)	65.9	10 (67)	Retrospective study	26	BNT162b2 mRNA COVID-19 vaccine or the mRNA-1273 COVID-19 vaccine
Torres[13] 2022	Chile	NR	NR	NR	NR	Prospective observational study	1262	BNT162b2 and CoronaVac

[a] Age data presented as median (IQR) or mean (SD); NR: not reported.

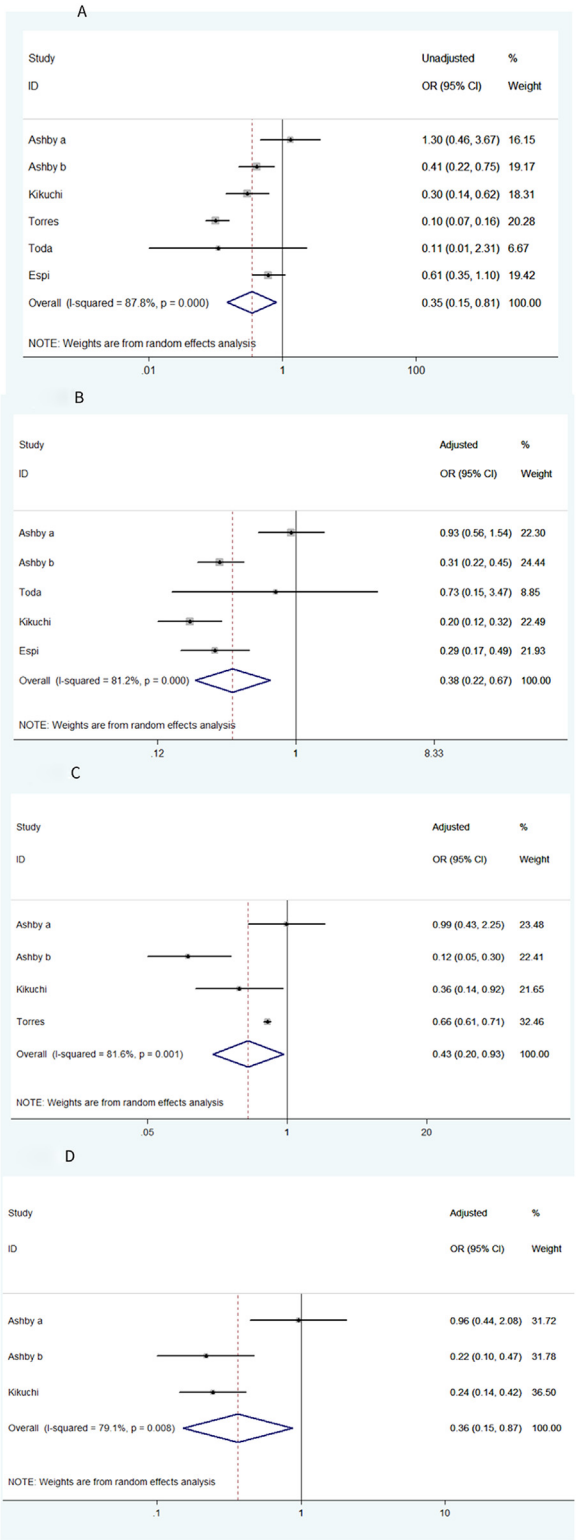

Fig. 1A. Meta-analysis of unadjusted results of mortality in hemodialysis patients after the second dose of vaccine compared to unvaccinated hemodialysis patients.

Beyond reduced morbidity and mortality, the improved prognostic outcomes of hemodialysis patients with COVID-19 following SARS-CoV-2 vaccination have added benefits as well. A reduced need for oxygen supplementation may mitigate any disruptions to patient's hemodialysis schedule. Patients on hemodialysis have scheduled periods each week to filter waste, toxins, electrolytes,

and fluid. Disruptions in this schedule may lead to uremic symptoms, electrolyte abnormalities, and other sequelae that increase the likelihood of hospitalization and mortality.[14] The reduce need for oxygen supplementation also benefits the quality of life of patients and increases their independence for their activities of daily living.

While double vaccination has prognostic value in reducing overall mortality and need for oxygen supplementation, the newest SARS-CoV-2 subvariants have demonstrated progressing neutralization escape properties against not only immunization but also prior infections by COVID-19.[15] Furthermore, SARS-CoV-2 mutations have even resulted in certain neutralizing monoclonal antibodies specifically developed to treat COVID-19 infection as having reduced efficacy leading to their removal from clinical practice guidelines.[16] This continuing evolution of SARS-COV-2 reinforces the importance of having preventative and prophylactic options in particular to protect patients with a higher baseline mortality and severity risk. A third mRNA vaccine dose has been shown to significantly reduce the likelihood of symptomatic illness in an outpatient setting, suggesting value in booster doses of SRS-CoV-2 vaccines.[17] In addition, the development of bivalent vaccines that targets both the newer Omicron sequence as well as the original wildtype COVID-19 sequence may considerably mitigate the neutralization escape properties being exhibited by the Omicron sublineages.[18]

Our study has several limitations that should be recognized. The meta-analysis had a small sample size of six included studies, potentially leaving the results vulnerable to publication bias. In addition, the results for both mortality and need for oxygen therapy had significant heterogeneity ($I^2 > 75\%$). Furthermore, while most studies included patients who solely received mRNA SARS-CoV-2 vaccines, Torres et al. also included patients who received a whole inactivated virus SARS-CoV-2 vaccine while Ashby et al. also included patients who received an adenovirus-vectored SARS-CoV-2 vaccine.[9,13] The studies likely also had different dominant SARS-CoV-2 variants of concern circulating during their investigation. Despite these limitations, our study is the first meta-analysis in the literature to investigate the effect of SARS-CoV-2 double vaccination on the outcomes of hemodialysis patients with COVID-19.

In conclusion, two doses of SARS-CoV-2 vaccination is associated with reduced mortality and need for oxygen supplementation in hemodialysis patients with COVID-19. Additional research is needed to provide a larger sample size and better understand this association to provide insight on the value of booster doses of SARS-CoV-2 vaccines.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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