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Original Article

Survival benefit of a third dose of the COVID-19 vaccine among hemodialysis patients: A prospective cohort study

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KEYWORDS
Coronavirus disease 2019 (COVID-19);
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2);
COVID-19 vaccine;
Anti-spike protein receptor-binding domain antibody

Abstract *Background:* Hemodialysis (HD) patients are particularly vulnerable to severe coronavirus disease 2019 (COVID-19) due to their immunocompromised state and comorbid conditions. Timely vaccination could be the most effective strategy to reduce morbidity and mortality. However, data on the survival benefit of the COVID-19 vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and death among HD patients are limited, especially during the Omicron-dominant period.
Methods: In this prospective hospital-based cohort study, we identified HD patients from July 1, 2021, to April 29, 2022. The patients were divided into fully vaccinated and partially vaccinated groups. We compared the humoral response, risk of developing SARS-CoV-2 infection, and all-cause mortality between the two groups.
Results: Among the 440 HD patients included, 152 patients were fully vaccinated, and 288 patients were partially vaccinated. Patients in the fully vaccinated group exhibited higher anti-spike protein receptor-binding domain (S protein RBD) antibody levels and lower risks of all-cause mortality (adjusted hazard ratio, 0.35; 95% confidence interval, 0.17—0.73; $p = 0.005$) than the partially vaccinated group. However, the risk for SARS-CoV-2 infection did not significantly differ between the two groups. Irrespective of the number of vaccinations, the risk of all-cause mortality was lower in patients with anti-S protein RBD antibody levels in the higher tertile.
Conclusion: A third dose of the COVID-19 vaccine was associated with a decreased risk of all-cause mortality among HD patients during the Omicron-dominant period. A higher post-vaccination anti-S protein RBD antibody level was also associated with a lower risk of mortality.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic that began the end of 2019 has greatly affected the global economy and healthcare system. This ongoing crisis has become a serious challenge, especially for patients receiving chronic hemodialysis (HD). Among patients undergoing in—center HD, infection clusters can easily occur due to difficulty in maintaining social distancing and frequent hospital traveling for HD treatment.[1] Furthermore, end-stage renal disease and its comorbid medical conditions, such as diabetes and protein-energy wasting, are linked to increased risks of severe COVID-19 infection and mortality.[2] To prevent COVID-19-associated morbidity and mortality, timely vaccination may be the most efficient and effective strategy.

Previous studies have shown that vaccination against COVID-19 reduced the rates of infection, severe disease, hospitalization from COVID-19, and mortality in the general population.[3,4] However, HD patients are considered relatively immunodeficient. Diminished humoral and cellular immune responses to vaccination among this vulnerable population have been reported. In a study investigating the immunogenicity of the COVID-19 vaccine, HD patients exhibited lower plasma anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike (S) protein receptor-binding domain (RBD) IgG titers and reduced neutralization capacity and T-cell responses after the second dose of the Pfizer-BioNTech BNT162b2 vaccine compared with a non-dialysis group. A rapid decrease in antibody titers 16 weeks after vaccination was also observed.[5] Another study showed that booster doses significantly increased the anti-RBD IgG titer and T cell responses and reduced the COVID-19 infection rate in both HD patients and non-dialysis controls.[6] These findings suggested that repeat vaccination may be important to provide a robust and durable immune response against COVID-19, especially in HD patients. Based on the current published evidence, the Taiwan Centers for Disease Control (CDC) has also recommended an additional dose and a booster dose following a primary COVID-19 vaccine series for immunocompromised individuals as well as dialysis patients.

Previous studies have mostly focused on antibody and T-cell responses after vaccination in HD patients. In addition, existing evidence on vaccine effectiveness against COVID-19 was largely based on non-Omicron variants. Real-world data on the effectiveness of the COVID-19 vaccine among HD patients after the emergence of the Omicron variant are scarce. Herein, we conducted a prospective cohort study to examine the survival benefit of a third vaccination against COVID-19 and to investigate the effect of post-vaccination anti-S protein RBD antibody levels on clinical outcomes in HD patients during the Omicron-dominant period.

Methods

Study design and participants

This prospective hospital-based cohort study was conducted in Taipei Veterans General Hospital, which is a tertiary medical center. We enrolled patients undergoing chronic hemodialysis aged ≥20 years from July 1, 2021, to April 29, 2022. Patients with a previous diagnosis of COVID-19 were identified and excluded through a review of medical record. We also excluded patients who got SARS-CoV-2 infection or died within three months of receiving the

first or second dose of the vaccine. Baseline demographic data were obtained from the patients' electronic medical records. The participants were divided into a fully vaccinated group and a partially vaccinated group according to their vaccination status. Full vaccination was defined as completion of three doses of the COVID-19 vaccine for more than 14 days, regardless of the vaccine type. The partially vaccinated group included HD patients who received less than three doses of the COVID-19 vaccine. After completion of three doses of COVID-19 vaccines, all patients were followed up until October 24, 2022. During this study period, the Omicron variant was the predominant circulating SARS-CoV-2 strain in Taiwan.[7] This study was approved by Institutional Review Board of Taipei Veterans General Hospital (VGH-2021-07-001AC).

COVID-19 vaccination program for HD patients in Taiwan

The Taiwan CDC classifies dialysis patients as an immunocompromised group and recommends an additional primary dose as a third dose for these patients aged 12 years or older. Participants in this study were able to freely select a two-dose primary series and a third dose of the COVID-19 vaccine among three different brands available in Taiwan during the study period, including ChAdOx1, mRNA1273 and BNT162b2. The interval between the second and third doses of the COVID-19 vaccine was at least four weeks.

Laboratory testing for anti-S protein RBD antibody titers

Blood samples for anti-S protein RBD antibody titers were collected from the included HD patients before a routine hemodialysis treatment two weeks after vaccination including from July 14, 2021, to August 13, 2021, after the first dose (T1); from October 6, 2021, to December 5, 2021, after the second dose (T2); and from March 6, 2022 to March 27, 2022 after the third dose (T3). For the partially vaccinated group, blood samples were collected in parallel to the fully vaccinated cohort, ensuring a consistent timeframe across both groups.

Serum binding antibody levels against the S protein were determined using an Elecsys Anti-SARS-CoV-2 Assay (Roche Molecular System Inc., CA, USA). This is an immunoassay for the *in vitro* quantitative determination of antibodies (including IgG) to the SARS-CoV-2 S protein RBD in human serum and plasma. The Elecsys Anti-SARS-CoV-2 S assay uses a recombinant protein representing the RBD of the S protein antigen in a double-antigen sandwich assay format, which favors the quantitative determination of high-affinity antibodies against SARS-CoV-2. The test was considered positive if the anti-S protein RBD antibody level was 0.80 U/ml or above. This assay was run on a Roche cobas e801 automatic system according to the manufacturer's instruction.

Outcomes

The outcomes included SARS-CoV-2 infection and all-cause mortality. The diagnosis of SARS-CoV-2 infection was made by detection of SARS-CoV-2 RNA using polymerase chain reaction (PCR) or by detection of viral protein using an antigen test. Of noted, routine COVID-19 testing was not implemented for asymptomatic individuals in our dialysis unit. Instead, when patients exhibited symptoms associated with COVID-19, some chose to perform an antigen test at home, while others came to the hospital for a PCR or antigen test. Patients were followed until death or until the end of the study, whichever occurred first.

Statistical analysis

We described the cohort by the COVID-19 vaccination status. For continuous data, we calculated the mean $\pm$ standard deviation (SD) for data exhibiting normal distribution. For non-normally distributed data, medians and interquartile ranges (IQRs) were calculated to characterize the study population at baseline. Categorical variables are expressed as frequencies and percentages. For comparisons of baseline characteristics between groups, Pearson's chi-square tests were used to compare categorical variables, while the independent t-test and Mann—Whitney U test were used to compare parametric and non-parametric continuous variables, respectively. When comparing continuous variables across three or more groups, we employed the Kruskal—Wallis test. We calculated survival curves of the proportions of patients without SARS-CoV-2 infection and all-cause mortality using Kaplan—Meier analysis. Statistical significance was estimated using the log-rank test. Multivariate Cox regression analysis were used to evaluate the relative hazards of the outcomes in the two study groups. The effect of anti-S protein RBD antibody titers on outcomes was also accessed using Cox regression analysis. To provide a more balanced comparison between the two groups, we performed propensity score matching analysis. The propensity scores matching models included the following baseline variables: age; sex; smoking status; hypertension; diabetes mellitus; coronary artery disease; heart failure; peripheral artery disease; stroke; malignancy; blood urea nitrogen; serum albumin; calcium; total cholesterol; glucose; hemoglobin; potassium; sodium; triglyceride; uric acid; and urea reduction rate. We matched each patient in the fully vaccinated group to two patients in the partially vaccinated group according to propensity scores using nearest neighbour matching without replacement. Following the propensity score matching, we further conducted a Cox regression analysis on the matched dataset to evaluate the hazards of the outcomes between the fully vaccinated and partially vaccinated groups. Data were analyzed with SPSS version 24 for Windows (IBM Company, Chicago, USA) and SMART version 2,2.[8] A p value < 0.05 was considered to indicate statistical significance.

Results

Among 440 HD patients, 152 patients were fully vaccinated, and 288 patients were partially vaccinated. The baseline characteristics of the study subjects are listed in Table 1. Patients in the partially vaccinated group were older, were more likely to have stroke, and had lower blood urea

Table 1 Baseline demographic data.

Characteristics	All patients (n = 440)	Fully vaccinated (n = 152)	Partially vaccinated (n = 288)	P value
Demographic				
Age, years	66.0 [56.0,75.8]	63.0 [54.5,71.0]	67.0 [56.0,78.0]	0.006
Male	241 (54.8)	82 (54.0)	159 (55.2)	0.879
Smokers	69 (15.7)	23 (15.1)	46 (16.0)	0.926
Comorbidities				
Hypertension	383 (87.0)	133 (87.1)	250 (86.8)	0.955
Diabetes mellitus	220 (50.0)	80 (52.6)	140 (48.6)	0.483
Coronary artery disease	147 (33.4)	55 (36.2)	92 (31.9)	0.429
Heart failure	130 (29.6)	42 (27.6)	88 (30.6)	0.597
Peripheral artery disease	26 (5.9)	8 (5.3)	18 (6.3)	0.838
Stroke	67 (15.2)	14 (9.2)	53 (18.4)	0.016
Malignancy	80 (18.2)	30 (19.7)	50 (17.4)	0.628
Laboratory data				
Albumin, g/dL	4.1 [3.9,4.3]	4.2 [3.9,4.4]	4.1 [3.8,4.2]	<0.001
Blood urea nitrogen, mg/dL	36.0 [27.0,45.0]	34 [26.0,43.0]	38 [28.0,46.0]	0.036
Calcium, mg/dL	9.08 ± 0.53	9.07 ± 0.50	9.08 ± 0.54	0.780
Total cholesterol, mg/dL	148.0 [126.5,170.5]	150.0 [128.5,177.5]	147.0 [126.0,168.0]	0.279
Glucose, mg/dL	145.6 [125.0,182.0]	139.0 [123.0,172.5]	149.0 [127.5,189.5]	0.067
Hemoglobin, g/dL	9.3 [8.6,11]	10.6 [8.7,11.1]	9.1 [8.6,10.9]	0.011
Potassium, meq/L	4.55 ± 0.52	4.62 ± 0.49	4.52 ± 0.53	0.060
Sodium, meq/L	137.0 [136.0,139.0]	138.0 [136.0,139.0]	137.0 [136.0,138.0]	0.046
Triglyceride, mg/dL	142.5 [72.0,193.0]	149.5 [72.5,197.5]	136.5 [72.0,189.5]	0.163
Uric acid, mg/dl	6.0 [4.8,6.8]	6.0 [5.1,6.9]	5.9 [4.8,6.8]	0.330
Urea reduction rate %	73.1 [67.9,77.4]	74.1 [69.6,76.7]	72.5 [67.2,77.6]	0.328
Anti-S RBD antibody level[a]				
T1	16.7 [0.5,65.7]	26.9 [4.7,94.0]	9.6 [0.4,55.1]	<0.001
T2	325.5 [38.1,2304.0]	711.0 [156.5,2500.0]	250.0 [18.5,1762.0]	0.001
T3	1485.0 [173.5,2500.0]	2500.0 [532.5,2500.0]	1039 [98.1,2500.0]	<0.001
Vaccination status				
Unvaccinated	89 (20.2)	0 (0)	89 (30.9)	
One dose	50 (11.4)	0 (0)	50 (17.4)	
Two doses	149 (33.9)	0 (0)	149 (51.7)	
Vaccination regimens				
A[b]	13 (3.0)	0 (0)	13 (4.5)	
M[c]	37 (8.4)	0 (0)	37 (12.9)	
A/A	68 (15.5)	0 (0)	68 (23.6)	
A/M	13 (3.0)	0 (0)	13 (4.5)	
M/M	68 (15.5)	0 (0)	68 (23.6)	
A/A/M	86 (19.6)	86 (56.6)	0 (0)	
M/M/M	66 (15.0)	66 (43.4)	0 (0)	

[a] Blood samples for anti-S RBD antibodies were collected from the dialysis patients at T1 (two weeks after the first dose), T2 (two weeks after the second dose) and T3 (two weeks after the third dose). Blood samples were also obtained from patients in the partial vaccinated group at the same timing.
[b] A refers to ChAdOx1 vaccine.
[c] M refers to mRNA vaccine.
Values for categorical variables are given as numbers (percentages); values for continuous variables are given as mean ± SD or median and IQR.
Abbreviations: anti-S RBD antibody, anti-spike protein receptor-binding domain antibody; BUN, blood urea nitrogen.

nitrogen, serum albumin, serum sodium, and hemoglobin levels and urea reduction rates. Of the vaccine products administered in the fully vaccinated group, 56.6% were a heterologous regimen with ChAdOx1/ChAdOx1/mRNA (A/A/M), and 43.4% were a homologous regimen with mRNA/mRNA/mRNA (M/M/M). The post-vaccination humoral response is shown in Fig. 1 and Supplementary Fig. S1. Patients in the fully vaccinated group had a significantly higher anti-S protein RBD antibody level after administration of the third dose of the COVID-19 vaccine.

During the follow-up period, the incident rates of SARS-CoV-2 infection and all-cause mortality were 17.1% and 5.9%, respectively, in the fully vaccinated group and 19.4% and 23.6%, respectively, in the partially vaccinated group

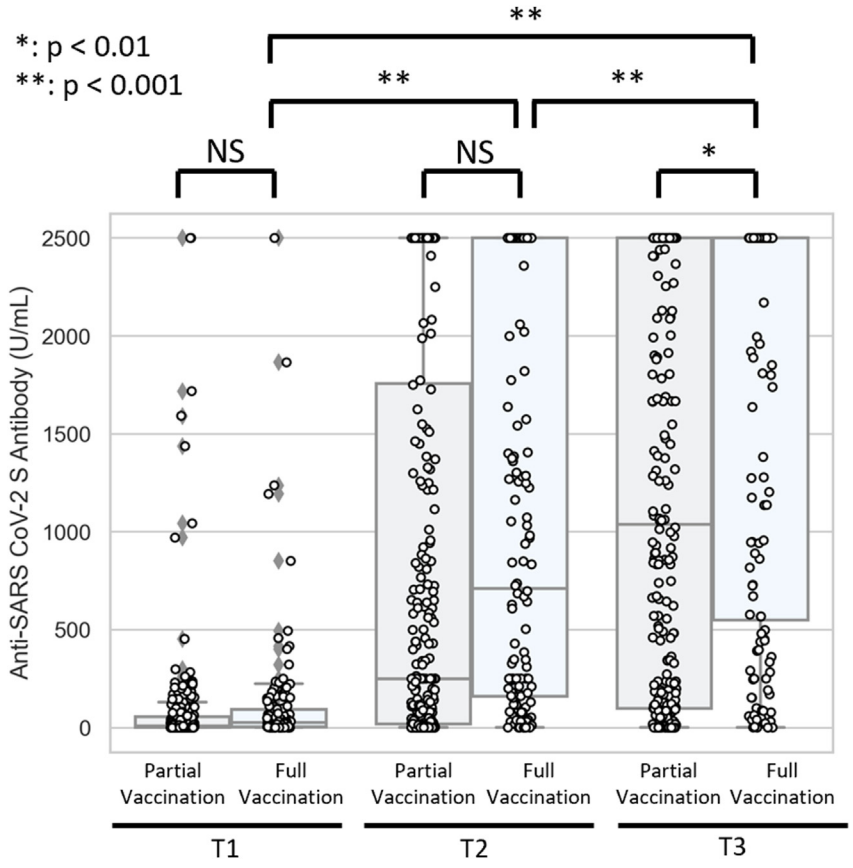

Figure 1. Comparisons of anti-S protein RBD antibody levels between the fully vaccinated and the partially vaccinated group at T1, T2, T3. Abbreviations: anti-S protein RBD antibody, anti-spike protein receptor-binding domain antibody; T1, two weeks after the first vaccination; T2, two weeks after the second vaccination; T3, two weeks after the third vaccination.

(Table 2). The results of the Kaplan—Meier survival analysis according to the development of SARS-CoV-2 infection and all-cause mortality are shown in Fig. 2. Patients in the fully vaccinated group had significantly lower risks of all-cause mortality (log-rank test, $p < 0.001$) than those in the partially vaccinated group. However, the risk of developing SARS-CoV-2 infection showed no significant difference between the two groups (log-rank test, $p = 0.19$).

In a multivariate Cox regression analysis adjusted for the baseline demographic data, comorbidities and laboratory data listed in Table 1, the fully vaccinated group exhibited lower risks of all-cause mortality (adjusted hazard ratio (aHR), 0.35; 95% confidence interval (CI), 0.17—0.73; $p = 0.005$; Table 2). There was no significant difference in the risk of developing SARS-CoV-2 infection between the two groups (aHR, 0.87; 95% CI, 0.53—1.44; $p = 0.594$). When we further divided patients in the fully vaccinated group into the A/A/M group and M/M/M group based on their vaccine regimen, the A/A/M group exhibited a significantly reduced risk of all-cause mortality compared to the partially vaccinated group (aHR, 0.27; 95% CI, 0.09—0.76; $p = 0.013$). However, there was no statistically

Table 2 Risks of developing SARS-CoV-2 infection and all-cause mortality in HD patients with full vaccination versus partial vaccination.

	Number of subjects	Number of event (%)	Crude HR (95% CI)[a]	*P*	Adjusted HR (95% CI)[b]	*P*
SARS-CoV-2 infection						
Partially vaccinated	288	56 (19.4)	Reference		Reference	
Fully vaccinated	152	26 (17.1)	0.73 (0.46—1.17)	0.191	0.87 (0.53—1.44)	0.578
All-cause mortality						
Partially vaccinated	288	68 (23.6)	Reference		Reference	
Fully vaccinated	152	9 (5.9)	0.21 (0.11—0.43)	<0.001	0.35 (0.17—0.73)	0.005

[a] Crude model was an unadjusted crude hazard ratio.
[b] Adjusted model was adjusted for baseline demographic data, comorbidities and laboratory data listed in Table 1.
Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; HD: hemodialysis; HR, hazard ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

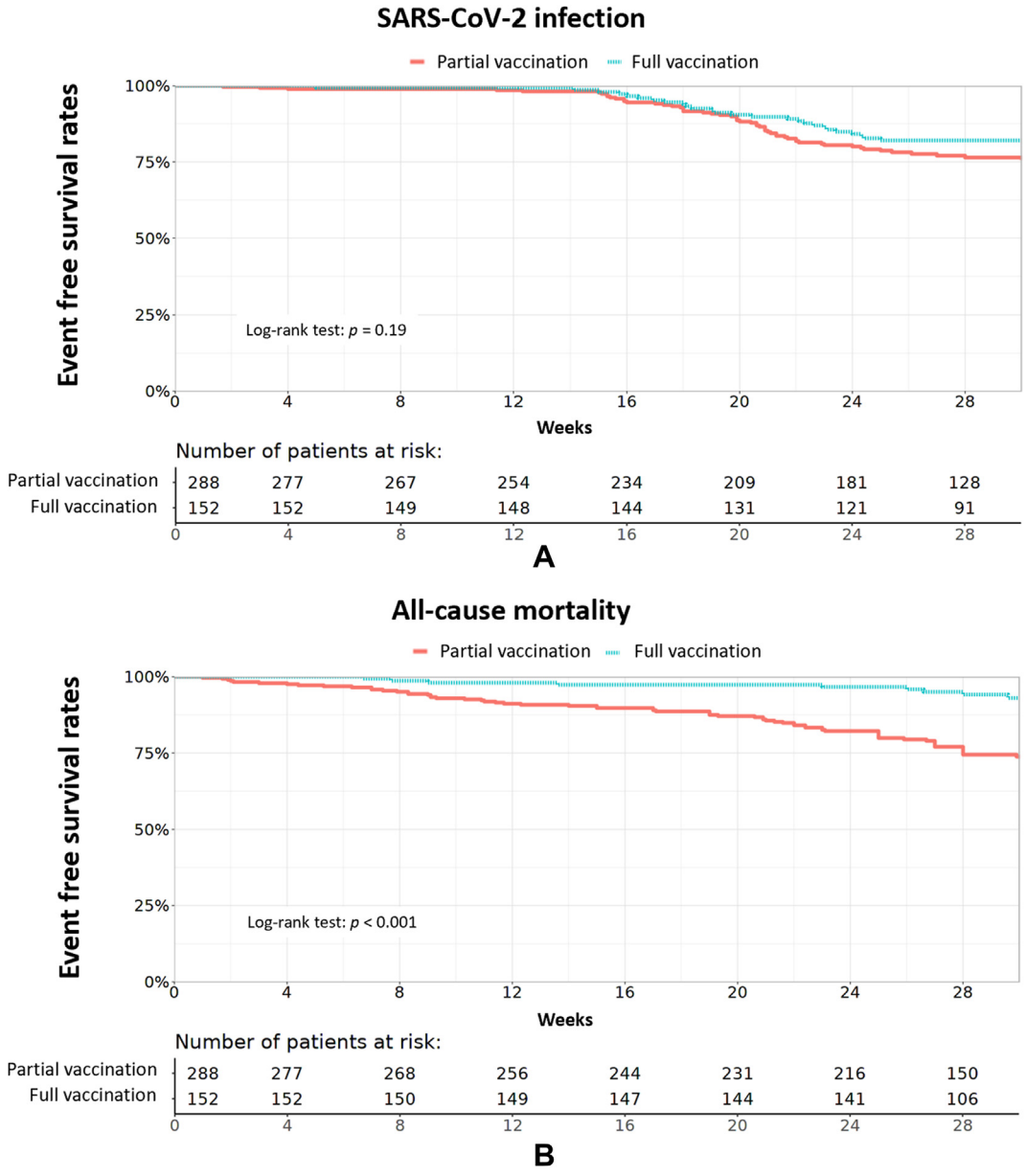

Figure 2. Kaplan–Meier curves for the risk of (A) SARS-CoV-2 infection and (B) all-cause mortality in the fully vaccinated group versus the partially vaccinated group. The event-free survival curves with the log-rank test showed that the risks of all-cause mortality were higher in the partially vaccinated group. However, the risk of developing SARS-CoV-2 infection showed no significant difference between the two groups.

significant difference in all-cause mortality risk between the M/M/M group and the partially vaccinated group (aHR, 0.47; 95% CI, 0.18–1.23; $p = 0.124$). Additionally, there were no significant differences in the risk of SARS-CoV-2 infection among the A/A/M, M/M/M, and partially vaccinated groups. These findings are further detailed in Supplementary Tables S1 and S2.

All patients were then grouped in tertiles according to their anti-S protein RBD antibody titers (lower, <498 U/ml; middle, <498 U/ml to < 2500 U/ml; upper, ≥2500 U/ml). Using patients in the lower tertile as the reference group, patients with anti-S protein RBD antibody levels in the higher tertiles had lower risks of all-cause mortality (aHR, 0.37; 95% CI, 0.19–0.76; $p = 0.006$; Table 3). However, the risk of SARS-CoV-2 infection did not reach statistical significance among the three groups. (Middle: aHR, 0.99; 95% CI, 0.55–1.79; $p = 0.977$; higher: aHR, 0.83; 95% CI, 0.48–1.44; $p = 0.509$; Table 3).

In the propensity scores matching model, we matched 116 patients from the fully vaccinated group to 232 patients from the partially vaccinated group. The baseline characteristics of the matched groups were shown in Supplementary Table S4. Upon analyzing the matched dataset using the Cox regression model, the results remained consistent with the unmatched analysis (Supplementary Tables S5 and S6).

Table 3 Risks of developing SARS-CoV-2 infection and all-cause mortality in each tertile of HD patients according to anti-S protein RBD antibody titers.

	Number of subjects	Number of event (%)	Crude HR (95% CI)[a]	*P*	Adjusted HR (95% CI)[b]	*P*
SARS-CoV-2 infection						
[c]Lower tertile	148	31 (20.9)	Reference		Reference	
Middle tertile	113	20 (17.7)	0.89 (0.51—1.56)	0.684	0.99 (0.55—1.79)	0.977
Upper tertile	179	31 (17.3)	0.69 (0.42—1.14)	0.146	0.83 (0.48—1.44)	0.509
All-cause mortality						
Lower tertile	148	37 (25)	Reference		Reference	
Middle tertile	113	28 (24.8)	1.02 (0.62—1.67)	0.936	1.11 (0.66—1.87)	0.696
Upper tertile	179	12 (6.7)	0.23 (0.12—0.44)	<0.001	0.37 (0.19—0.76)	0.006

[a] Crude model was an unadjusted crude hazard ratio.
[b] Adjusted model was adjusted for baseline demographic data, comorbidities and laboratory data listed in Table 1.
[c] Patients were grouped in tertiles according to their anti-S RBD antibody titers (Lower, <498 U/ml; middle, 498 U/ml to <2500 U/ml; upper, ≥2500 U/ml).
Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; HD, hemodialysis; HR, hazard ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Discussion

In this prospective cohort study, we found that a third dose of the COVID-19 vaccination in HD patients elicited higher serum anti-S protein RBD antibody titers and was associated with a lower risk of all-cause mortality than less than three doses of vaccination. While the A/A/M vaccine regimen in the fully vaccinated group demonstrated a notable reduction in all-cause mortality compared to the partially vaccinated group, the M/M/M regimen did not show a statistically significant difference in mortality risk when compared to those partially vaccinated. In addition, our data showed that a higher circulating anti-S protein RBD antibody level was an independent predictor of a lower risk of all-cause mortality. The outcomes remained consistent with our primary analysis even after employing propensity score matching. To the best of our knowledge, this is one of the original studies to demonstrate the real-world survival benefit of heterologous and homologous vaccination regimens in patients undergoing chronic HD during the Omicron-dominant period.

Vaccination has been one of the most cost-effective strategies for protecting humans from infectious diseases. However, diminished immune responses against COVID-19 in HD patients have already been reported.[9] Factors including advanced age, uremic toxin accumulation, malnutrition, and intestinal dysbiosis may all contribute to decreased postvaccination immunogenicity.[10—12] Patients undergoing chronic dialysis may have a lower seroconversion rate for the anti-S protein RBD antibody and lower neutralizing capacity and T-cell responses after vaccination than those in the non-dialysis group.[13,5,14,15] Therefore, a third dose of the COVID-19 vaccine may be needed to decrease the COVID-related morbidity and mortality in this vulnerable population. Previous studies have shown that a COVID-19 booster or an additional dose can increase the rate of seroconversion and increase antibody titers in HD patients with an inadequate response to the primary series.[16] In a study including 45 HD patients without previous SARS-CoV-2 infection, Duclous et al. found that a third dose of the COVID-19 vaccine induced a robust humoral response in 93% of patients, with a median 580% increase in antibody titers. The effect was even greater in those with lower antibody titers after two doses.[17] Our data are consistent with those of previous reports showing that a third vaccination significantly increased serum anti-S protein RBD antibody titers in HD patients.

As HD patients have been excluded from most of the large vaccine trials for safety reasons, direct evidence of vaccine efficacy among these patients is primarily limited to observational studies. In a Canadian cohort study including 13,759 dialysis patients, two doses of either the BNT162b2 or mRNA1273 vaccine was associated with lower risks of SARS-CoV-2 infection (HR 0.31, 95% CI, 0.22—0.42) and a composite outcome of hospitalization or death (HR 0.17, 95% CI, 0.10—0.30).[18] Similarly, in a cohort study of 15,852 HD patients in Chile, Torres et al. found that two doses of the BNT162b2 or CoronaVac vaccine significantly decreased the risks of SARS-CoV-2 infection and death associated with COVID-19 compared with only one dose. Notably, the BNT162b2 vaccine had higher efficacy in preventing infection (effectiveness: 42.6% vs. 15.0%) and death (effectiveness: 90.4% vs.64.8%) than CoronaVac.[19] Although previous data have shown promising results for the COVID-19 vaccine in HD patients, most of the published studies were based on non-Omicron variants.

Since the end of 2021, Omicron has emerged as the dominant variant, resulting in another surge in new cases of COVID-19 globally.[20] Recent studies have shown that the neutralizing antibodies induced by a two-dose primary vaccine series may no longer be effective because of limited cross-reactivity with the Omicron variant. Nevertheless, a third dose of vaccination leads to a substantial increase in Omicron neutralizing antibodies.[21,22] Different from most European countries and the United States, the Taiwan CDC classifies HD patients as an immunocompromised group and recommends an additional primary dose rather than a booster dose as a third dose for these patients. Our study found that HD patients who received an additional primary dose of the COVID-19 vaccine demonstrated a stronger humoral response and a significantly decreased risk of all-cause mortality even in the Omicron-

dominant period. Furthermore, when we grouped patients according to their levels of anti-S protein RBD antibody, a strong association between a high antibody titer and a lower mortality risk was observed. This suggests that a strategy integrating anti-S protein RBD antibody monitoring to guide revaccination in HD patients may be reasonable and could be the subject of a future study. Regarding the incidence of SARS-CoV-2 infection, our study did not find a significant difference between the groups. A plausible explanation for this may be that the vaccines administered during our study period were originally developed targeting earlier strains of the virus, rather than the Omicron variant.

The main strength of our study is the prospective design with the inclusion of 440 HD patients. Blood samples were collected from each patient at three time points and tested for anti-S protein RBD antibody using standardized assays, which allowed us to investigate the postvaccination humoral response and correlate the antibody titer with clinical outcomes. Although our cohort study initially exhibited disparities in baseline characteristics between the two groups, the consistent results we obtained after conducting propensity score matching further validate our findings.

There are some limitations in this study that should be acknowledged. First, the use of antiviral agents may have affected the clinical outcomes of our patients, but data on such factors were not address in this study. Second, we did not have genomic data identifying the subtype of the Omicron variant. Third, T-cell responses were not examined in our study, which may play a significant role in protection against COVID-19. Fourth, given the observational design of this study, the correlation between vaccination status and outcome does not imply causality. In addition, the decision on the number of vaccine doses to administer was primarily based on individual patient preferences, potentially introducing confounding variables in our assessment of the survival benefit of COVID-19 vaccine. The reasons for not receiving the complete vaccination regimen could be multifactorial, such as the patients being too elderly and frail, having experienced side effects from previous doses, or simply a personal preference not to have the third dose. Our study did not capture these specific reasons in detail. Fifth, routine COVID-19 PCR or antigen testing was not implemented for asymptomatic individuals in our dialysis unit. Certain cases may have been overlooked, particularly if patients undertook home antigen testing without reporting the results to the hospital, or if asymptomatic infections did not undergo screening. Finally, this study included only HD patients in Taiwan; thus, the external validity for other ethnicities and populations is uncertain.

In conclusion, administration of a third dose of the COVID-19 vaccine was associated with a lower risk of all-cause mortality among patients undergoing chronic HD during the Omicron-dominant period. The results of our study provided valuable experience in elucidating the postvaccination immune characteristics of HD patients, allowing improved preparation for COVID-19-like pandemics in the future.

Author notes

Declaration of competing interest

All authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

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