SARS-CoV-2 Vaccination and Severe COVID-19 Infection and Reinfection Outcomes among Patients with ESKD from a National Dialysis Provider

Monica M. Shieu,[1] Nien Chen Li,[1] Harold J. Manley,[1] Antonia Harford,[1] Caroline M. Hsu,[2] Daniel E. Weiner,[2] Dana Miskulin,[2] Doug Johnson,[1] and Eduardo K. Lacson Jr.[1,2]

Kidney360 5: 1186–1190, 2024. doi: https://doi.org/10.34067/KID.0000000000000494

Introduction

Patients receiving maintenance dialysis are more likely to be hospitalized or die of coronavirus disease 2019 (COVID-19), reflecting an older population with serious comorbid conditions, high rates of immunocompromise in the setting of kidney failure,[1] and limited ability to distance because of health care needs and/or socioeconomic challenges.[2,3] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines are protective against severe illness, hospitalization, and death,[4] and accordingly, many nephrologists considered dialysis patients as immunocompromised, therefore using an initial three-dose vaccine regimen.[3]

Given limited research on risk factors of COVID-19 severe outcomes among maintenance dialysis patients after vaccine availability,[5,6] we evaluated risk factors of COVID-19–related hospitalization and death after (*1*) initial infection and (*2*) reinfection among dialysis patients treated at a medium-sized national dialysis organization, with specific interest on the number of vaccine doses administered.

Methods

Adults receiving maintenance dialysis at Dialysis Clinic Inc. clinics who tested positive for SARS-CoV-2 between February 1, 2021, and June 30, 2023, were included in this retrospective cohort study. SARS-CoV-2 infection was identified either by a reverse transcriptase polymerase chain reaction test or a home test kit. SARS-CoV-2 reinfection was defined as an infection that occurred >90 days after an initial COVID-19 diagnosis.

SARS-CoV-2–related hospitalization was defined as a hospitalization episode within 30 days of COVID-19 diagnosis with ICD-10 UO7.1 documented as the primary hospital diagnosis. SARS-CoV-2–related death was defined as death within 90 days of coronavirus disease diagnosis. Outcomes were assessed through July 31, 2023, for hospitalization and September 30, 2023, for death.

Vaccination status at initial and recurrent COVID-19 diagnosis was documented. Unvaccinated status included patients who never received a vaccine during the entire study period extending through 13 days after the first vaccine dose. One-dose vaccine status applied only to mRNA vaccines and was defined as the period starting 14 days after the first mRNA vaccine dose to <14 days after the second mRNA vaccine dose. An initial single dose of adenovirus vaccine (Ad26.COV2.S/Janssen) was counted as equivalent to two mRNA vaccine doses. With each additional dose, patients were considered to have reached full immunity on the 14th day after vaccine administration.

Study variables included date of vaccine administration, age, sex, race, ethnicity, dialysis modality, immunemodulating medications, transplant history, immunodeficiency disorder, tobacco use, other comorbid conditions, residence in a congregate setting, and use of a central venous catheter at the time of infection. Laboratory data on dialysis adequacy, serum albumin, and hemoglobin were obtained from the record before infection. International classification of diseases (ICD) codes and medication names used to define variables are listed in Supplemental Table 1.

Logistic regression was used to adjust for demographic and clinical characteristics. Analyses of hospitalization after

[1]Dialysis Clinic Inc., Nashville, Tennessee
[2]Tufts Medical Center, Boston, Massachusetts

Correspondence: Dr. Eduardo K. Lacson, email: Eduardo.Lacson@dciinc.org

Received: March 4, 2024 **Accepted:** June 21, 2024
Published Online Ahead of Print: July 8, 2024

M.M.S. and N.C.L. contributed equally to this work.

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reinfection were limited to patients whose reinfection occurred during February 1, 2021, to June 30, 2023. Exposure time was the number of days from infection (or reinfection) date to the end date, defined by hospitalization/death or absence thereof at 30/90 days after the infection (or reinfection), or the study end date, whichever came first. All logistic regression models were weighted for the logarithmic transformation of the exposure time.

Results

From February 1, 2021, to June 30, 2023, among 23,016 dialysis patients, 4948 patients were diagnosed with COVID-19, including 676 diagnosed with reinfection (Supplemental Figure 1); 70% of total study population was 55+ years, 46% were non-Hispanic White, and 55% were male. Seventy-seven percent of infections occurred during the Omicron period. Among those with reinfection, 22% were unvaccinated or received only one dose of vaccine, 26% had two vaccine doses, and 53% had 3+ vaccine doses at the time of COVID-19 diagnosis (Supplemental Table 2). Greater than 95% of all vaccine doses received were mRNA vaccines.

Among 4948 patients, 1094 (22.1%) patients were hospitalized after their initial COVID-19 infection. The risk of hospitalization was lower with more vaccine doses. Compared with two vaccine doses, the odds ratio (OR) for hospitalization in patients with unvaccinated/one vaccine dose was 1.32 (95% confidence intervals, 1.21 to 1.43) and for 3+ vaccine doses the OR was 0.63 (0.58 to 0.68). Hospitalization risk was higher among older patients, patients with infections during the Delta variant period, Black patients and patients living in a congregate setting, patients receiving immune-modulating medications, patients with no history of kidney transplant, patients with a longer dialysis vintage, patients receiving in-center hemodialysis, and patients with inadequate dialysis, lower hemoglobin, and more comorbid conditions (Figure 1 and Table 1).

There were 204 (4.1%) deaths within 90 days after initial COVID-19 infection. Risk factors of COVID-19–related death included infection during the Delta variant period, age ≥55 years, obesity, tobacco usage, having hypertension, diabetes, chronic heart failure, with a longer dialysis vintage, stroke/cerebrovascular disease, inadequate dialysis dose, low albumin, and low hemoglobin. Recipients of 3+ vaccine doses had the lowest risk of COVID-19 death (ref. two vaccine doses OR, 0.31; 0.25 to 0.39, $P < 0.001$) (Figure 1 and Table 1).

Among 676 patients with reinfections, 105 (15.5%) were hospitalized within 30 days, and one patient died within 90 days after reinfection. The risk of hospitalization decreased as the number of vaccine doses increased. Compared with two-vaccine doses, OR for unvaccinated/one dose was 1.70 (1.30 to 2.22), and OR for 3+ vaccine dose was 0.77 (0.61 to 0.99). The risk of hospitalization after reinfection was higher

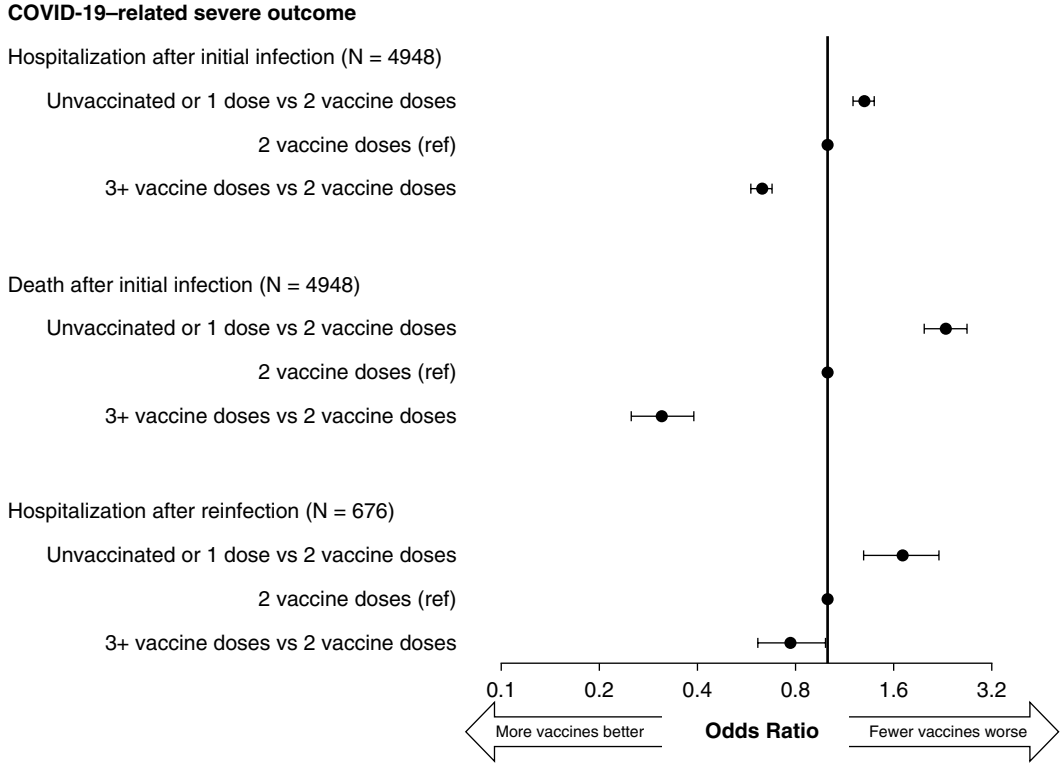

Figure 1. ORs[a] of vaccine dose for COVID-19–related severe outcomes for vaccine dose status. [a]Number of people in the 3+ vaccine doses category: initial infection (three doses: 1522, four doses: 448, five doses: 126) and reinfection (three doses: 215, four doses: 110, five doses: 32). Logistic regression models were adjusted for dominant variant, age, sex, race/ethnicity, obesity, congregate setting, immunocompromise, smoking, dialysis vintage, modality, comorbidities, inadequate dialysis dose, serum albumin, hemoglobin, and catheter usage. COVID-19, coronavirus disease 2019; OR, odds ratio.

Table 1. Odds ratios of risk factors of coronavirus disease 2019–related severe outcomes (hospitalization after initial infection, death after initial infection, and hospitalization after reinfection) during the vaccine era, February 1, 2021, to June 30, 2023[a]

Characteristics	Hospitalization after Initial Infection[b]		Death after Initial Infection[b]		Hospitalization after Reinfection[b]	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Vaccination						
Unvaccinated/one vaccine dose	1.32 (1.21 to 1.43)	<0.001	2.32 (1.98 to 2.71)	<0.001	1.70 (1.30 to 2.22)	<0.001
Two vaccine doses	1	—	1	—	1	—
3+ vaccine doses	0.63 (0.58 to 0.68)	<0.001	0.31 (0.25 to 0.39)	<0.001	0.77 (0.61 to 0.99)	0.04
Dominant variant						
Omicron (December 19, 2021, to June 30, 2023)	1	—	1	—	1	—
Delta (June 20, 2021, to December 18, 2021)	1.51 (1.39 to 1.65)	<0.001	2.85 (2.45 to 3.31)	<0.001	1.89 (1.20 to 2.97)	0.006
Pre-Delta (February 1, 2021, to June 19, 2021)	1.09 (0.95 to 1.26)	0.08	0.88 (0.67 to 1.14)	0.33	1.29 (0.54 to 3.07)	0.56
Age category						
Age 75+	1.82 (1.64 to 2.01)	<0.001	4.87 (3.91 to 6.07)	<0.001	1.21 (0.87 to 1.67)	0.27
Age 65–74	1.39 (1.27 to 1.53)	<0.001	2.44 (1.96 to 3.04)	<0.001	1.31 (0.99 to 1.73)	0.06
Age 55–64	1.38 (1.26 to 1.51)	<0.001	2.24 (1.81 to 2.77)	<0.001	1.75 (1.33 to 2.29)	<0.001
Age 18–54	1	—	1	—	1	—
Race/ethnicity						
White	1	—	1	—	1	—
Black	1.32 (1.22 to 1.43)	<0.001	0.67 (0.57 to 0.79)	<0.001	1.06 (0.84 to 1.34)	0.62
Hispanic	1.08 (0.94 to 1.25)	0.28	0.61 (0.44 to 0.85)	0.004	1.37 (0.95 to 1.99)	0.10
Other	0.99 (0.87 to 1.13)	0.73	0.40 (0.28 to 0.58)	<0.001	0.76 (0.51 to 1.14)	0.21
Unknown	0.96 (0.84 to 1.10)	0.36	1.32 (1.03 to 1.69)	0.03	0.70 (0.40 to 1.20)	0.20
Male	0.94 (0.88 to 0.99)	0.03	1.05 (0.92 to 1.21)	0.46	0.97 (0.79 to 1.19)	0.75
Obesity (>30 kg/m^2)	1.01 (0.95 to 1.09)	0.66	1.22 (1.06 to 1.42)	0.007	0.84 (0.68 to 1.03)	0.10
Congregate setting	1.34 (1.02 to 1.75)	0.03	1.18 (0.71 to 1.96)	0.51	0.18 (0.09 to 0.36)	<0.001
Immune-modulating medications	1.16 (1.02 to 1.33)	0.02	0.96 (0.74 to 1.25)	0.77	1.30 (0.91 to 1.88)	0.15
Immunodeficiency disorder	1.05 (0.92 to 1.18)	0.59	1.24 (0.97 to 1.57)	0.08	1.35 (0.96 to 1.90)	0.08
Transplant history	0.80 (0.67 to 0.92)	0.002	0.33 (0.20 to 0.55)	<0.001	1.54 (1.05 to 2.24)	0.03
Tobacco use	1.06 (0.95 to 117)	0.33	1.31 (1.08 to 1.59)	0.007	2.03 (1.55 to 2.65)	<0.001
Dialysis vintage, d						
≤120	0.76 (0.70 to 0.84)	<0.001	0.52 (0.42 to 0.65)	<0.001	1.49 (1.05 to 2.11)	0.02
121–365	0.88 (0.79 to 0.99)	0.03	0.51 (0.39 to 0.65)	<0.001	0.66 (0.46 to 0.97)	0.03
366–1095	0.97 (0.89 to 1.08)	0.44	0.61 (0.51 to 0.73)	<0.001	1.10 (0.87 to 1.41)	0.43
>1095	1	—	1	—	1	—
Treatment method						
In-center hemodialysis	1	—	1	—	1	—
Home hemodialysis	1.27 (1.08 to 1.49)	0.002	1.28 (0.94 to 1.74)	0.11	0.56 (0.34 to 0.93)	0.03
Peritoneal dialysis	0.59 (0.48 to 0.72)	<0.001	0.82 (0.54 to 1.24)	0.35	0.30 (0.13 to 0.72)	0.007
Comorbidities						
Hypertension	0.83 (0.76 to 0.90)	<0.001	1.39 (1.14 to 1.71)	0.002	1.15 (0.83 to 1.58)	0.41
Diabetes mellitus	1.14 (1.06 to 1.22)	<0.001	1.26 (1.08 to 1.46)	0.003	1.40 (1.12 to 1.75)	0.003
Chronic heart failure	1.15 (1.05 to 1.26)	<0.001	1.25 (1.06 to 1.47)	0.009	1.92 (1.49 to 2.47)	<0.001
Peripheral vascular disease	1.14 (1.0 to 1.33)	0.02	1.25 (0.95 to 1.64)	0.11	1.07 (0.66 to 1.72)	0.80
Stroke/cerebrovascular disorder	1.30 (1.11 to 1.52)	<0.001	1.36 (1.01 to 1.83)	0.04	2.41 (1.61 to 3.60)	<0.001
COPD	1.27 (1.13 to 1.43)	<0.001	1.23 (1.00 to 1.51)	0.04	1.13 (0.81 to 1.58)	0.47
Thyroid disease	0.99 (0.90 to 1.11)	0.86	0.80 (0.65 to 0.99)	0.04	1.64 (1.22 to 2.20)	0.01
Cancer	0.96 (0.84 to 1.12)	0.55	1.18 (0.91 to 1.54)	0.21	1.25 (0.87 to 1.79)	0.18
Inadequate dialysis dose[c]	1.38 (1.23 to 1.55)	<0.001	1.52 (1.22 to 1.90)	<0.001	1.30 (0.93 to 1.83)	0.12
Low serum albumin (≤3.5 g/dl)	1.06 (0.98 to 1.15)	0.15	2.18 (1.89 to 2.52)	<0.001	2.06 (1.63 to 2.60)	<0.001
Low hemoglobin (<10 g/dl)	1.47 (1.36 to 1.59)	<0.001	1.26 (1.08 to 1.48)	0.003	1.74 (1.36 to 2.21)	<0.001
Catheter usage	1.00 (0.86 to 1.17)	0.99	0.56 (0.39 to 0.81)	0.002	0.35 (0.17 to 0.72)	0.004

CI, confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds ratio.
[a]All models were weighted for the logarithmic transformation of the exposure time. Exposure time was the number of days from infection (or reinfection) date to the end date, defined by hospitalization/death or absence thereof at 30/90 days after the infection (or reinfection), or the study end date, whichever came first.
[b]Models adjusted for all the variables listed below.
[c]Defined as hemodialysis single-pool Kt/V ≥1.2 or peritoneal dialysis weekly Kt/V ≥1.7.

for patients with older age, during the Delta variant period, receiving in-center hemodialysis, with prior transplant, having diabetes, chronic heart failure, stroke/cerebrovascular disease, thyroid disease, low albumin, or low hemoglobin (Figure 1 and Table 1).

Discussion

Among maintenance dialysis patients, receipt of three or more doses of SARS-CoV-2 vaccine was associated with a lower risk of hospitalization and death for COVID-19, whereas being unvaccinated was associated with higher risk for these severe adverse outcomes. In addition, maintenance dialysis patients with certain clinical characteristics, including older age, immunocompromised status, greater comorbid condition burden, and receipt of in-center hemodialysis were at a higher risk of COVID-19–related severe events and for worse outcomes after reinfection. These factors are consistent with findings in the general population, where a study conducted among 258 COVID-19 reinfected patients showed that older age, obesity, asthma, diabetes, and previous severe initial COVID-19 infection were risk factors of severe SARS-CoV-2 reinfections.[7]

A recent national meta-analysis reported that undervaccination relative to recommended number of doses was associated with an elevated risk of severe COVID-19 outcomes.[8] Our previous work in dialysis patients demonstrated that three COVID-19 vaccine doses had maintained antispike IgG levels compared with two vaccine doses at 6 months.[9] This work supports the idea that a minimum of three vaccine doses appears to be most protective against hospitalization and death in the high-risk maintenance dialysis population.

In this study, all-cause mortality was 10.3% within 90 days of initial infection and 5.6% for reinfection. Although COVID-19 was not the primary cause of death, all-cause mortality remained high for dialysis patients. It is possible that COVID-19 may have also accelerated or potentiated non-COVID death risk within 180 days postinfection as noted in a study of more than 200,000 US veterans.[10]

Risk of hospitalization was lower with reinfection but remained high, particularly among unvaccinated patients, highlighting the medical vulnerability of this population. It is possible that susceptibility to reinfection with severe outcomes after vaccination is a marker of greater immune dysfunction associated with CKD, potentially amenable to more frequent booster dosing.[10] Research supports the protective effect of vaccination against developing a severe outcome among health care workers and the general population,[11–13] including among those with a prior diagnosis of COVID-19.

Our study has several strengths. First, we have a large national sample with longitudinal outcomes. Second, our study reduced misclassification by focusing only on chronic patients on dialysis. An extensive list of confounders and exposure time were accounted for in the model. Furthermore, approaches were taken to lessen the burden of selection bias and collider bias, such as including all COVID-19 severe events as the outcome. Finally, we had validated outcome documentation in a population with frequent and regular health care encounters.

Some limitations include potential undiagnosed and asymptomatic COVID-19 patients particularly later in the pandemic.[9] Nondifferential misclassification of the outcome tends to bias toward the null. Therefore, results presented could be an underestimate of effects. However, COVID-19 severe events were used as the outcome because of the accuracy in documentation. In addition, comorbidities captured by ICD code could lead to misclassification of covariates. Nevertheless, comorbid conditions were captured from multiple sources in the data set including the ESKD Medical Evidence Report and subsequent episodes of care documented in the electronic health record.

Patients receiving maintenance dialysis are at increased risk of severe COVID-19–related events, including hospitalization and death. Dialysis-specific factors that indicate greater risk of severe complications include longer vintage, in-center hemodialysis, lower serum albumin and hemoglobin levels, and being unvaccinated. The vulnerability of patients on dialysis to severe COVID-19 outcomes emphasizes the need to vaccinate dialysis patients with updated vaccine doses per guidelines, even as the overall attention to COVID-19 wanes. Critically, vaccine administration in dialysis facilities results in improved access and reduced disparity for dialysis patients.[14] Initial vaccination with three doses, and additional boosters provide a feasible way to protect against severe COVID-19 events.

Disclosure

Disclosure forms, as provided by each author, are available with the online version of the article at http://links.lww.com/KN9/A564.

Funding

None.

Author Contributions

Conceptualization: Eduardo K. Lacson Jr., Nien Chen Li, Harold J. Manley, Monica M. Shieu.
Formal analysis: Monica M. Shieu.
Investigation: Monica M. Shieu.
Methodology: Nien Chen Li, Monica M. Shieu.
Supervision: Eduardo K. Lacson Jr., Nien Chen Li, Harold J. Manley.
Validation: Eduardo K. Lacson Jr., Nien Chen Li, Harold J. Manley, Monica M. Shieu.
Writing – original draft: Monica M. Shieu.
Writing – review & editing: Antonia Harford, Caroline M. Hsu, Doug Johnson, Eduardo K. Lacson Jr., Nien Chen Li, Harold J. Manley, Dana Miskulin, Monica M. Shieu, Daniel E. Weiner.

Data Sharing Statement

Data cannot be shared. Our data contain patient information. Therefore, they cannot be shared without any application process.

Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/KN9/A563.

Supplemental Table 1. List of ICD codes and medication names used to identify variables in the study.

Supplemental Figure 1. Study flow chart of maintenance dialysis patients with COVID-19 infection, vaccine era.

Supplemental Table 2. Summary statistics—mean (SD) and prevalence (n and %) of selected variables, by number of vaccine doses, vaccine era, February 1, 2021 to June 30, 2023.

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