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CLINICAL RESEARCH

Longitudinal Characterization of SARS-CoV-2 Immunity in Hemodialysis Patients Post Omicron

Andrew H. Karaba[1], Jiashu Xue[1], Trevor S. Johnston[1], Caroline C. Traut[1], Lorien S. Dalrymple[2], Robert J. Kossmann[2], Joel N. Blankson[1], Chirag R. Parikh[3,4] and Stuart C. Ray[1,4]

[1]Department of Medicine, Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [2]Global Medical Office, Fresenius Medical Care, Waltham, Massachusetts, USA; and [3]Department of Medicine, Division of Nephrology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Introduction: Individuals receiving hemodialysis (HD) are at risk for severe COVID-19 and have attenuated responses to COVID-19 vaccines. Evolution of immunity and risk for subsequent infection with additional vaccinations and infections in this population is poorly understood.

Methods: An observational multicenter cohort of 55 patients receiving HD in community HD centers, majority (85%) with at least 2 doses of COVID-19 vaccine (56% female, age [median; interquartile range, IQR] of 67, [58.0–74.0] years), was followed-up with for 50 weeks between December, 2021 and April, 2023 and collected blood samples at enrollment, 8 weeks, and 24 weeks thereafter. Anti-SARS-CoV-2 IgG and ACE2 inhibition (surrogate neutralization) against ancestral, Delta, and Omicron subvariants was measured. T-cell responses to Spike and Mucleocapsid proteins were measured via enzyme-linked immunosorbent spot. Changes in antibody and T cell responses were assessed by paired Wilcoxon rank-sum testing and Fisher exact testing. Antibody responses were compared to thrice vaccinated healthy controls (HCs) as a benchmark for what optimal responses could have been in the early Omicron period.

Results: Neutralization did not increase over time, and HD participants had lower neutralization than HCs. Only 56% of HD participants had a positive T cell response to spike after the BA.1/2 wave. Antibody and cellular responses were concordant in only 34.5% at final visit. Antibody responses trended higher among those with prior COVID-19, but spike-specific T cell responses did not vary.

Conclusions: Original vaccine formulations and previous infection are insufficient to induce reliable SARS-CoV-2 responses in individuals on HD, suggesting that updated annual COVID-19 vaccines and transmission-based precautions remain critical in this population.

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People with end-stage kidney disease (ESKD) who are receiving kidney replacement therapy via HD are at increased risk for severe COVID-19 outcomes[1,2] and respond less robustly to COVID-19 vaccines than HCs.[3,4] In addition, because of frequent health care encounters, they may be exposed to SARS-CoV-2 more often with little ability to modulate their exposure because of to the necessity of dialysis.[1]

Though the original COVID-19 vaccines provided excellent protection from severe disease,[5,6] effectiveness waned with the emergence of novel variants.[7,8] This was particularly true during the rise of the original Omicron variant (BA.1), which evaded vaccine responses to such a degree that the efficacy of the original ancestral-based COVID-19 vaccine to protect against infection, fell to 45%.[7] This led to the recommendation for additional booster doses of the original vaccine; however, the optimal schedule, particularly when considering the additive effect of infection episodes and hybrid immunity, has not been determined.

Thus, specific guidance for people with ESKD on HD regarding timing and number of vaccine doses is lacking owing to the absence of longitudinal data on immunogenicity and breakthrough infections in this vulnerable population. To address this knowledge gap, we followed patients receiving HD through the beginning of the Omicron era, quantifying antibody and cellular immune responses to SARS-CoV-2, and assessed these measures of immunity in the context of

Correspondence: Chirag R. Parikh, 1830 E Monument St, Ste 412, Baltimore, Maryland 21205, USA. E-mail: chirag.parikh@jhmi.edu

[4]CRP and SCR are co-senior authors

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previous and intercurrent infection. To make the data more generalizable, we sought to recruit participants from distinct clinical locations. Our data reveal poor correlation between antibody and T cell immunity in this population and little impact of infection on SARS-CoV-2 specific immunity. This suggests that previous infection in addition to vaccination likely does not provide significant and long-lasting protection in people with ESKD who are on HD, and argues for continued updated vaccination in this population.

METHODS

Study Population and Sample Acquisition

People with ESKD on chronic HD at 3 outpatient dialysis facilities in 3 different states in the USA, were enrolled in a prospective observational cohort study from December 15, 2021 through May 20, 2022. This trial was approved by the Johns Hopkins Medicine IRB (IRB00264536). Demographic, clinical, and laboratory data were collected and stored via REDCap.[9] Blood was collected in acid citrate dextrose tubes at the time of enrollment and 8 and 24 weeks thereafter (i.e., week 0, 8, and 24). Not all participants provided blood samples at all time points. Participants were followed-up for up to 50 weeks after enrollment. Distribution of sample collection over time and in relation to the predominant circulating SARS-CoV-2 variants in the USA are displayed in Figure 1. Plasma from HCs was obtained via a separate study as previously described and approved by the Johns Hopkins IRB (IRB00027183).[10,11]

Blood samples were shipped overnight to Johns Hopkins where peripheral blood mononuclear cells were separated from plasma via centrifugation as described previously.[12] Plasma was stored at −80 °C until utilized in assays described below. Most T cell assays were performed on fresh peripheral blood mononuclear cells, whereas a minority were stored in liquid nitrogen, thawed, and then tested.

Antibody Measurement

Anti–SARS-CoV-2 nucleocapsid and anti–SARS-CoV-2 spike IgG was measured in thawed plasma using the multiplex chemiluminescent Meso Scale Diagnostics V-PLEX COVID-19 respiratory panel 3 Kit (Meso Scale Diagnostics, Rockville, MD) according to the manufacture's protocol at a dilution of 1:5000. Conversion to World Health Organization binding units was performed by multiplying arbitrary units by the manufacture's conversion factor.

ACE2 binding inhibition (surrogate neutralization) was measured using the Meso Scale Diagnostics V-PLEX SARS-CoV-2 panel 29 ACE2 kit according to the manufacturer's protocol at a dilution of 1:100 as

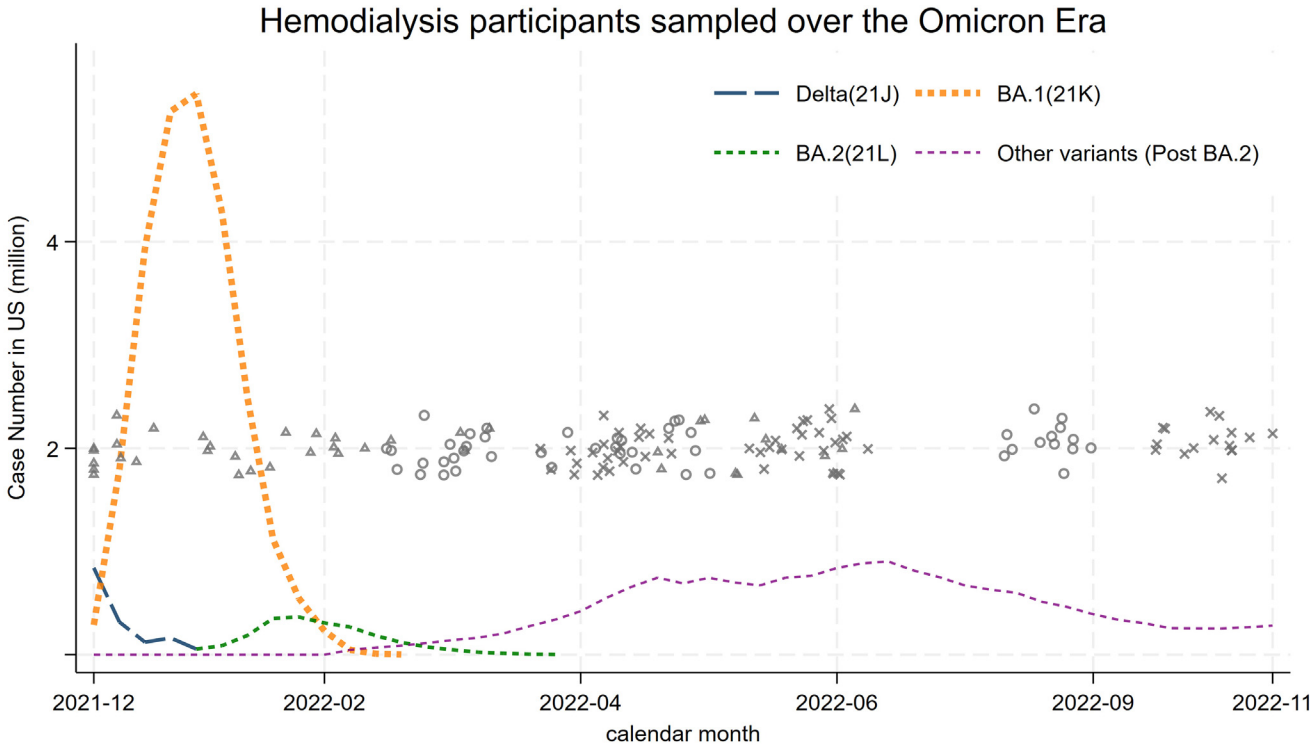

Figure 1. Sample collection over time relative to dominant circulating SARS-CoV-2 variant. COVID-19 weekly case counts caused by the indicated SARS-CoV-2 variants (y-axis) are graphed over time (x-axis). The timing of study samples collected from participants on hemodialysis are displayed, with distinct symbols for the 3 different clinics (the y-axis value for sample collection times is irrelevant and these data are included for reference to the circulating variants only).

previously described.[11] This assay measures the ability of participant plasma to inhibit ACE2 binding to spike proteins of interest. All Meso Scale Diagnostics assays were read on a Meso QuickPlex SQ 120 instrument. Results were reported as percent ACE2 inhibition based on the equation provided by the manufacturer ([1 − average sample ECL/average ECL signal of blank well] ×100).

T Cell Assays

Cellular immunity to the SARS-CoV-2 spike and nucleocapsid proteins was determined by performing an interferon gamma enzyme-linked immunosorbent spot assay with unfractionated peripheral blood mononuclear cells as previously described.[13,14] Peptide pools were obtained from Biodefense and Emerging Infections Research Resources Repository and used at a concentration of 10 ug/ml. Peripheral blood mononuclear cells were incubated with peptides for 20 to 24 hours before the plates were developed as described.[14]

Statistical Analysis

All analyses were performed using Stata 17.0 for windows (College Station, Texas) and Rstudio (Version 4.3.2, Boston, MA).[15] Median and IQR were used to describe continuous variables, and frequency and percentages used to describe the categorical variables. We used an alpha of 0.05 to indicate a statistically significant difference. Differences in categorical variables and continuous variables were determined via Fisher exact and Wilcoxon rank sum testing, respectively.

RESULTS

Cohort Demographics

Fifty-five participants with ESKD on HD and 11 HCs were enrolled and provided at least 1 blood sample. The HD group was older (mean = 67 years [IQR: 57–74] vs. 45 [35–50], $P < 0.001$) and contained a higher percentage of female participants (56% vs. 36%) than the HC group (Table 1). The cause of ESKD for most of the cohort was either diabetes or hypertension, and more than half of the HD participants were on kidney replacement therapy for more than 3 years. Five (9%) reported taking glucocorticoids. Of the participants, 29.1% reported a history of COVID-19 before enrollment and 85% received at least 2 doses of mRNA-based COVID-19 vaccine before enrollment. Additional details of the cohort can be found in Table 1.

Antibody Responses to SARS-CoV-2 Over Time

To evaluate immune responses over time, we divided the samples into 3 eras by the predominant circulating variants, as follows: "Delta," September, 2021 to December 18, 2021; "BA.1/2," December 19, 2021 to April, 2022; and "post-BA.2," May, 2022 to November, 2022. IgG responses to spike and nucleocapsid proteins did not significantly change over time (Supplementary Figure S1A). The proportion with a positive anti–

Table 1. Clinical and demographic characteristics

Characteristics	HD Group (n = 55)	HC Group (n = 11)	P value
Age at enrollment, yr [IQR]	67 [58–74]	45 [35–50]	<0.001
Female, n (%)	31 (56.4%)	4 (36.4%)	0.378
Race			0.117
Black or African American, n (%)	17 (30.9%)	<5	
White, n (%)	37 (67.3%)	9 (81.8%)	
Others, n	<5	<5	
History of failed kidney transplant, n (%)	4 (7.3%)	–	–
Years on hemodialysis (IQR)	3.65 [1.96–6.13]	–	–
History of COVID-19 before enrollment (%)[a]	16 (29.1%)	–	–
Immunosuppressive medications, n (%)			
Glucocorticoids	5 (9.1%)	–	–
Vaccinated # at enrollment[b]			0.502
0	7 (7.3%)	0 (0)	
1	1 (1.8%)	0 (0)	
2	2 (3.6%)	0 (0)	
3	45 (81.8%)	11 (100%)	
Vaccination manufacturer (Pfizer %)	16 (33%)	10 (91%)	<0.001
Cause of ESKD (%)			
Diabetes	26 (47.3%)	–	–
HTN/large vessel disease	12 (21.8%)	–	
Other[c]	17 (30.9%)	–	

ESKD, end-stage kidney disease; HTN, hypertension; IQR, interquartile range.
[a]16 patients with 19 episodes of infections reported before the study enrollment.
[b]Received at least 2 doses of mRNA based COVID-19 vaccine.
[c]Other: transplant complication, cystic/hereditary/congenital, glomerulonephritis.

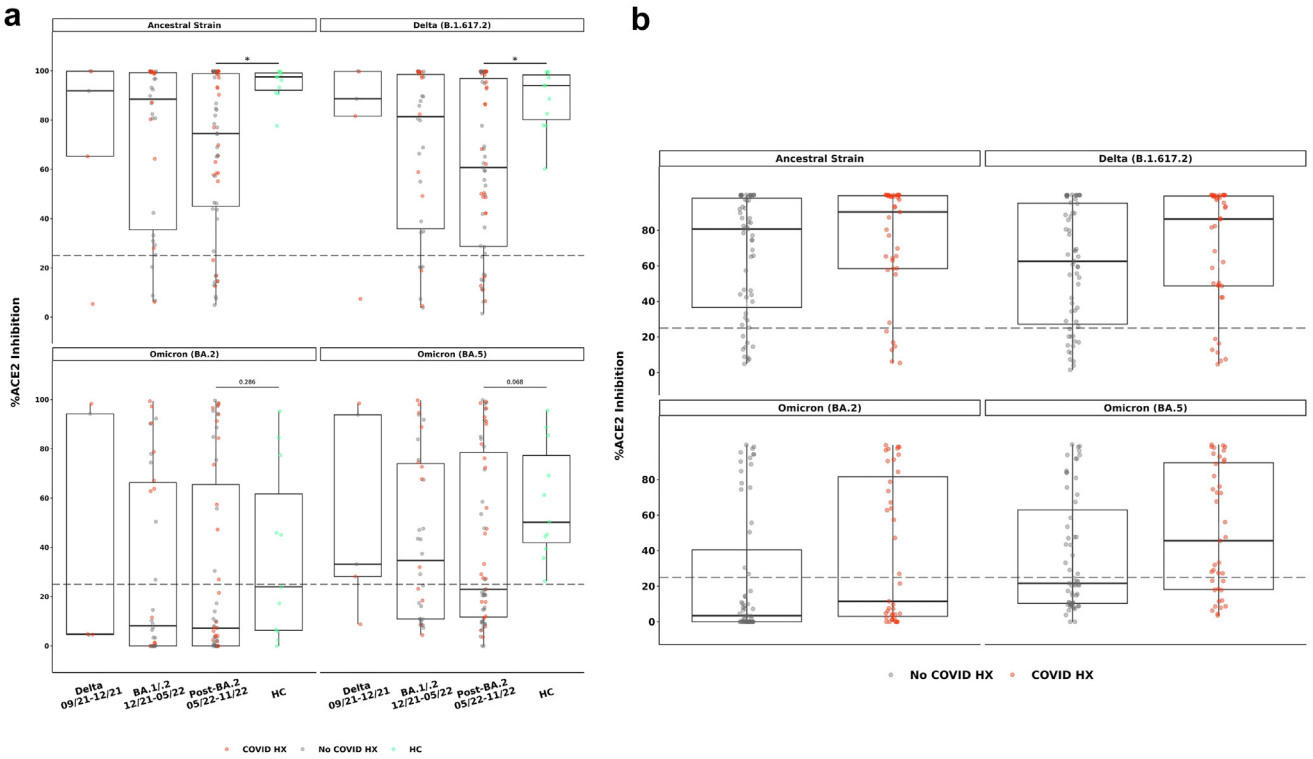

Figure 2. Surrogate neutralization of SARS-CoV-2 variants of concern among hemodialysis patients over time compared to healthy controls. (a) Percent ACE2 inhibition of indicated variants (y-axis) is plotted over time for samples from patients receiving HD during the Delta (September, 2021–December 18, 2021), Omicron BA.1/2 (December 19, 2021–April, 2022), and post-BA.2 (May, 2022–November, 2022) time periods. Samples from healthy controls after 3 vaccine doses are plotted at the right of each panel and are in green. Each dot represents an individual sample. Box-plots represent median and IQR with whiskers representing 1.5× the nearest quartile. Orange dots represent individuals with a history of COVID-19 before study entry. Grey dots represent individuals without a history of COVID-19. The dashed line at 25% inhibition represents cutoff with high specificity for live-virus neutralization. (b) percentage ACE2 inhibition of indicated variants (y-axis) is plotted for samples from HD participants with (right, orange dots) and without (left, grey dots) a history of COVID-19. Each dot represents an individual sample. Box-plots represent median and IQR with whiskers representing 1.5× the nearest quartile. The dashed line at 25% inhibition represents cutoff with high specificity for live-virus neutralization. HD, hemodialysis; IQR, interquartile range.

SARS-CoV-2 nucleocapsid IgG response did not significantly increase between the pre-BA.2 and post-BA.2 eras (12/39 [31%] to 20/59 [34%], $P = 0.82$) (Supplementary Figure S1B). There was no significant difference in anti–SARS-CoV-2 spike IgG levels between those with and those without a history of COVID-19 before enrollment ($P = 0.25$) (Supplementary Figure S2A). Anti–SARS-CoV-2 nucleocapsid IgG levels were significantly higher ($P < 0.001$) in those individuals with a previous history of COVID-19 (Supplementary Figure S2B).

Similarly, we measured surrogate neutralization of SARS-CoV-2 variants of concern over time and found no significant increases in neutralization of the ancestral, BA.2, or BA.5 variants from the late Delta to post-BA.2 era (Figure 2a). Given that HD participants were eligible for a third dose of vaccine, we chose to compare responses during these periods to thrice-vaccinated HCs as a point of reference of what optimal responses could have been. When compared to HCs who had received 3 doses of vaccine, neutralization was lower in samples from participants with ESKD on HD at later time points, specifically in the post-BA.2 era. This difference was statistically significant for the ancestral variant ($P = 0.03$), but not for BA.2 or BA.5 ($P = 0.286$ and 0.068, respectively). We previously reported that ACE2 binding inhibition of 25% was highly specific for the presence of live-virus neutralization in immunocompromised patients.[11,16] The proportion of samples from participants on HD above 25% inhibition of BA.5 did not change significantly over time between the BA.1/2 era and post-BA.2 era (19/34 [56%] to 29/59 [49%], $P = 0.67$). The proportion of HC samples above the 25% threshold was significantly higher than post-BA.2 HD samples for BA.5 (11/11 [100%] vs. 29/59 [49%], $P < 0.001$). Among HD participants with 3 doses of vaccine, there was marked heterogeneity in neutralizing responses (Supplemental Figure S3). When we compared this post–3-dose subset of HD participants to the HCs, we found higher neutralization in HCs, but this did not reach statistical significance (Supplementary Figure S3). However, the proportion of HCs above the 25% inhibition threshold was significantly higher than the HD participants ($P = 0.009$).

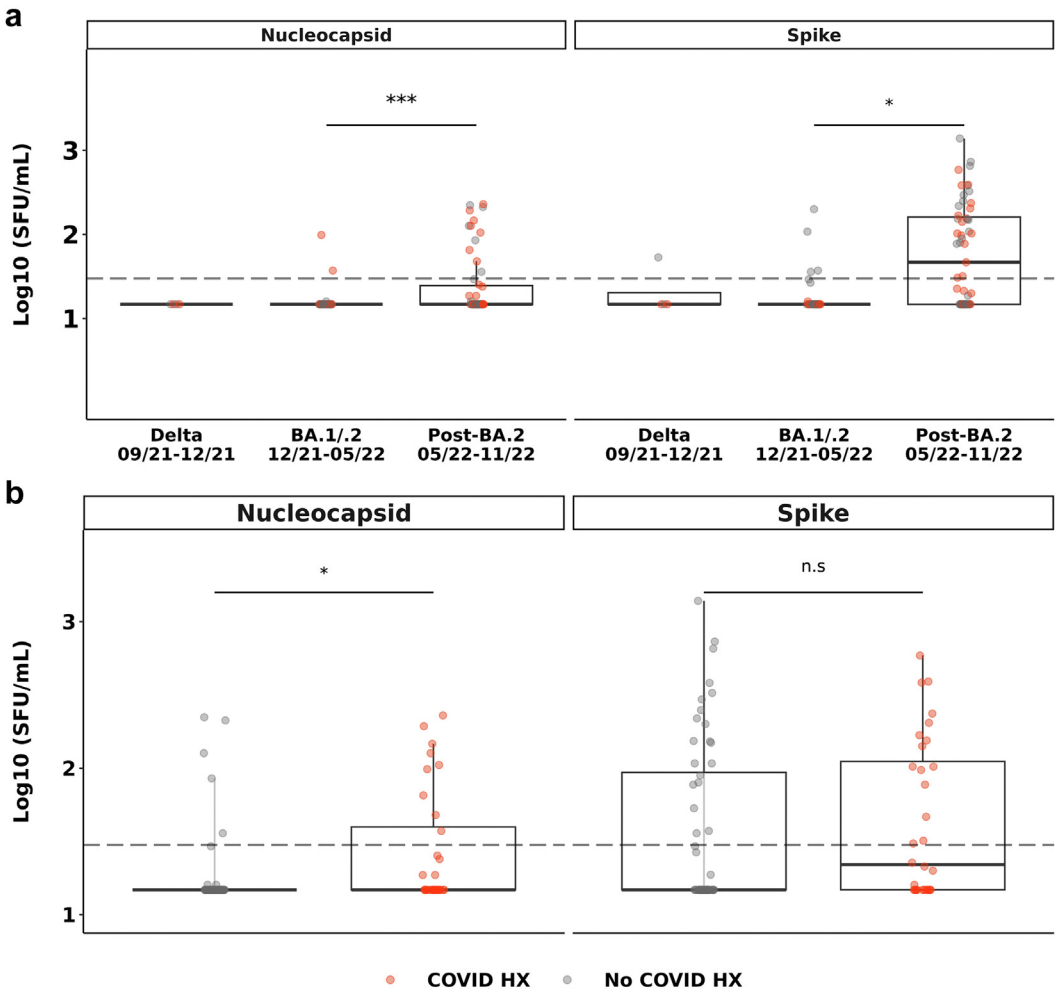

Figure 3. T cell responses to SARS-CoV-2 peptides in patients on hemodialysis. (a) Interferon gamma (IFN-γ)–producing T cell spots after stimulation with SARS-CoV-2 nucleocapsid (left) or spike (right) as measured by enzyme-linked immunosorbent spot (ELISpot) in HD participants over time during the Delta (September, 2021–December 18, 2021), Omicron BA.1/2 (December 19, 2021–April, 2022), and post-BA.2(May, 2022–November, 2022) waves. Each dot represents an individual sample. Box-plots represent median and IQR with whiskers representing 1.5x the nearest quartile. Orange dots represent individuals with a history of COVID-19 before study entry. Grey dots represent individuals without a history of COVID-19. The dashed line indicates the lower limit of quantification above media control. (b) IFN-γ–producing T cell spots after stimulation with SARS-CoV-2 nucleocapsid (left) or spike (right) as measured by ELISpot in HD participants with (right, orange dots) and without (left, grey dots) a history of COVID-19. Each dot represents an individual sample. Box-plots represent median and IQR with whiskers representing 1.5× the nearest quartile. Orange dots represent individuals with a history of COVID-19 before study entry. Grey dots represent individuals without a history of COVID-19. The dashed line indicates the lower limit of quantification above media control. HD, hemodialysis; IQR, interquartile range.

Neutralizing capacity in HD participants with a previous history of COVID-19 was higher than those without a history of COVID-19, but that did not reach statistical significance for any variant of concern (Figure 2b). However, the proportion of samples above the 25% threshold for BA.5 was higher among HD participants with a previous history of COVID-19 than those without a history of COVID-19 (26/39 [66.7%] vs. 26/59 [44.1%], $P = 0.03$).

T cell Responses to SARS-CoV-2 Over Time

T cell responses to spike and nucleocapsid proteins over time were measured via interferon gamma enzyme-linked immunosorbent spot, and both significantly increased over time from the BA.1/2 era to the post-BA.2 era in HD participant samples ($P < 0.001$ and $P = 0.02$, respectively) (Figure 3a). Moreover, the proportion of samples with values above the lower limit of quantification against spike increased significantly over time (14% [4/29] to 56% [31/55], $P < 0.001$), whereas responses to nucleocapsid increased but did not reach statistical significance (7% [2/29] to 22% [12/55], $P = 0.123$). Nucleocapsid T cell responses were higher among those with a history of COVID-19 ($P = 0.005$) before enrollment, and the proportion of samples above the lower limit of quantification of nucleocapsid T cell response was significantly higher for those with a history of COVID-19 (28% [9/32] vs.

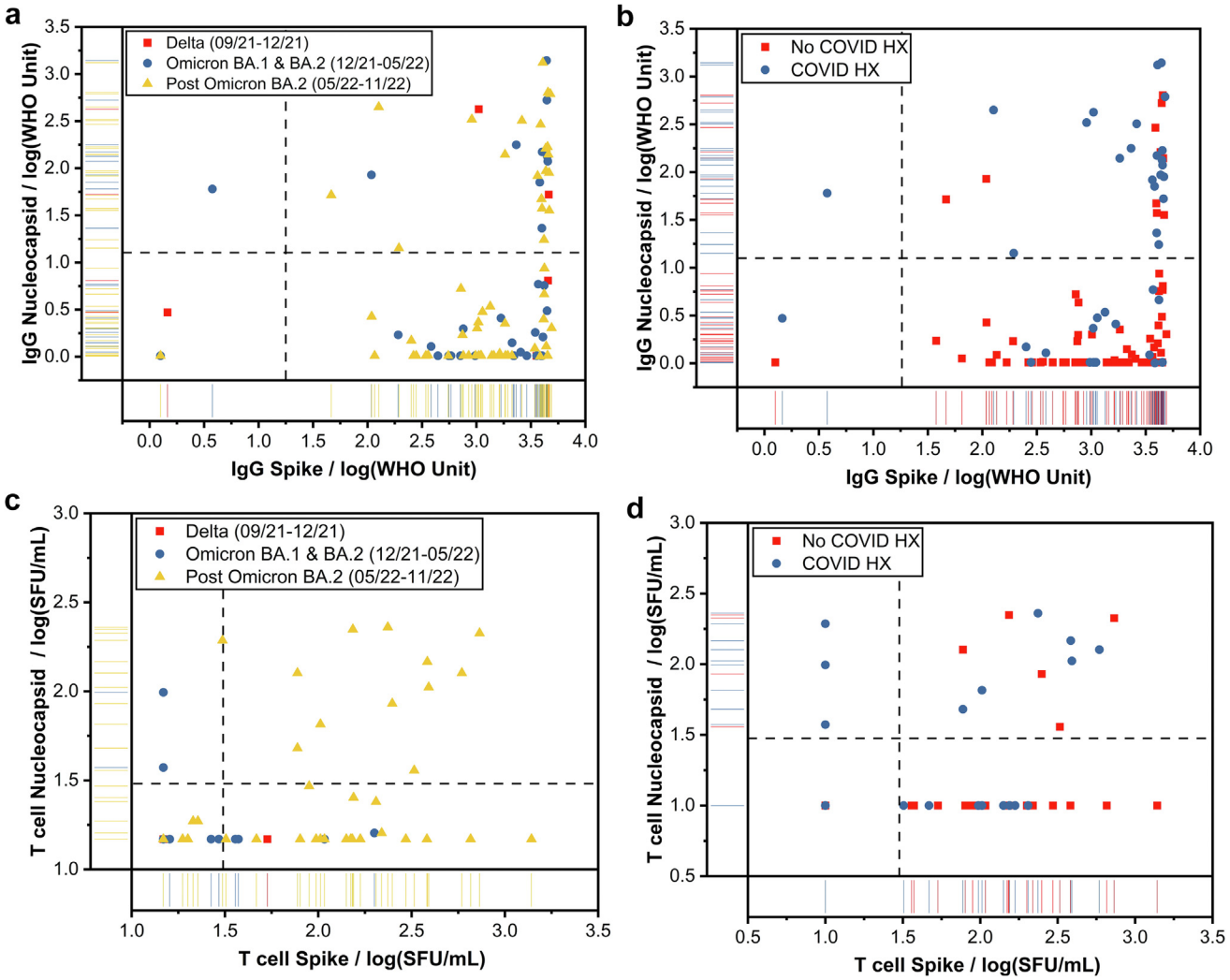

Figure 4. SARS-CoV-2 spike versus nucleocapsid responses in patients on hemodialysis. Rugplots of IgG (a and b) and interferon gamma (IFN-γ)–producing T cell spots (c and d) against SARS-CoV-2 spike (x-axis) and IgG (a and b) and IFN-γ–producing T cell spots (c and d) against SARS-CoV-2 nucleocapsid (y-axis) in World Health Organization binding units/ml in participants on HD. Dashed lines represent cutoff for seropositivity. (a/c) Samples from delta (September 2021–December 18, 2021, red squares), BA.1/2 (December 19, 2021–April 2022, blue circles), and post-BA.2 (May, 2022–November, 2022, yellow triangles) are displayed. (b/d) Samples from participants with (blue circles) and those without (red squares) a history of COVID-19 are displayed. Dashed lines represent seropositivity cutoffs (a/b) or lower limit of quantification (c/d).

9% [5/56], $P = 0.031$) (Figure 3b). However, spike T cell responses did not differ based on COVID-19 status before enrollment ($P = 0.50$).

Changes in Concomitant Spike and Nucleocapsid Responses Over Time

Given that community transmission during the Omicron era was much higher than earlier, we sought to determine if samples collected later would demonstrate higher levels of spike and nucleocapsid (dual) responses. In fact, the proportion of samples seropositive for both spike and nucleocapsid IgG was similar over time between pre- and post-BA.2 eras (12/39 [31%] vs. 20/59 [34%], $P = 0.828$), likely owing to high levels of spike seropositivity at study entry (Figure 4a). There was a clear distinction in dual positivity between samples from participants with and without a history of COVID-19 before enrollment (21/39 [54%] vs. 10/81 [12.3%], $P < 0.001$) (Figure 4b).

When evaluating T cell responses, samples from the post-BA.2 era were the only samples demonstrating enzyme-linked immunosorbent spot responses above lower limit of quantification for both spike and nucleocapsid ($P < 0.001$) (Figure 4c); however, there was not a clear distinction in T cell responses between those with and without a history of COVID-19 before enrollment ($P = 0.92$) (Figure 4d). In fact, among the 23 participants with T cell data and no known history of COVID-19, 5 had positive antibody or cellular responses to both nucleocapsid and spike, suggesting asymptomatic or undiagnosed infection.

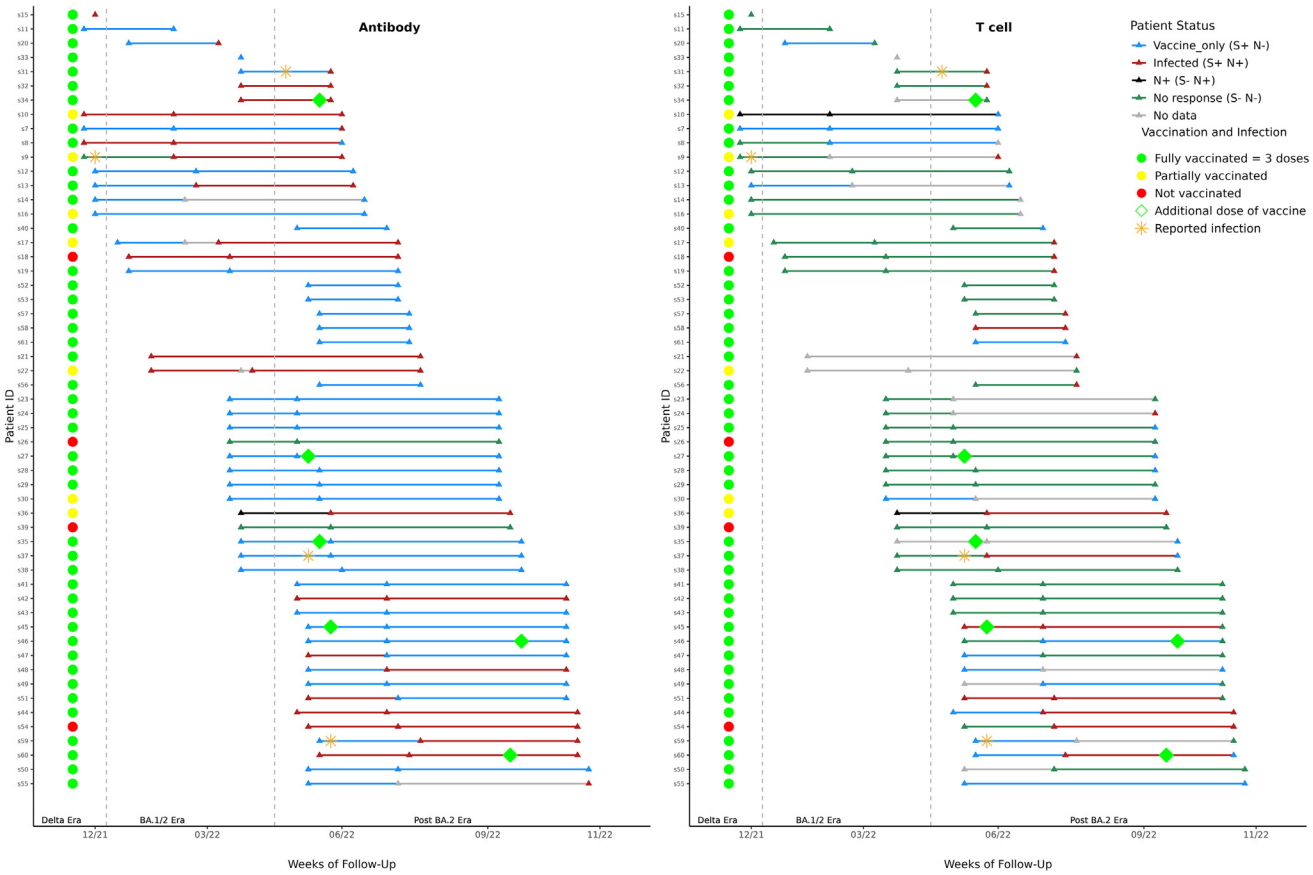

Figure 5. Antibody and T cell immune states over time in patients on hemodialysis. Swimmer plot of immune states at time of enrollment (0), 8, and 24 weeks after enrollment plotted over calendar time. Antibody immunity as determined by IgG against spike (S) and nucleocapsid (N) (left) and enzyme-linked immunosorbent spot (ELISpot) responses to S and N (right) are displayed. Each line represents an individual over time and the immunity state is indicated by color where blue is vaccine only (S+, N−), red is infection (S+, N+), black is N+ only, green is no immunity (S−, N−), and grey are missing data. Colored circles at the far left of the graphs indicate vaccination status at enrollment (green = at least 3 doses of vaccine, yellow = 1 or 2 doses of vaccine, red = no doses of vaccine). Additional vaccines during blood collection follow-up are noted with an open green triangle whereas reported infections are noted with an asterisk. A significantly higher proportion of the population had some evidence of S+ antibody immunity compared to S+ T cell immunity ($P < 0.001$).

Antibody and Cellular Responses to SARS-CoV-2 are Discordant in Patients Receiving HD

Next, we examined the trajectory of each participant's antibody and cellular responses to spike and nucleocapsid (Figure 5). Participants were more likely to have a positive antibody response to spike than a positive cellular response to spike at their final study visit (51/55 [92.7%] vs. 14/48 [29.2%], $P < 0.001$). Antibody and cellular immunological concordance (i.e., having the same antibody response, either positive or negative, as cellular response at a given time point) was rare at study entry (12/48 [25%]). This increased insignificantly at final study visit, and remained uncommon (19/50 [34.5%], $P < 0.196$).

Infection Was Common During Follow-Up

Finally, we examined clinical, demographic, and immunological factors associated with those who did and those who did not experience a SARS-CoV-2 infection from study entry through final follow-up (50 weeks). The infection group did not significantly differ from the no-infection group regarding key clinical and demographic factors (Table 2). It was more common to have a history of COVID-19 in the no-infection group, but this was not statistically significant (14/37 [37.8%] vs. 2/18 [11.1%], $P = 0.083$). The groups did not significantly differ immunologically, because neither peak spike antibody nor peak spike T cell responses were significantly different between the 2 groups. When we restricted the analysis to only 180 days after final study visit, the findings were similar.

DISCUSSION

In this first longitudinal assessment of humoral and cellular responses to SARS-CoV-2 in a community dialysis setting during the Omicron era, we found increasing T cell responses to both spike and nucleocapsid; however, heterogenous neutralizing responses were generally diminished compared with thrice-

Table 2. Clinical and demographic characteristics of participants who experienced COVID-19 after enrollment versus those who did not

Characteristics	No infection after enrollment (n = 37)	Infection during study period (n = 18)	P-value
Age at enrollment, yr			0.693
Median [IQR]	68 [59–74]	64 [57.25–73.25]	
Gender			0.708
Male, n (%)	15 (40.5%)	9 (50.0%)	
Race, n (%)			0.246
African American	13 (35.1%)	<5	
White	24 (64.9%)	13 (72.2%)	
Cause of ESKD, n (%)			0.952
Diabetes	18 (48.6%)	8 (44.4%)	
HTN/large vessel disease	8 (21.6%)	<5	
Other[a]	11 (29.7%)	6 (33.3%)	
History of failed transplant	<5	<5	0.833
Peak antibiotic spike (BAU/ml)	3472 [1105–4367]	3568 [1105–4404]	0.802
Peak T cell spike (SFU/ml) [IQR]	36 [8–219]	11 [5–147]	0.384
Vaccines at end of 2021[b] [IQR]	3 [2–3]	3[3–3]	0.244
Previous infection[c] n (%)	14 (37.8%)	2 (11.1%)	0.083

BAU, binding units; ESKD, end-stage kidney disease; HTN, hypertension; IQR, interquartile range.
[a]Other: transplant complication, cystic/hereditary/congenital, glomerulonephritis.
[b]Number of mRNA vaccines before January 1, 2022, and all study participants had either Moderna or BNT.
[c]Previous infection: indicate any infection before study enrollment.

vaccinated HCs. Importantly, whereas responses among those with a history of COVID-19 were generally higher, this was also inconsistent, indicating that hybrid immunity in this population may be less robust than the general population. Further, we detected positive nucleocapsid (both antibody or cellular) responses in 22% of participants with no known history of COVID-19, suggesting that asymptomatic infection is relatively common in the HD population. During follow-up, 16 participants experienced an infection including 2 with previous infections, again highlighting the need for ongoing immunization in this vulnerable population that is frequently exposed to SARS-CoV-2.

Our findings of impaired cellular responses in this population are in agreement with previous reports that found, particularly in previously uninfected patients on HD, lower T cell responses than in HCs.[17–19] In terms of longitudinal analysis, 1 study reported decreasing antibody responses and stable T cell responses up to 16 weeks postvaccination, whereas both responses were stable or increasing over time in the present study.[20] This discrepancy is likely due to the previous study being conducted after only 2 doses of mRNA vaccine and in an era where infection rates were lower than in the present study where many participants had received 3 or more doses and the cases of infection were higher. Further, both the decreased neutralizing response to Omicron subvariants, and the number of infections during follow-up, are consistent with previous findings that 2 and even 3 doses of ancestral mRNA vaccine are inadequate to induce high-titer neutralizing antibody responses against Omicron variants in people on HD.[21–23] A study evaluating the effect of a fourth dose of original vaccine formulation found a modest improvement.[24]

What remains unique about the present study is the longitudinal characterization of both antibody and cellular responses in a community HD population, the finding that there is significant discordance between these 2 responses, and that neither immune compartment necessarily correlates well with known previous exposures (infection or vaccination). Although previous studies have demonstrated significant waning of antinucleocapsid responses and shown discordance between humoral and antibody responses following infection, this has not been studied in the postvaccine and post-Omicron era.[25,26] Given the discrepancies between and among previous antigen exposures and the immunological responses noted here, it is important for clinicians and patients on HD to recognize that previous infection, receipt of vaccines based on older variants, or both do not guarantee robust protection from subsequent infection. Thus, people with ESKD on HD should continue to follow guidance regarding updated boosters, and HD centers must have a high index of suspicion for SARS-CoV-2 among their patients when community prevalence is high regardless of the patients' recent COVID-19 history or vaccination status.

This study is limited to a relatively small observational sample of people with ESKD undergoing HD in the USA in an era before Omicron-specific vaccine formulations. Therefore, it was not powered or designed to make definitive statements about current vaccine efficacy or correlates of protection. This is

balanced by the multisite, longitudinal, and community-based nature of the study. Furthermore, although Omicron spike–containing vaccines exist, their effectiveness, even in the general population, against novel variants of concern is similar to that of ancestral formulations against BA.1.[27] Our comparison with HCs is also limited by significant difference in age distribution; the latter being much younger than the former. Therefore, differences observed between the groups may be attributable to age and not just the presence of ESKD. However, comparisons with these HCs are useful because the controls likely represent the optimal response achievable, and in some cases the HD participants were not significantly different. Although we did not define the specific T cell subsets (CD8 vs. CD4) responsible for the cellular responses, it is thought to be largely driven by CD4 cells in this population.[28]

In summary, our findings indicate that vaccination and infection before Omicron do not necessarily guarantee robust immune responses, particularly cellular responses, in patients receiving HD in the community. This implies that, as variants continue to emerge and vaccines are updated, people with ESKD on HD should continue to receive updated COVID-19 vaccines, take reasonable precautions in the community and health care settings to prevent infection when community transmission is high (as it was during summer of 2024), and remain cautious even if previously infected with SARS-CoV-2. Furthermore, HD centers should help patients mitigate risk by following Centers for Disease Control and Prevention recommendations on ventilation and return-to-work guidance.[29] This study also emphasizes that additional research of immune responses to respiratory viral infections and vaccines in the HD population, is urgently needed to understand both the immunological heterogeneity and immune discordance seen in this relatively immunosuppressed population with frequent health care exposures.

DISCLOSURE

AHK reports receiving consulting fees from Hologic Inc. LD is employed by and has share options in Fresenius Medical Care and owns stock in General Electric & GE HealthCare; LD's spouse owns shares in TPMG. RJK is employed by Fresenius Medical Care. All the other authors declared no competing interests.

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AUTHOR CONTRIBUTIONS

LSD, RJK, CRP, and SCR conceptualized and designed the study. TSJ and CCG performed the assays. AHK, JX, and SCR performed the analysis. LSD, RJK, CRP, and SCR acquired funding. JNB, AHK, and SCR provided supervision. AHK wrote the original draft. All the authors edited and revised the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Anti-SARS-CoV-2 IgG over time in participants on hemodialysis.

Figure S2. Anti-SARS-CoV-2 IgG in participants with and without a history of COVID-19.

Figure S3. Surrogate neutralization of SARS-CoV-2 variants of concern among patients on hemodialysis who received 3 doses of vaccine compared to healthy controls.

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