

Antibody Status, Disease History, and Incidence of SARS-CoV-2 Infection Among Patients on Chronic Dialysis

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ABSTRACT

Background Although reinfection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is rare among individuals with few coronavirus disease 2019 (COVID-19) risk factors, the ability of naturally acquired immunity to prevent reinfection among patients with ESKD is not known.

Methods This prospective study was conducted among adults with ESKD treated with in-center hemodialysis (ICHD) in the United States. Exposure was ascribed on the basis of the presence or absence of IgG against SARS-CoV-2 at baseline, and separately, a history of documented COVID-19 before study entry. Outcomes were assessed after an infection-free period, and were any SARS-CoV-2 infection (*i.e.*, detected by protocolized PCR tests or during routine clinical surveillance), and clinically manifest COVID-19 (consisting of only the latter).

Results Of 2337 consented participants who met study inclusion criteria, 9.5% were anti-SARS-CoV-2 IgG positive at baseline; 3.6% had a history of COVID-19. Over 6679 patient-months of follow-up, 263 participants had evidence of any SARS-CoV-2 infection, including 141 who had clinically manifest COVID-19. Presence of anti-SARS-CoV-2 IgG (versus its absence) at baseline was associated with lower risk of any SARS-CoV-2 infection (incidence rate ratio, 0.55; 95% confidence interval, 0.32 to 0.95) and clinically manifest COVID-19 0.21 (95% confidence interval, 0.07 to 0.67).

Conclusion Among patients with ESKD, naturally acquired anti-SARS-CoV-2 IgG positivity is associated with a 45% lower risk of subsequent SARS-CoV-2 infection, and a 79% lower risk of clinically manifest COVID-19. Because natural immunity is incomplete, patients with ESKD should be prioritized for SARS-CoV-2 vaccination, independent of their COVID-19 disease history.

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The coronavirus disease 2019 (COVID-19) pandemic was caused by the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.¹ The pandemic has posed a particular threat to patients with ESKD treated with in-center hemodialysis (ICHD). Such patients, by definition, cannot self-isolate; they need to attend thrice-weekly treatments at a dialysis center, to which they are often transported by a shared-ride vehicle or public transit.

Compounding these risks, patients treated with ICHD tend to be elderly, from racial/ethnic minority groups, socioeconomically disadvantaged, have a high comorbidity burden, and live in geographies hit hard by COVID-19.² High prevalence of these risk factors among the ESKD population has resulted in such patients bearing a disproportionate burden of COVID-19 morbidity and mortality.^{3,4} However, the extent to which prior infection with SARS-CoV-2

might confer protection against subsequent reinfection in these vulnerable patients has not yet been clarified.

Several recent studies have examined the implications of prior SARS-CoV-2 infection with respect to subsequent reinfection. A prospective study among healthcare workers found that prior infection appeared to provide robust protection against subsequent reinfection,⁵ a finding that was generally corroborated by two large observational studies.^{6,7} Although these studies provide reassuring signals with respect to the general population, the degree to which these findings extend to high-risk populations, such as patients with ESKD, is not yet known. In light of recent evidence suggesting that patients with ESKD may not mount as robust an immune response to SARS-CoV-2 antigens as other individuals,⁸ a more complete understanding of humoral immunity to the virus in patients with ESKD is urgently needed.

To clarify the role of naturally acquired humoral immunity among, and to inform vaccination policies for, patients

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with ESKD, we undertook this prospective cohort study to estimate how anti-SARS-CoV-2 serostatus, history of known COVID-19, and their combination affect risk of future SARS-CoV-2 infection.

METHODS

Study Protocol and Timeline

The study protocol was reviewed and approved by an Institutional Review Board before commencement of the study (Integ Review Institutional Review Board, protocol DCR 20-M-0044-00, July 2, 2020). Eligible subjects were patients aged 18–80 years who were receiving hemodialysis at participating clinics operated by a large dialysis organization in the United States (participating clinics were in California, Connecticut, Minnesota, Nevada, New York, Ohio, Texas, Virginia, and Wisconsin) who were able to provide written informed consent (ClinicalTrials.gov Identifier: NCT04495764).

At the time the study was designed (Figure 1), public health authorities anticipated the COVID-19 wave in the spring of 2020 would be followed by disease hiatus over the summer, and then a fall surge. The study protocol was designed on the basis of this prediction. Baseline assessment was undertaken at study Visit 1 (beginning in July 2020); that is, after the spring wave period. Follow-up started at Visit 2 (beginning in October 2020), which was timed to coincide with the anticipated start of the fall surge in disease.

At Visit 1, informed consent was obtained and a sample collected for assessment of anti-SARS-CoV-2 IgG antibodies (see below). At Visit 2, samples were obtained for assessment of anti-SARS-CoV-2 IgG antibodies, and SARS-CoV-2 RNA (protocolized PCR). Visits 3, 4, and 5 occurred within 4 weeks (± 7 days) from the prior study visit, and with the same procedures as Visit 2. Sample collection for protocolized PCR was not performed for participants who had ongoing PCR-confirmed COVID-19. Subjects could

decline to provide samples at any study visit while remaining enrolled in the study, or withdraw from the study at any time.

Visit 2 marked the beginning of the outcome period. During follow-up, participants continued to undergo disease surveillance at the dialysis clinic as per standard protocol. Per routine clinical procedures, all patients received a standardized screen for symptoms and COVID-19 contacts at each thrice weekly clinic visit; diagnostic workup (including PCR testing) was performed for all positive screens. Clinic personnel also recorded any interim hospitalizations, with a particular focus on COVID-19 diagnoses and testing.

SARS-CoV-2 PCR and Antibody Testing

Patients could undergo PCR testing during the follow-up period via two mechanisms. First, patients could undergo PCR testing as part of their routine care, in response to clinical circumstance (symptomatology or known exposure, as detected by clinic entrance screening). Results of such PCRs, which were performed on varying sample types and using various PCR assays depending on the setting (*e.g.*, dialysis clinic, emergency department, hospital), were then abstracted from the patient's electronic health record for consideration in the study. Second, patients underwent monthly surveillance PCRs as part of the study protocol.

PCR testing for protocolized PCRs was conducted primarily using saliva samples. Saliva samples were collected using the SDN-1000 Whole Saliva Collection Device (Spectrum Solution, Inc). If a patient was unable to produce a saliva sample, a swab sample (nasal or mid-turbinate) was instead collected in 0.9% physiologic saline. Samples were then shipped to a centralized, accredited, high-complexity clinical laboratory (DaVita Labs). Nucleic acids were extracted using a chemagic 360 Instrument (PerkinElmer, Inc.). SARS-CoV-2 RNA in both sample types was detected using the New Coronavirus Nucleic Acid Detection Kit (PerkinElmer, Inc.), which amplifies two targets in the viral genome.

Significance Statement

Among the general population, infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) robustly protects against subsequent reinfection. Whether this finding extends to patients with ESKD was not previously known. Here, we prospectively studied patients treated with hemodialysis in the United States, and compared SARS-CoV-2 infection rates among patients with and without evidence of prior SARS-CoV-2 infection (either baseline antibodies or history of disease). We found that although prior SARS-CoV-2 infection protected against subsequent reinfection, the effect was not as strong as in the general population. This study indicates that prior infection with SARS-CoV-2 provides incomplete protection in patients with ESKD, and argues in favor of prioritizing such patients for vaccination regardless of prior infection status.

Per manufacturer protocol, samples in which either or both regions were detected were scored as positive, and samples in which neither region was detected were scored as negative.

Blood samples for antibody analysis were collected before hemodialysis treatment in a 5 ml serum separation tube, clotted for 30 minutes, centrifuged, and refrigerated before shipment to the centralized clinical laboratory (DaVita Labs). Indirect chemiluminescence immunoassays for anti-SARS-CoV-2 IgG antibodies (Diazyme Laboratories, Inc.) were performed according to the manufacturer's protocol. The assay detects both antispike and antinucleocapsid protein antibodies. Per the manufacturer's recommendation, samples were scored as IgG positive if the corresponding test reading was >1 arbitrary unit/ml, and negative otherwise.

Construction of the Analytic Cohort

A total of 2530 patients met initial inclusion and exclusion criteria and provided written informed consent (Figure 2). Of these, 98 either did not undergo baseline serologic testing for anti-SARS-CoV-2 IgG or had indeterminate/missing IgG data. A further 43 participants withdrew from study before the start of follow-up. An

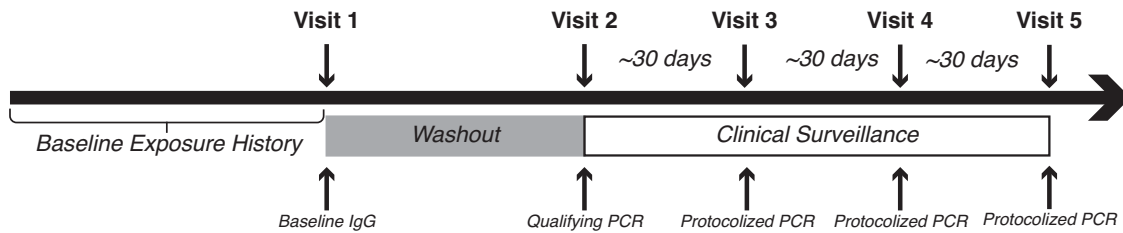


Figure 1. Timeline of study events. Baseline IgG serostatus is on the basis of serologic testing at Visit 1. Baseline history of COVID-19 considers all data up through Visit 1. Participants who manifested COVID-19 during the infection-free period (between Visits 1 and 2) were excluded from analysis, as were those who had a positive PCR test at Visit 2. Follow-up began immediately after Visit 2. Participants were followed for clinical evidence of disease through the first of withdrawal, death, or end of study (Visit 5). Participants underwent protocolized PCR testing at Visits 3, 4, and 5 except for those who were known to have COVID-19 at the corresponding time point or who declined or were unable to provide a sample for PCR analysis.

additional 20 participants were excluded for having manifest COVID-19 during the infection-free period (between Visits 1 and 2), and 32 for having had a positive qualifying SARS-CoV-2 PCR at the start of follow-up (*i.e.*, Visit 2); exclusion of such subjects from the analysis ensures outcome events observed during follow-up were incident and not carried over from an earlier episode of SARS-CoV-2 infection.⁹ The total analytic sample for these analyses consisted of the remaining 2337 participants.

Exposure Assignment and Analysis

Patients were assigned to coprimary exposure groups on the basis of anti-SARS-CoV-2 IgG status (either positive, IgG+, or negative, IgG-) as determined at study Visit 1, documented medical history of COVID-19 before

study Visit 1 (had such a history, Hx+, or did not have such a history, Hx-). Secondary analyses considered combinations of these two exposures. In the first instance, exposure was assigned to capture any evidence of prior SARS-CoV-2 infection (*i.e.*, IgG+, Hx+, or both IgG+/Hx+), contrasted to no evidence of SARS-CoV-2 infection (*i.e.*, IgG-/Hx-). In the second instance, all four possible combinations of the two coprimary exposures were considered separately (*i.e.*, IgG+/Hx+, IgG+/Hx-, IgG-/Hx+, IgG-/Hx-).

Outcomes were considered from the day after Visit 2 through the earliest of study withdrawal, death, or completion of the follow-up period (*i.e.*, Visit 5). Two outcomes were considered. First, any SARS-CoV-2 infection, whether detected during routine

clinical surveillance or via a protocolized PCR test at Visits 3, 4, or 5, was considered. Secondly, only those SARS-CoV-2 infections detected during routine clinical surveillance (hereafter termed clinically manifest COVID-19), because these represent symptomatic infections.

Patient characteristics, as abstracted from electronic medical records, were described as of study Visit 1, and summarized as means, standard deviations, counts, frequencies, medians, and interquartile ranges as dictated by data type. Crude rates were estimated as number of events divided by patient time at risk and reported as events per 100 patient-months (pt-mo). Comparisons across exposure groups were made using generalized linear models (Poisson distribution, log link) and reported as

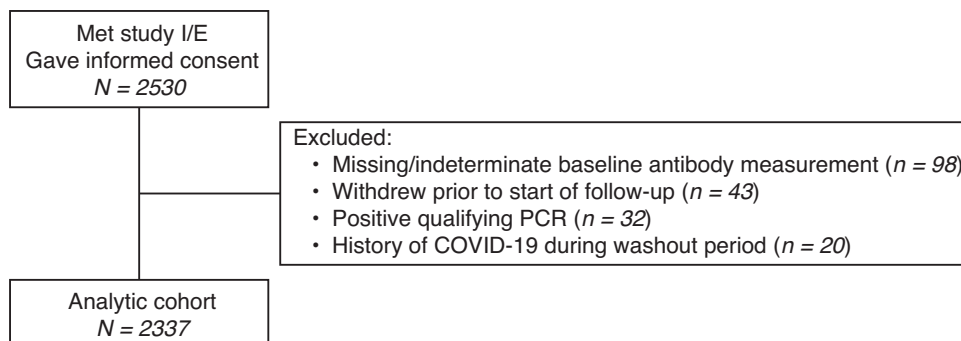


Figure 2. CONSORT diagram. A total of 2530 patients met initial inclusion and exclusion criteria (I/E) and provided written informed consent. Of these, 98 did not undergo baseline serologic testing for anti-SARS-CoV-2 IgG, 43 withdrew from study before the start of follow-up. For these analyses an additional 20 participants were excluded for having manifest COVID-19 during the infection-free period and 32 for having had a positive SARS-CoV-2 PCR at the start of follow-up. The analytic sample for these analyses consisted of the remaining 2337 participants.

incident rate ratios (95% confidence intervals; 95% CI). The main analyses considered unadjusted models. Models adjusted for age, sex, race, diabetes status, dialysis vintage, Charlson comorbidity index, and body weight were also evaluated.

Sensitivity Analyses

To account for the fact that a minority of patients changed IgG status during the study, a sensitivity analysis was performed in which time-updated IgG status (on the basis of each subject's most recent available IgG measurement) was used as the exposure. The original study design, incorporating the requirement for an infection-free period before the start of follow-up, was implemented based on the predicted course of the pandemic, which included a disease hiatus during the summer months. Given this did not come to pass, a sensitivity analysis was performed in which the requirement for the infection-free period between Visit 1 and Visit 2 was eliminated, and outcomes were considered beginning the day after Visit 1 (see Supplemental Methods and Supplemental Figure 2 for additional details).

All analyses were performed with SAS Enterprise Guide Version 7.1 (SAS Institute).

RESULTS

Overall, 2530 participants provided written informed consent to participate in this study. Of these, 2337 subsequently met all criteria for inclusion in these analyses (Figure 2). A description of study participants overall and by baseline serostatus is provided in Table 1. At baseline, 221 participants (9.5%) were anti-SARS-CoV-2 IgG positive, with the remaining 2116 being IgG-. Subjects who were IgG+ at baseline were less likely to be of self-reported White race compared with IgG- subjects; all other examined demographic and clinical factors were comparable between the two groups. Among the 104 subjects who had a documented history of SARS-CoV-2 infection before baseline IgG assessment, no relationship was observed between the time since SARS-CoV-2 infection and the IgG antibody level detected (Supplemental Figure 1).

During follow-up, 249 SARS-CoV-2 infections were detected over 6062 pt-mo of follow-up time among IgG-subjects (4.1 per 100 pt-mo; Table 2). Of these, 138 were clinically manifest COVID-19 (2.3 per 100 pt-mo). Among IgG+ subjects, 14 SARS-CoV-2 infections were detected over 617 pt-mo of follow-up (2.3 per 100 pt-mo), of which three were clinically

manifest COVID-19 (0.5 per 100 pt-mo). Thus, baseline anti-SARS-CoV-2 IgG seropositivity was associated with a lower risk of SARS-CoV-2 infection during follow-up: incidence rate ratio 0.55 (95% CI, 0.32 to 0.95) (Figure 3). This association was more potent for clinically manifest COVID-19 during follow-up: 0.21 (95% CI, 0.07 to 0.67). A total of 49 COVID-19-related hospitalizations were recorded during the outcome period, as were 13 deaths that occurred among subjects with evidence of SARS-CoV-2 infection; the paucity of these more severe outcome events precluded their further analysis.

The above relative risk estimates were not meaningfully affected by statistical adjustment for baseline clinical and demographic factors: the adjusted incidence rate ratio with respect to any SARS-CoV-2 infection was 0.55 (95% CI, 0.32 to 0.95), and with respect to clinically manifest COVID-19, 0.22 (95% CI, 0.07 to 0.69). Associations between each of the clinical and demographic factors examined and the risk of SARS-CoV-2 infection were weak (Supplemental Table 1). Similarly, when time-updated IgG status was used as the exposure variable, the unadjusted incidence rate ratio with respect to any SARS-CoV-2 infection was 0.58 (95% CI, 0.34 to 0.97), and with

Table 1. Patient characteristics at study enrollment

Characteristics	Overall (n=2337)	Baseline IgG- (n=2116)	Baseline IgG+ (n=221)
Age, years, mean±SD	59.5±12.3	59.5±12.4	58.9±11.9
Sex, n (%)			
Male	1392 (59.6)	1265 (59.8)	127 (57.5)
Female	945 (40.4)	851 (40.2)	94 (42.5)
Race/ethnicity, n (%)			
White	669 (28.6)	641 (30.3)	28 (12.7)
Black	923 (39.5)	817 (38.6)	106 (48.0)
Hispanic	570 (24.4)	500 (23.6)	70 (31.7)
Asian	38 (1.6)	36 (1.7)	2 (0.9)
Other/unknown	137 (5.9)	127 (5.8)	15 (6.8)
Etiology of ESKD, n (%)			
Diabetes	920 (39.4)	828 (39.1)	92 (41.6)
Hypertension	496 (21.2)	448 (21.2)	48 (21.7)
Other	921 (39.4)	840 (39.7)	81 (36.7)
Weight, kg, mean±SD	86.8±24.4	87.0±24.5	84.3±24.1
Time on dialysis, months, median (p25, p75)	39 (17, 75)	38 (17, 75)	41 (18, 76)
CCI, median (p25, p75)	5 (4, 6)	5 (4, 6)	5 (4, 6)
Diabetes, n (%)	1574 (67.4)	1419 (67.1)	155 (70.1)

CCI, Charlson comorbidity index; p25, 25th percentile; p75, 75th percentile.

Table 2. Outcome events during follow-up by exposure status

Status	N	At-risk Time (pt-mo)	Any SARS-CoV-2 Infection		Clinically Manifest COVID-19	
			n	Rate ^a	n	Rate ^a
Baseline IgG+ versus IgG-						
IgG+	211	6062	14	2.3	3	0.5
IgG-	2116	617	249	4.1	138	2.3
Baseline Hx+ versus Hx-						
Hx+	104	282	6	2.1	0	0
Hx-	2233	6397	257	4.0	141	2.2
Baseline IgG+ and/or Hx+ versus IgG-/Hx-						
IgG+ and/or Hx+	238	659	14	2.1	3	0.5
IgG-/Hx-	2099	6020	249	4.1	138	2.3
Baseline IgG+/Hx+ versus IgG+/Hx- versus IgG-/Hx+ versus IgG-/Hx-						
IgG+/Hx+	87	240	6	2.5	0	0
IgG+/Hx-	134	377	8	2.1	3	0.8
IgG-/Hx+	17	42	0	0	0	0
IgG-/Hx-	2099	6020	249	4.1	138	2.3

^aExpressed as events per 100 pt-mo.

respect to clinically manifest COVID-19, 0.28 (95% CI, 0.10 to 0.75). Likewise, when data were evaluated using an alternative design that eliminated the requirement for the infection-free period between Visits 1 and 2 (see Supplemental Methods for details), the unadjusted incidence rate ratio with respect to any SARS-CoV-2 infection was 0.51 (95% CI, 0.30 to 0.85), and with respect to clinically manifest COVID-19, 0.31 (95% CI, 0.13 to 0.75).

Baseline history of COVID-19 (which was observed in 104 subjects) was associated with a numerically lower risk of subsequent infection, but associations were not statistically significant, possibly due to a paucity of observations (Table 2 and Figure 3). When exposure status was considered as either baseline IgG+ and/or Hx+, risk estimates were similar to those observed for baseline IgG seropositivity overall.

Risk of any SARS-CoV-2 infection during follow-up was not statistically

different between participants with baseline IgG+/Hx- (*i.e.*, undetected and likely asymptomatic infection) versus IgG+/Hx+ (*i.e.*, clinically detected prior infection) status: for infection overall β -difference (standard error) -0.17 (0.54; $P=0.76$). Risk of clinically manifest COVID-19 could not be compared between these two groups due to data sparseness. Likewise, no risk estimate can be provided for participants with baseline IgG-/Hx+ status.

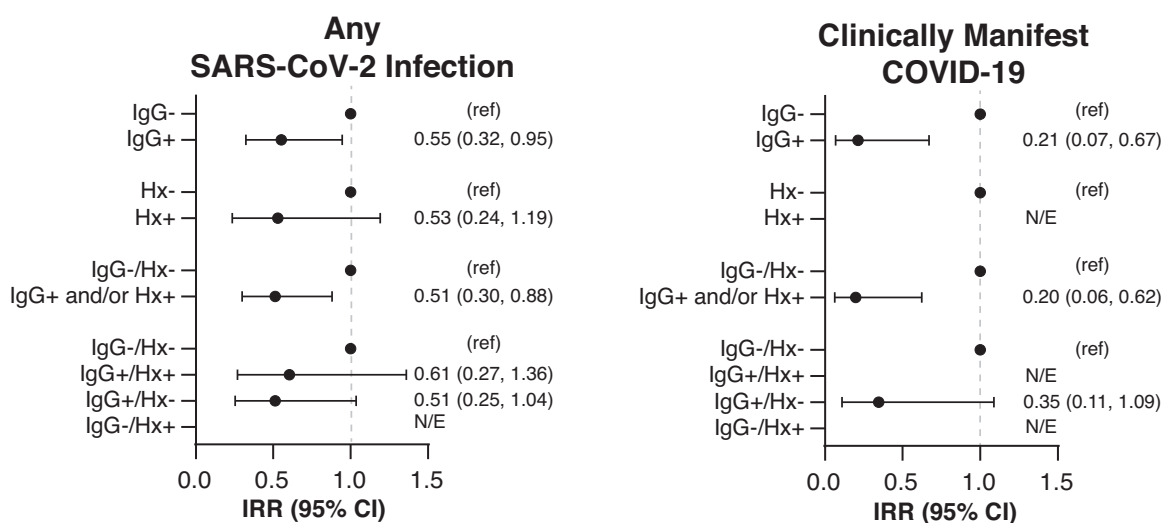


Figure 3. Relative risk of SARS-CoV-2 infection by exposure status. The incidence rate ratio (95% CI) for SARS-CoV-2 infection by exposure status compared with the indicated referent group is shown for any SARS-CoV-2 infection (detected either clinically or via study surveillance PCR, left panel) or for clinically manifest COVID-19 only (right panel). N/E, nonestimable; ref, referent.

DISCUSSION

The primary finding of this prospective observational cohort study is that naturally acquired humoral immunity, defined by anti-SARS-CoV-2 IgG seropositivity, was associated with 45% lower relative risk of subsequent SARS-CoV-2 infection overall and 79% lower relative risk of clinically manifest COVID-19 among persons at high COVID-19 risk due to ESKD. Moreover, disease history does not seem to materially affect the prognostic significance of seropositivity.

Although the baseline rate of diagnosed COVID-19 in this cohort was lower than that described in contemporaneous publicly reported data in ESKD,³ the 9.5% seroprevalence is similar to published data collected among patients with ESKD during a roughly contemporaneous period.¹⁰

Overall, it is reassuring that naturally acquired seropositivity was associated with a decreased risk of subsequent SARS-CoV-2 infection among patients with ESKD. Protective associations were greater with respect to clinically manifest COVID-19 versus SARS-CoV-2 infection overall, supporting the hypothesis that natural immunity may reduce disease severity even when it does not prevent reinfection entirely. Importantly, prior infection was markedly less protective in this high-risk population compared with what has been elsewhere observed in younger, healthier subjects, where prior infection was associated approximately 70%–90% lower relative risk of subsequent SARS-CoV-2 infection, depending on the study considered.^{6,7,10} One prior study noted the protection from subsequent infection afforded by prior SARS-CoV-2 infection was markedly attenuated among subjects aged ≥ 65 ; in older subjects, protection was estimated to be only 47%, compared with over 80% protection in younger age groups.⁶ Together with the findings presented here, these results suggest the degree of protection provided by natural immunity may vary substantially on the basis of age, comorbidity, or other risk factors. Findings from the general population

may therefore not be generalizable to more vulnerable individuals, including those requiring maintenance dialysis for the treatment of ESKD.

The strengths of this study include prospective enrollment, detailed characterization of participants, and robust surveillance mechanisms, including both clinical and protocol-driven disease status assessments. Some limitations should be noted. First, SARS-CoV-2 antibody and PCR tests have imperfect sensitivity and specificity. However, any related misclassification bias is expected to be nondifferential and would not explain the associations observed. Second, independent of assay limitations, antibody testing is an imperfect surrogate of overall immunity, because it elides the possibility that patients can have low circulating antibody levels, despite having retained immunologic memory. No evaluations of cellular immunity were performed as part of this study. Third, this study pertains only to naturally acquired immunity; extrapolation to vaccine-acquired immunity is not appropriate. Fourth, severity of SARS-CoV-2 infections (as indicated by hospitalization or mortality) could not be analyzed due to a paucity of recorded events and insufficient run-out time to allow for complete data capture with regard to these outcomes. Fifth, although every effort was made analytically to include only true *de novo* infections as study outcomes, the possibility that a minority of positive PCR tests represent viral shedding due to a prior infection cannot be excluded. Finally, some caution is warranted in extrapolating findings from patients on chronic dialysis to other high-risk populations; dedicated studies should be conducted where feasible.

In summary, these data demonstrate that protection afforded by natural immunity to SARS-CoV-2 among patients treated with ICHD is present but incomplete, and is of lower magnitude than in younger, relatively healthy populations. These findings support two current recommendations^{11,12}: first, that older individuals and those with chronic disease should be prioritized for COVID-19 vaccination; and second,

that decisions on vaccine candidacy should be made independent of prior disease history or serologic status.

DISCLOSURES

A. Young, D.E. Cohen, F. Tentori, G. Marlowe, J. Connaire, K. Bludorn, S. Sibbel, S.M. Brunelli, and T. Kelley are employees of DaVita Clinical Research. D. Miller is an employee of DaVita Labs. S.M. Brunelli's spouse is an employee of AstraZeneca. D. Cohen, G. Marlowe, S. Sibbel, and T. Kelley all have an ownership interest in DaVita. F. Tentori reports Scientific Advisor or Membership with Ardelyx Medical Advisory Board. J. Connaire reports Consultancy Agreements with Relypsa, Inc., Dynavax, Sanifit, GSK, and Diality; Ownership Interest in DaVita, Inc.; Research Funding from Akebia, Otsuka, AstraZeneca, Sanifit, GSK, Sera Trials, Travere, Ardelyx, Goldfinch Bio, Chinook, and Merck; and Scientific Advisor or Membership with GSK, and Sanifit.

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S.M. Brunelli, J. Connaire, S. Sibbel, and F. Tentori designed the study. K. Bludorn, J. Connaire, T. Kelley, F. Tentori, and A. Young provided clinical/logistical leadership and oversight; D. Miller oversaw all laboratory testing; G. Marlowe prepared the analytic data files; D.E. Cohen and S. Sibbel verified the analytic data files; D.E. Cohen performed the data analysis; S. M. Brunelli, D.E. Cohen, S. Sibbel, and F. Tentori interpreted the findings; S.M. Brunelli and D.E. Cohen drafted the manuscript; all authors reviewed and approved the manuscript before submission.

SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at <http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2021030387/-/DCSupplemental>.

Supplemental Methods.

Supplemental Figure 1. Antibody levels at baseline by time since first documented positive SARS-CoV-2 PCR test.

Supplemental Figure 2. Timeline of study events: sensitivity analysis eliminating infection-free period.

Supplemental Table 1. Adjusted relative risk of any SARS-CoV-2 Infection by IgG status and demographic characteristics.

Supplemental Table 2. Sensitivity analysis eliminating infection-free period: outcome events during follow-up by exposure status.

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