

Immune Senescence Markers Predict the Cellular Immune Response to BNT162b2 Vaccination in Hemodialysis Patients

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Background. Chronic kidney disease is associated with increased risk of frailty and accelerated immune senescence, potentially affecting the immune response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination.

Methods. Humoral and cellular responses against the spike protein of SARS-CoV-2 were determined in 189 COVID-naïve hemodialysis patients at week 4 and 8 after vaccination with 2 doses of BNT162b2. Frailty indicators and immune senescence markers were determined at baseline to identify predictors of the immune response.

Results. Controlling for age, activities of daily living (ADLs), instrumental ADLs, walking pace, and the clinical frailty score correlated negatively and hand grip strength positively with the humoral response. Controlling for age, the proportions of memory CD4⁺ T cells, memory CD8⁺ T cells, CD28^{null} T cells, and CD57⁺CD8⁺ T cells correlated negatively with the humoral response, whereas the proportions of memory CD4⁺ T cells and CD28^{null} T cells correlated negatively and the CD4/CD8 ratio positively with the cellular response. In a multivariate model, only the proportions of memory CD4⁺ T cells and CD28^{null} T cells independently predicted the cellular response.

Conclusions. Markers of immune senescence, but not frailty indicators, independently predict the cellular immune response after vaccination in hemodialysis patients, overruling the effect of chronological age.

Keywords. BNT162b2 vaccination; COVID-19; frailty; hemodialysis; immune response; immune senescence; SARS-CoV-2.

Established risk factors for progression of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection to severe coronavirus disease 2019 (COVID-19) include advanced age and underlying comorbidities. Patients with end-stage renal disease requiring dialysis have been shown to have an increased risk for death due to COVID-19 [1, 2]. Prospective studies have documented a delayed humoral immune response and blunted cellular response after vaccination against COVID-19 in hemodialysis patients [3]. In addition, marked heterogeneity of the immune response has been found, and the use of immunosuppressive drugs, low serum albumin, decreased lymphocyte

count, hepatitis B vaccine nonresponder status, and dialysis vintage have been shown to be independent predictors of the immune response [3, 4].

Patients with chronic kidney disease (CKD) are characterized by augmented frailty indicators and accelerated aging of the immune system [5]. Frailty is a clinical syndrome characterized by reduced cognitive and physiologic reserves leading to a state of increased vulnerability associated with disability, hospitalizations, and an increased mortality risk [6, 7]. Frailty scores were developed in order to identify the most vulnerable individuals in older populations, going beyond traditional risk factors such as age and comorbidities [8]. No studies, however, have linked these scores to infection risk and vaccination responses in patients with CKD. The premature aging of the immune system in CKD patients appears from alterations in the T-cell compartment, which are similar to those of older individuals [9]. In childhood, there is a predominance of naïve T cells, whereas elderly people and patients with CKD have increased proportions of memory and terminally differentiated CD57⁺ T cells [10, 11]. Furthermore, there is accumulation of phenotypically senescent CD28^{null} T cells [11, 12]. Finally, the enhanced loss of total CD4⁺ T cells results in a decrease of the CD4/CD8 ratio [11, 12]. Although these markers of

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immune senescence can be readily measured in clinical practice by flow cytometry, few studies have linked them to infection rates and none to vaccination responses [10].

Here, we investigate whether frailty indicators and immune senescence markers predict the humoral and cellular response to BNT162b2 vaccination in COVID-naïve hemodialysis patients and explore how these markers interrelate and relate to other predictors of the immune response.

METHODS

Study Subjects and Design

The study was conducted at the hemodialysis units of AZ Sint-Jan Brugge and AZ Damiaan Oostende in Belgium. Hemodialysis patients received 2 intramuscular doses of the BNT162b2 messenger RNA (mRNA) COVID-19 vaccine (Pfizer/BioNTech, Mainz, Germany) with an interval of 3 weeks. Demographic, clinical, and biochemical data were extracted from the electronic medical records and stored in the Electronic Data Capture system Castor. Blood samples were taken at baseline, for determination of immune senescence markers, and at 4 and 8 weeks after the first vaccine dose, for assessment of the immune response. A full assessment of frailty metrics was performed by 2 experienced occupational therapists within 4 weeks of receipt of the first vaccine dose.

Frailty Indicators

The Katz scale was used to assess basic activities of daily living (ADLs) [13], which measures the level of dependency and includes the following domains: bathing, dressing, transfers and displacements, toilet visits, urinary and fecal continence, and feeding. The Lawton and Brody Scale was used to assess instrumental activities of daily living (IADLs) [14]. Patients were interviewed about using the telephone, shopping, traveling, cooking, household activities, medication intake, and finance management. The Mini-Mental State Examination (MMSE) was used as a screening tool for cognitive impairment [15]. The short form of the Geriatric Depression Scale (GDS-15) was used to screen for depressive symptoms in older adults [16]. Hand grip strength was measured in a seated position using a hand dynamometer. When possible, both arms were examined during 3 efforts. The highest score was used in our analysis. Gait speed was evaluated by asking participants to walk 4 meters, using their walking aid if applicable. The following cutoff points were used to assess sarcopenia: gait speed ≤ 0.8 meter/second and handgrip strength < 27 kg for men and < 10 kg for women, as proposed in a European Consensus statement [17]. The Fried Frailty Phenotype is a commonly used screening tool composed of 5 criteria: unintentional weight loss ($> 5\%$ or > 4.5 kg during the past year), weakness (hand grip strength < 30 kg for men or < 18 kg for women), slowness (gait speed ≤ 0.76 meter/second), low physical activity

(sedentary lifestyle > 4 hours/day or < 1 walk per month), and self-reported exhaustion. A subject is considered frail if at least 3 or more criteria are present [6]. The Rockwood Clinical Frailty Scale (CFS) is a judgment-based frailty tool that evaluates several domains including comorbidity, function, and cognition and provides 9 levels of frailty ranging from 1 (very fit) to 9 (terminally ill) [18]. The score was given by a single treating nephrologist who had access to the medical records.

Flowcytometry for Immune Senescence Markers

Flow cytometry was performed on blood collected at baseline in ethylenediaminetetraacetic acid tubes (Sarstedt, Nümbrecht, Germany) on a FACSCanto II flow cytometer (Becton Dickinson, San Jose, California) using a single 8-color reagent panel (20 000–150 000 events per sample). Methods for sample preparation and instrument set-up were in accordance with the recommendations of the EuroFlow consortium [19]. Monoclonal antibodies used were: CD3 (APC, clone SK7), CD4 (HV450, clone RPA-T4), CD8 (APC-H7, clone SK1), CD28 (FITC, clone CD28.2), CD45 (HV500, clone HI30), CD45RA (PerCP-Cy5.5, clone HI100), CD57 (PE, clone NK-1), and CCR7 (PE-Cy7, clone 3D12) (all Becton Dickinson). Data were analyzed using FACSDiva software (Becton Dickinson). The following subsets were used to assess immune senescence: CD4/CD8 ratio, proportion of memory CD4 and CD8 T cells (sum of the frequencies of CD45RA⁻CCR7⁺, CD45RA⁻CCR7⁻, and CD45RA⁺CCR7⁻ subpopulations), frequency of CD28^{null} T cells, and frequency of CD57⁺CD8 T cells. A detailed gating strategy for the various cell subset is shown in [Supplementary Figure 4](#).

Humoral and Cellular Response

Immunoglobulin class G (IgG) antibodies, including neutralizing antibodies, to the receptor binding domain of the S1 subunit of the spike protein of SARS-CoV-2 were determined in serum by a chemiluminescent microparticle immunoassay on the ARCHITECT i System according to the manufacturer's instructions (SARS-CoV-2 IgG II Quant assay, Abbott). The cutoff for positivity is 50 arbitrary units (AU) per milliliter.

Cellular immunogenicity was assessed by measuring the secretion of interferon- γ by peripheral blood lymphocytes upon SARS-CoV-2 glycoprotein stimulation using the QuantiFERON SARS-CoV-2 test (Qiagen). The QuantiFERON SARS-CoV-2 Starter Set blood collection tube consists of 2 antigen tubes, SARS-CoV-2 Ag1 and SARS-CoV-2 Ag2, that use a combination of SARS-CoV-2-specific antigens, predominantly spike-derived, to stimulate lymphocytes (CD4 by Ag1, both CD4 and CD8 by Ag2) in heparinized whole blood. The tubes were gently mixed with the whole blood, to resuspend the contents that had been dried onto the inner walls. Interferon- γ was measured by enzyme-linked immunosorbent assay in plasma from the stimulated and incubated (37°C for 16–24 hours) samples. QuantiFERON nil and mitogen blood collection

Table 1. Demographic and Clinical Characteristics of Severe Acute Respiratory Syndrome Coronavirus 2–Naive Patients at Baseline and Humoral and Cellular Response to BNT162b2 Vaccine at 4 and 8 Weeks

Characteristic	All Patients (N = 189)	Patients With Information on Frailty (n = 75)
Age		
<75 y	91 (48.1)	26 (34.7)
75–84 y	74 (39.2)	38 (50.7)
≥85 y	24 (12.7)	11 (14.7)
Mean ± SD	71.4 ± 14.6	75.1 ± 13.1
Male sex		
	131 (69.3)	46 (61.3)
BMI, kg/m ² , mean ± SD	26.2 ± 5.1	26.5 ± 5.3
Current smoker	36 (19.0)	8 (10.7)
Comorbid disease		
Coronary artery disease	83 (43.9)	28 (37.3)
Heart failure	42 (22.2)	16 (21.3)
Cerebrovascular disease	46 (24.3)	19 (25.3)
Peripheral vascular disease	43 (22.8)	18 (24.0)
Abdominal vascular disease	24 (12.7)	13 (17.3)
COPD	14 (7.4)	7 (9.3)
Diabetes, type 1 or 2	68 (36.0)	22 (29.3)
Liver disease	4 (2.1)	1 (1.3)
Immunodeficiency	19 (10.1)	4 (5.3)
Malignancy	41 (21.7)	17 (22.7)
Hepatitis B vaccine nonresponder	22 (14.2)	10 (15.9)
ESRD causes		
Diabetes	42 (22.2)	14 (18.7)
Vascular disease	59 (31.2)	27 (36.0)
Glomerular disease	29 (15.3)	10 (13.3)
Tubulointerstitial disease	15 (7.9)	6 (8.0)
ADPKD or other genetic disease	9 (4.8)	3 (4.0)
Other	35 (18.5)	15 (20.0)
Dialysis vintage, y ^a	2.1 (1.1–4.6)	2.6 (1.3–5.6)
Hemodiafiltration	176 (93.1)	73 (97.3)
Online Kt/V, mean ± SD	1.50 ± 0.40	1.47 ± 0.31
Medication		
ACEI/ARB	55 (29.1)	28 (37.3)
Immunosuppressive drugs	28 (14.8)	10 (13.3)
Humoral response to BNT162b2 vaccine, AU/mL^a		
4 weeks	627.8 (62.7–2753.0)	278.4 (6.8–2385.0)
8 weeks	1890.0 (570.8–4538.4)	1466.0 (230.7–4186.4)
Cellular response to BNT162b2 vaccine, IU/mL^a		
4 weeks	0.76 (0.11–2.75)	0.54 (0.06–2.76)
8 weeks	0.12 (0.03–0.61)	0.12 (0.02–0.67)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; standard deviation.

^aMedian (25th–75th percentile).

tubes were used as negative and positive controls, respectively. The threshold for positivity is 0.15 IU/mL.

Statistical Analysis

Data analyses were undertaken using SAS statistical software (release 9.4). Descriptive statistics used were proportions and frequencies, means, standard deviations, medians and interquartile ranges. Partial Spearman rank correlations were used to study associations controlling for chronological age. The impact of immune senescence markers on humoral and cellular

immune response at 4 and 8 weeks, independent of potential confounders, was evaluated according to linear regression models. Given their high degree of skewness, distributions of anti-spike IgG titers and interferon- γ concentrations by QuantiFERON were log₁₀-transformed when fitting these models. Offsets of 10 AU/mL for anti-spike IgG titers and 0.01 IU/mL for QuantiFERON levels were used before transformation. Model fits were checked by graphical analysis of the residuals. By means of variance inflation factors, no collinearity between covariates was detected. A receiver operating

characteristic curve (ROC) analysis was carried out to evaluate the predictive value of the proportion of memory CD4⁺ T cells toward impaired cellular response at 8 weeks, defined as a QuantiFERON response to antigen 2 <0.15 IU/mL. In this analysis, Youden J statistics were calculated to find the optimal cutoff for the proportion of memory CD4⁺ T cells. A type I error level of $\alpha = .05$ was used to indicate statistical significance.

RESULTS

Participants

A total of 250 hemodialysis patients were evaluated for inclusion and 237 were enrolled. A total of 49 patients was excluded due to incomplete follow-up ($n = 1$), development of symptomatic or asymptomatic SARS-CoV-2 infection during the study ($n = 2$), irregularities in vaccine administration ($n = 2$), death ($n = 3$), absence of determination of immune senescence markers ($n = 19$), or history of COVID-19 ($n = 21$) (Supplementary Figure 1). The final study population ($n = 189$) was almost exclusively of Western European ancestry, had a male-to-female ratio of 69:31, a median age of 71.4 years, and a median dialysis vintage of 2.1 years. All patients received 2 BNT162b2 vaccine doses. Humoral and cellular responses were measured at week 4 and 8 (for schematic study design, see Supplementary Figure 2). Immune senescence markers were determined in all patients at baseline, and frailty scores were assessed in a subgroup of 75 patients from the hemodialysis unit in AZ Sint-Jan. Baseline clinical characteristics and immune responses are given in Table 1.

Relation of Frailty Status and Immune Senescence Markers

As expected, most frailty indicators and immune senescence markers were higher in older age categories (Supplementary

Tables 1 and 2). Overall, no statistically significant associations were found between frailty indicators and immune senescence markers, except for the correlation between the proportion of CD8⁺ memory T cells and IADLs, walking pace, and CFS (Table 2). However, the significance of these correlations was lost after controlling for age ($r = +0.16, +0.16, \text{ and } +0.14$, respectively; all $P > .05$).

Humoral and Cellular Immune Response in Relation to Frailty Indicators

The humoral immune response was associated with age at 4 weeks ($r = -0.44, P < .0001$) and 8 weeks ($r = -0.23, P = .0014$) after vaccination, whereas the cellular immune response was independent of age (at 4 weeks: $r = -0.09, P = .24$; at 8 weeks: $r = -0.08, P = .30$). Controlling for age, ADLs, IADLs, walking pace, and the CFS correlated negatively and hand grip strength positively with the humoral response at week 4, and to a somewhat lesser extent at week 8 (Table 3). No correlation was found between the Fried Frailty Phenotype, a composite frailty screening tool, and the humoral and cellular response after controlling for age (data not shown). No significant correlations were observed between the frailty indicators and the cellular response.

Humoral and Cellular Immune Response in Relation to Immune Senescence Markers

The proportions of memory CD4⁺ T cells, memory CD8⁺ T cells, CD28^{null} T cells, and CD57⁺CD8⁺ T cells correlated significantly and negatively with the humoral response at 4 and particularly at 8 weeks (Table 4), independent of age. The proportions of memory CD4⁺ T cells and CD28^{null} T cells correlated negatively and the CD4/CD8 ratio correlated positively with the cellular responses at week 4 and 8.

Table 2. Association Between Frailty Status and Immune Senescence Markers

Characteristic	Marker of Immune Senescence				
	Memory CD4 ⁺ T Cells	Memory CD8 ⁺ T Cells	CD28 ^{null} T Cells	CD4/CD8 Ratio	CD57 ⁺ CD8 ⁺ T Cells
Age	+0.01	+0.38 ^a	+0.14	+0.04	+0.25 ^a
ADLs	+0.18	+0.17	+0.21	-0.05	+0.10
IADLs	+0.16	+0.26 ^b	+0.16	-0.08	+0.08
MMSE	-0.11	-0.10	+0.00	+0.02	+0.16
GDS score	+0.07	-0.01	-0.08	-0.01	-0.07
Walking pace	+0.04	+0.27 ^b	+0.08	+0.06	+0.01
Hand grip strength	-0.08	-0.21	-0.15	-0.01	+0.01
Clinical frailty score	+0.15	+0.24 ^b	+0.09	+0.09	-0.05

Values represent Spearman correlations.

Abbreviations: ADLs, activities of daily living; GDS, Geriatric Depression Scale; IADLs, instrumental activities of daily living; MMSE, Mini-Mental State Examination.

^a $P < .001$.

^b $P < .05$.

Table 3. Humoral and Cellular Immune Response in Relation to Frailty Indicators, Controlling for Age

Characteristic	Humoral Immune Response		Cellular Response (Antigen 2)	
	4 Weeks	8 Weeks	4 Weeks	8 Weeks
ADLs	-0.36 ^a	-0.29 ^b	-0.11	-0.10
IADLs	-0.30 ^a	-0.17	-0.09	-0.12
MMSE	+0.02	-0.03	-0.09	-0.03
GDS score	+0.02	+0.04	+0.04	+0.02
Walking pace	-0.42 ^c	-0.27 ^b	-0.06	-0.04
Hand grip strength	+0.28 ^b	+0.19	-0.05	-0.13
Clinical frailty score	-0.45 ^c	-0.30 ^a	-0.12	-0.08

Values represent partial Spearman correlations, controlling for age.

Abbreviations: ADLs, activities of daily living; GDS, Geriatric Depression Scale; IADLs, instrumental activities of daily living; MMSE Mini-Mental State Examination.

^a $P < .01$.

^b $P < .05$.

^c $P < .001$.

Table 4. Humoral and Cellular Immune Response in Relation to Immune Senescence Markers, Controlling for Age

Marker	Humoral Immune Response		Cellular Response (Antigen 2)	
	4 Weeks	8 Weeks	4 Weeks	8 Weeks
Memory CD4 T cells	-0.24 ^a	-0.28 ^b	-0.32 ^b	-0.29 ^b
Memory CD8 T cells	-0.12	-0.16 ^c	-0.14	-0.06
CD28 ^{null} T cells	-0.16 ^c	-0.21 ^a	-0.20 ^a	-0.18 ^c
CD4/CD8 ratio	+0.09	+0.13	+0.16 ^c	+0.16 ^c
CD57 ⁺ CD8 ⁺ T cells	-0.08	-0.16 ^c	-0.05	-0.05

Values represent Spearman correlations, controlling for age.

^aP < .01.

^bP < .001.

^cP < .05.

Immune Senescence Markers Independently Predict the Humoral and Cellular Immune Response

We fitted linear models to study the associations between the different immune senescence markers and immune responses at 4 and 8 weeks, correcting for all variables that predicted these responses in a previous analysis, including age, dialysis vintage, serum albumin, lymphocyte count, IgG, previous response to hepatitis B vaccination, and use of immunosuppressive drugs (Table 5) [3]. At week 8, the proportions of memory CD4⁺ T cells and CD28^{null} T cells predicted the cellular response independently. With the simultaneous inclusion of both markers in the model, only the proportion of memory CD4⁺ T cells remained a significant predictor. At week 8, a ROC analysis of the proportion of memory CD4⁺ T cells in the prediction of an impaired cellular response, defined as QuantiFERON response to antigen 2 <0.15 IU/mL, had an area under the curve

of 0.64 at an optimal threshold for of 78.6% (corresponding to a sensitivity of 46.9% and specificity of 82.1%) (Supplementary Figure 3).

DISCUSSION

Here, we report that frailty indicators, including ADLs, IADLs, walking pace, CFS, and hand grip strength correlate with the humoral response after BNT162b2 vaccination in COVID-naive hemodialysis patients. Furthermore, we found significant correlations of various T-cell immune senescence markers with the humoral and cellular immune response. Finally, we demonstrate that the proportions of memory CD4⁺ T cells and CD28^{null} T cells have predictive value toward cellular response, independent of potential confounders.

The humoral and cellular immune response after vaccination against COVID-19 displays marked heterogeneity in hemodialysis patients and is primarily determined by COVID-19 experience and vaccine type [3]. In the present study, we therefore included only COVID-19-naive patients vaccinated with a single vaccine type. Other independent predictors of immunological response to vaccination include use of immunosuppressive drugs, serum albumin, lymphocyte count, hepatitis B nonresponder status, and dialysis vintage [2, 3]. In contrast, age was a predictor of the humoral response only at week 4, but not at week 8, and did not predict the cellular response. We therefore speculate that premature immune senescence or increased frailty risk in patients on hemodialysis may potentially overrule the effects of chronological age. In support of this hypothesis, we found that the proportions of memory CD4⁺ T cells and CD28^{null} T cells were independent

Table 5. Linear Models Studying the Association Between Markers of Immune Senescence and Immune Response to BNT162b2 Vaccine at 4 and 8 Weeks, Independent of Age, Dialysis Vintage, Serum Albumin, ln(Lymphocyte Count), Immunoglobulin G, Previous Response to Hepatitis B Vaccine, and Use of Immunosuppressive Drugs

Marker	Log ₁₀ (Humoral)			Log ₁₀ (Cellular [Antigen 2])		
	β (SE) ^a	T-Statistic ^a	P Value ^a	β (SE) ^a	T-Statistic ^a	P Value ^a
At 4 weeks						
Memory CD4 T cells	-0.0056 (0.0056)	-1.00	.319	-0.0114 (0.0044)	-2.61	.010
Memory CD8 T cells	-0.0028 (0.0056)	-0.49	.625	+0.0002 (0.0045)	+0.05	.959
CD28 ^{null} T cells	-0.0080 (0.0055)	-1.47	.145	-0.0103 (0.0043)	-2.38	.019
CD4/CD8 ratio	-0.0107 (0.0342)	-0.31	.756	+0.0111 (0.0271)	+0.41	.684
CD57 ⁺ CD8 ⁺ T cells	-0.0035 (0.0040)	-0.87	.386	-0.0014 (0.0032)	-0.42	.674
At 8 weeks						
Memory CD4 T cells	-0.0066 (0.0043)	-1.54	.127	-0.0112 (0.0044)	-2.56	.012 ^b
Memory CD8 T cells	-0.0012 (0.0043)	-0.29	.776	+0.0021 (0.0044)	+0.47	.641
CD28 ^{null} T cells	-0.0069 (0.0042)	-1.63	.105	-0.0096 (0.0044)	-2.17	.032 ^c
CD4/CD8 ratio	-0.0031 (0.0263)	-0.12	.907	+0.0238 (0.0272)	+0.88	.382
CD57 ⁺ CD8 ⁺ T cells	-0.0049 (0.0031)	-1.59	.115	-0.0022 (0.0032)	-0.68	.495

^aAdjusted for age, dialysis vintage, serum albumin, ln(lymphocyte count), immunoglobulin G, previous response to hepatitis B vaccine, and use of immunosuppressive drugs.

Abbreviation: SE, standard error of the estimated β-coefficient.

^bP = .047 after additional adjustment for CD28^{null} T cells.

^cP = .221 after additional adjustment for memory CD4 T cells.

predictors of the cellular response. Both markers indicate that a lower proportion of naive CD4 T cells responds to the vaccine antigen. Indeed, animal and human studies show that mRNA vaccines induce strong CD4 T-cell responses [20, 21]. Not unsurprisingly, these markers of T-cell aging did not predict the humoral response. In accordance, only B-cell immune markers (proportions of switched IgG⁺ memory B cells and IgG⁺ memory B cells) predicted the humoral response after hepatitis B vaccination [22]. Overall, our findings support the concept of enhanced immunological aging in CKD patients by associating it directly to decreased vaccine response.

The identification of predictors of the immune response after vaccination may allow better selection of patients for strategies to improve vaccine immunogenicity, including booster administration. Measurement of these markers may supersede chronological age in decision-making tools.

Our study has several strengths. Patients received a comprehensive functional, physical, cognitive, and depression assessment as well as determination of the immune senescence markers, performed according to a standardized protocol that can be implemented in daily clinical practice. The external validity of our findings is strengthened by the high participation rate. Limitations of our study comprise the exclusion of peritoneal dialysis patients, inability to include other COVID-19 vaccines, and the inclusion of only a small number of participants of nonwhite ethnicity, potentially affecting the generalizability of our findings.

In conclusion, our findings support the hypothesis that T-cell immune senescence overrules the effect of chronological age on the cellular immune response after mRNA vaccination in hemodialysis patients. However, the contribution of T-cell immune senescence to the response was moderate, suggesting the involvement of multiple other factors.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. J. T. V. P., M. D. G., and A. S. D. V. designed the study. A. S. D. V., J. E., M. R., E. V., J. T. V. P., and Z. W. collected the data. A. S. D. V., D. D. B., and J. T. V. P. analyzed the data. D. D. B. and J. T. V. P. created the figures. J. T. V. P. wrote the paper with input from A. S. V. D. and D. D. B. All authors approved the final version of the manuscript.

Patient consent. The study was approved by the local Institutional Review Board (advice number 2777 AM4) and registered on EudraCT (number 2021-000930-32). All participants provided written informed consent.

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