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Kinetics of Anti–SARS-CoV-2 IgG Antibodies in Hemodialysis Patients Six Months after Infection

Hamza Sakhi,[1,2] Djamal Dahmane,[1] Philippe Attias,[3] Thomas Kofman,[4] Magali Bouvier,[5,6] Nathanael Lapidus,[7,8] Slim Fourati,[5,6] and Khalil El Karoui,[1,2] on behalf of Mondor NephroCov Study Group*

Due to the number of contributing authors, the affiliations are listed at the end of this article.

ABSTRACT

Background The humoral response against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the hemodialysis population, including its dynamics over time, remains poorly understood.

Methods To analyze initial and long-term humoral responses against SARS-CoV-2 in a hemodialysis population, we retrospectively evaluated findings from SARS-CoV-2 IgG serologic assays targeting the nucleocapsid antigen or spike antigen up to 6 months of follow-up in patients on hemodialysis in the Paris, France, region who had recovered from coronavirus disease 2019 (COVID-19).

Results Our analysis included 83 patients (median age 65 years); 59 (71%) were male and 28 (34%) had presented with severe COVID-19. We observed positive initial SARS-CoV-2 IgG antinucleocapsid serology in 74 patients (89%) at a median of 67 days postdiagnosis. By multivariable analysis, immunocompromised status was the only factor significantly associated with lack of an IgG antinucleocapsid antibody response. Follow-up data were available at 6 months postdiagnosis for 60 of 74 patients (81%) with positive initial antinucleocapsid serology, and 15 (25%) of them had negative antinucleocapsid serology at month 6. In total, 14 of 15 sera were tested for antispike antibodies, 3 of 14 (21%) of which were also negative. Overall, 97% of antinucleocapsid-antibody–positive specimens were also antispike-antibody positive. Female sex, age >70 years, and nonsevere clinical presentation were independently associated with faster IgG antinucleocapsid titer decay in multivariable analysis. After adjustment for sex and age >70 years, nonsevere clinical presentation was the only factor associated with faster decay of IgG antispike antibodies.

Conclusions This study characterizes evolution of the SARS-CoV-2 antibody response in patients on hemodialysis and identifies factors that are associated with lack of seroconversion and with IgG titer decay.

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Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, is associated with a severe risk of mortality in patients on hemodialysis.[1,2] The humoral response against SARS-CoV-2 in the hemodialysis population, including its dynamics over time, remains poorly understood.[3,4] Given the pandemic's ongoing waves of new infections and the need for future vaccination strategies, the characterization of this response appears to be an important unmet need. In this study, we analyzed the initial and long-term humoral response against SARS-CoV-2 in a hemodialysis population.

METHODS

In this multicenter study, the study population included 83 patients undergoing hemodialysis in the Paris, France, area who had recovered from COVID-19; 76 patients were previously described.[2]

Clinical data were retrospectively recorded. A severe form of COVID-19 was defined by the need for oxygen therapy. Immunocompromised status was characterized by one of the following factors: former organ transplant, HIV infection, recent (within <6 months) immunosuppressive therapy, or chemotherapy.

We collected 241 sequential serum samples, which were analyzed with the

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Abbot SARS-CoV-2 IgG Architect system (targeting the nucleocapsid antigen). Of the 83 participants, 25 had two serial measurements of IgG levels, and 52 had at least three serial measurements. We used the Ortho Clinical Diagnostics Vitros IgG assay (targeting the spike antigen) to analyze 113 samples.

Data collection was declared to the French Commission Nationale de l'Informatique et des Libertés, registration 2218583. This protocol was submitted to the approbation of Paris Centre Institutional Review Board.

Statistical Analyses

Categorical and continuous variables were expressed as count (percentage) and median (interquartile range, IQR), respectively. When appropriate, chi-squared or Fisher's exact tests were used for categorical comparison, and *t* test or Mann–Whitney for continuous variables.

Variables associated with seroconversion were analyzed by logistic regression. All variables with a P value <0.2 in univariable analysis were included in the multivariable analysis. Stepwise backward selection on the basis of the Akaike information criterion was then used for the final multivariable model. In the subset of patients who experienced seroconversion, we modeled the SARS-CoV-2 antibody decay with random-intercept linear models to account for intrasubject correlations. Antibody titers were $\log_{10}$ transformed to estimate the evolution of geometric mean titers after their peaks were reached, and factors associated with their decrease were identified by testing the interaction between time and patients' characteristics.

Results were analyzed with GraphPad Prism software version 9.0.0 and R software version 4.0.3.

RESULTS

We retrospectively studied SARS-CoV-2 serologic assay findings in 83 patients who received in-center hemodialysis at five different centers in the Paris area, and who were still alive after their diagnosis with COVID-19 in March 2020. Baseline patient characteristics are described in Supplemental Tables 1 and 2.

The first serologic evaluation was performed a median of 67 (IQR 39) days after COVID-19 diagnosis. Among the 83 patients, 74 (89%) had positive SARS-CoV-2 IgG antinucleocapsid or antispike serology (Figure 1A). Nine patients had negative initial IgG serology on the basis of the antinucleocapsid assay at a median of 51 (IQR 32.5) days postdiagnosis; sera from six of these nine patients were also tested for antispike antibodies, which were similarly negative. Detailed characteristics of these patients are provided in Supplemental Table 3.

We found no association between the absence of IgG response and initial disease severity, but glomerular diseases and immunosuppression were more frequent among patients who did not exhibit a SARS-CoV-2 antibody response (Supplemental Table 2). We observed similar results after excluding patients without PCR-confirmed diagnosis (Supplemental Table 4).

By multivariable analysis, an immunocompromised status was the only factor significantly associated with the absence of IgG antinucleocapsid antibody response (odds ratio, 13.8; 95% confidence interval [95% CI], 2.76 to 69.13; $P=0.001$) (Supplemental Table 5).

Follow-up until month 6 was available for 65 patients (78%). In 60 of these patients with positive initial antinucleocapsid serology, 15 (25%) had an antinucleocapsid antibody level below the limit of positivity (index ratio <1.4). Among these 15 patients, 13 (87%) had an index ratio between 0.5 and 1.4, and two (13%) had an index ratio <0.49 (Figure 1A). Only a low initial SARS-CoV-2 antibody value was associated with long-term negative antinucleocapsid antibody level (7.1; IQR, 2.3 versus 3.44; IQR, 1.6; $P<0.0001$) (Supplemental Table 6). Of the 15 sera samples with antinucleocapsid antibody level below the limit of positivity, 14 were tested for antispike antibodies, and three of the 14 (21%) were also negative with this assay (Figure 2).

Significance Statement

The humoral response over time against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is poorly understood. The authors investigated the long-term kinetics of the antibody response to SARS-CoV-2 (specifically, IgG against nucleocapsid and spike antigens), in 83 patients on in-center hemodialysis who recovered from coronavirus disease 2019 (COVID-19). They found that 10% of patients had no initial seroconversion, which was associated with immunocompromised status; in patients with seroconversion, IgG antibodies decayed over time. Factors associated with this decline included older age, female sex, and nonsevere clinical presentation. About 25% of patients had negative IgG antinucleocapsid serology after 6 months, whereas most patients maintained antispike antibodies. By characterizing the evolution of the SARS-CoV-2 antibody response, these findings might help better define future therapeutic and preventive approaches against COVID-19 in patients on hemodialysis.

The estimated slope of IgG antinucleocapsid titer weekly decrease was $-0.022\ \log_{10}$ (95% CI, -0.03 to -0.02), meaning the geometric mean titer decreased weekly by 4.9% (95% CI, 4.1 to 5.7). Female sex ($-0.0081\ \log_{10}$; 95% CI, -0.00026 to -0.016; $P=0.05$), age >70 years ($-0.0091\ \log_{10}$; 95% CI, -0.017 to -0.0018; $P=0.02$), and nonsevere clinical presentation ($-0.014\ \log_{10}$; 95% CI, -0.0069 to -0.021; $P=<0.001$) were independently associated with a faster IgG antinucleocapsid titer decay in multivariable analysis (Figure 1B). Regarding antispike assay, all 74 antinucleocapsid-positive specimens were also antispike positive, except for two (3%) patients, who repeatedly tested negative for antispike antibodies despite being positive for antinucleocapsid antibodies. The estimated slope of the antispike IgG titer weekly decrease was $-0.0080\ \log_{10}$ (95% CI, -0.011 to -0.0045), meaning the geometric mean titer decreased weekly by 1.8% (95% CI, 1.0 to 2.6). After adjustment for sex and age >70 years, non-severe clinical presentation was the only factor associated with a steeper decay ($-0.0082\ \log_{10}$; 95% CI, -0.015 to -0.0015; $P=0.02$).

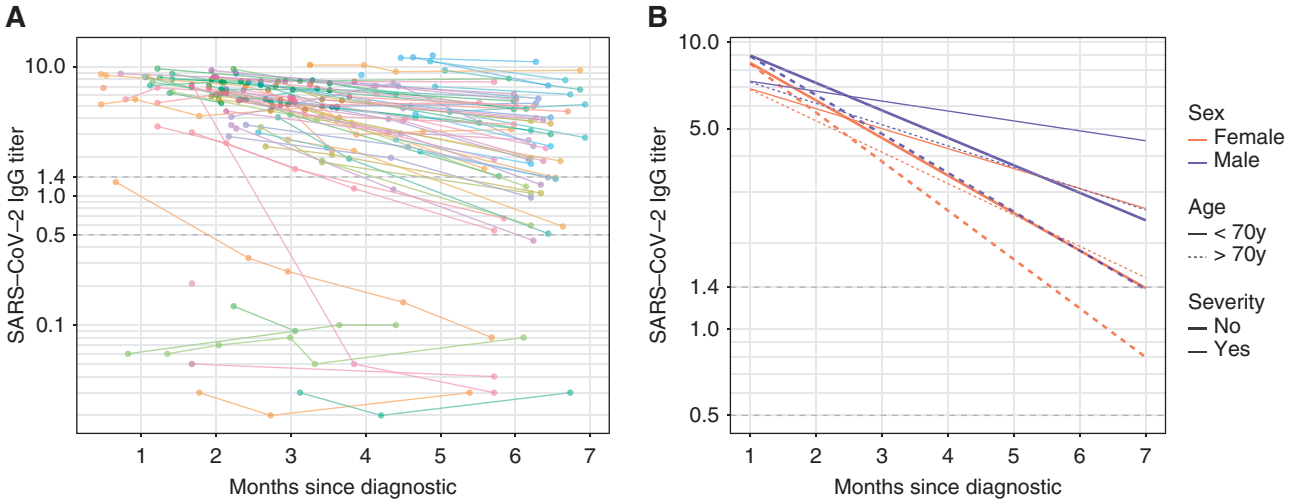

Figure 1. Evolution of SARS-CoV-2 IgG antinucleocapsid (NC) antibody titer until 6 months after diagnosis. (A) Evolution of SARS-CoV-2 IgG titer for each patient over time (spaghetti plot). Cutoff for negative serology was defined according to the manufacturer (Index sample/control <1.4: dashed line). The zone between the dashed lines (1.4 and 0.5) represents the equivocal zone. The *y*-axis is plotted in logarithmic scale. (B) Predicted SARS-CoV-2 antibody decay according to age, sex, and disease severity (multivariable model). Cutoff for negative serology: index sample/control <1.4; dashed line. The zone between the dashed lines (1.4 and 0.5) represents the equivocal zone.

DISCUSSION

In this study, we describe the 6-month kinetics of IgG antibody response against SARS-CoV-2 in patients on hemodialysis. On the basis of assay findings for antinucleocapsid and antispike antibodies, we observed a lack of seroconversion in 10% of patients, as previously suggested in the general population and in rare patients on hemodialysis.[4] Interestingly, we show that lack of seroconversion was associated with immunocompromised status, as previously suggested,[3] which may explain the frequency of patients with glomerular disease in this group. Whether immunosuppression also affects seroconversion in patients not on dialysis remains to be studied. Interestingly, a lack of seroconversion was observed in 7.9%–33% of patients (depending on the assay) of a recent cohort of patients who had undergone kidney transplant.[5]

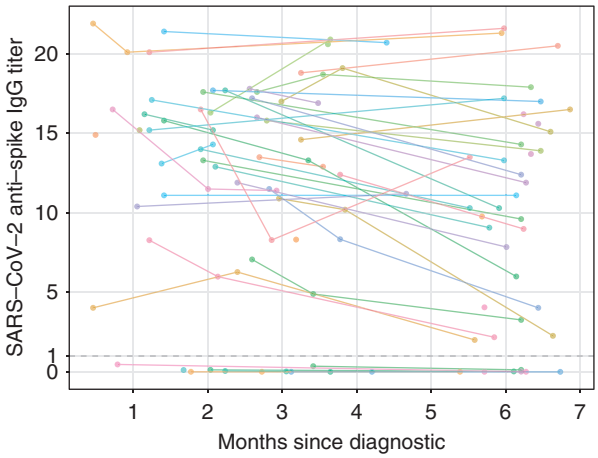

Figure 2. Evolution of SARS-CoV-2 IgG antispike antibody titers until 6 months after diagnosis. Evolution of SARS-CoV-2 IgG titer for each patient over time (spaghetti plot). Cutoff for negative serology was defined according to the manufacturer (Index S/C <1: dashed line).

Long-term evolution in anti–SARS-CoV-2 antibodies is still a matter of debate, although virus-specific IgG decline seems to occur in most individuals.[6,7] In our study, the antibody response of patients on hemodialysis seems similar to that of previously reported healthy individuals. Our models suggest IgG decline continues over time and is independently associated with female sex, nonsevere disease, and older age. Whether this decline is also associated with loss of neutralizing antibodies or cellular response to SARS-CoV-2 will require further study.[7] Of note, this IgG decline leads to antinucleocapsid antibody titers below the cutoff value in 25% of patients 6 months after diagnosis, although most patients had levels in the gray zone (signal to cutoff ratio between 0.5 and 1.4, Figure 1A) and maintain antispike antibodies.

This retrospective study has some limitations. Lack of seroconversion in patients who are RT-PCR negative should be interpreted with caution, although reported RT-PCR sensitivity is approximately 80% in the hemodialysis population.[3] In addition, our findings

would have been enriched by the use of different serologic assays, earlier in disease evolution (notably in patients who did not survive), by evaluating different antibody subclasses and characterizing cellular immunity, which is not necessarily parallel to the humoral response.

However, this characterization of the evolution of the SARS-CoV-2 antibody response in patients on hemodialysis, and the identification of factors associated with lack of seroconversion and with IgG titer decay, might help to better define future therapeutic and preventive approaches, including vaccination strategies.

DISCLOSURES

K. El Karoui reports receiving research funding from Amgen, Otsuka, and Sanofi, and honoraria from Alexion and Otsuka. S. Fourati reports receiving honoraria from Abbott Diagnostics. All remaining authors have nothing to disclose.

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SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2020111618/-/DCSupplemental.

Supplemental Table 1. Clinical and biological presentation of patients at diagnosis.

Supplemental Table 2. Clinical characteristics of patients according to SARS-CoV-2 IgG antinucleocapsid response.

Supplemental Table 3. Detailed characteristics of patients with absence of SARS-CoV-2 IgG antinucleocapsid response.

Supplemental Table 4. Clinical characteristics of patients with RT-PCR confirmed diagnosis, according to their initial SARS-CoV-2 IgG antinucleocapsid antibody response.

Supplemental Table 5. Multivariable analysis of factors associated with the absence of initial SARS-CoV-2 IgG antinucleocapsid antibody response.

Supplemental Table 6. Patient characteristics according to their long-term SARS-CoV-2 IgG antinucleocapsid antibody response.

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Supplemental data

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Supplemental Table 5. Patient characteristics according to their long-term SARS-CoV-2 IgG anti-NC antibody response

Supplemental Table 6. Clinical and biological presentation of patients at diagnosis

Supplemental Figure 1: Evolution of SARS-CoV-2 IgG anti-spike antibody titers until 6 months after diagnosis

Supplemental Table 1. Clinical characteristics of patients according to SARS-CoV-2 IgG anti-NC response

VARIABLE	ALL PATIENTS N = 83	SEROPOS. N = 74	SERONEG. N = 9	P VALUE
Age (years), median (IQR)	65 (19.5)	64 (19.5)	66 (22)	0.274
Male, n (%)	59 (71)	54 (73)	5 (56)	0.427
Cause of nephropathy				**0.002**
Diabetes and/or vascular nephropathy, n (%)	55 (66)	52 (70)	3 (33)	-
Glomerular disease, n (%)	16 (19)	10 (14)	6 (67)	-
Other, n (%)	12 (14)	12 (16)	0 (0)	-
Time from dialysis initiation (years), median (IQR)	3 (3.8)	3 (3.9)	2 (4.1)	0.584
Comorbidities				
Diabetes mellitus, n (%)	40 (48)	37 (50)	3 (33)	0.485
Hypertension, n (%)	79 (95)	71 (96)	8 (89)	0.374
BMI >25 kg/m^2, n (%)	40/76 (52)	37/68 (54)	3/8 (38)	0.465
Coronary disease, n (%)	21 (25)	17 (23)	4 (44)	0.221
Peripheral artery disease n (%)	28 (34)	24 (32)	4 (44)	0.483
Chronic heart failure	7 (8)	5 (6)	2 (22)	0.165
COPD/asthma	5 (6)	5 (6)	0 (0)	>0.999
Cirrhosis, n (%)	2 (2)	2 (2)	0 (0)	0.569
Cancer, n (%)	5 (6)	5 (7)	0 (0)	0.873
Auto-immune disease, n (%)	6 (7)	2 (3)	4 (44)	**0.001**
Immunocompromised, n (%)	16 (19)	10 (17)	6 (67)	**0.001**
Former kidney transplantation, n (%)	6 (7)	5 (6)	1 (11)	0.509
Other organ transplantation, n (%)	1 (11)	1 (13)	0 (0)	>0.999
Immunosuppressive treatment, n (%)	11 (13)	7 (9)	4 (44)	**0.016**
HIV, n (%)	4 (4)	3 (4)	1 (11)	0.374
RAS inhibitor, n (%)	41 (49)	38 (51)	3 (33)	0.483
ACE inhibitor, n (%)	16 (19)	14 (18)	2 (22)	<0.999
ARB, n (%)	25 (30)	24 (33)	1 (11)	0.264
Characteristics				
Clinical presentation				
Asymptomatic, n (%)	12 (14)	10 (14)	2 (22)	0.612
Mild presentation, n (%)	43 (52)	39 (53)	4 (44)	0.732
Severe presentation, n (%)	28 (34)	25 (34)	3 (33)	>0.999
Hospitalized, n (%)	41 (49)	36 (49)	5 (56)	0,696
Ct-scan (>50% lesions), n (%)	10/37 (26)	9/33 (27)	1/4 (25)	>0.999
RT-PCR diagnosis, n (%)	64/80 (80)	59/71 (83)	5/9 (56)	0.073
First SARS-CoV-2 IgG: value (Index S/C), median (IQR)	5.8 (4.56)	6.5 (3.84)	0.06 (0.14)	<0.0001
Time from diagnosis (days), median (IQR)	67 (39)	68 (41.5)	51 (32.5)	0.11

Specific therapy				
Hydrochloroquine, n (%)	2 (2.5)	2 (2.82)	0 (0)	>0.999
Macrolides, n (%)	14 (16.8)	13 (17.6)	1 (11.1)	>0.999
Convalescent plasma, n (%)	0 (0)	0 (0)	0 (0)	-

Severe or mild presentation was defined according to the need of oxygen therapy. ACE: angiotensin converting enzyme, ARB: angiotensin receptor blocker, COPD: chronic obstructive pulmonary disease, HIV: human immunodeficiency virus, RAS: renin angiotensin system

Supplemental table 2. Detailed characteristics of patients with absence of SARS-CoV-2 IgG anti-NC response

PAT.	AGE	SEX	CAUSE OF NEPHROPATHY	TIME FROM DIALYSIS INITIATION (YEARS)	CV RISK FACTOR	VASCU. DISEASE	ORGAN DYSF.	OTHER	IS THERAPY	DIAGNOSIS	SYMPTOMS	CT-scan	HOSPIT.	O_2 THERAPY
P1	63	M	ANCA vasculitis nephropathy	<1	HT ; DM ; smoker ; OW	Y	-	ANCA vasculitis	Steroid ; Cylcophosphamide	CT-scan	Cough, anosmia, agueusia	severe	Y	Y
P2	66	F	AA amyloidosis	1	HT ; OW	N	-	Rheumatoid arthritis with amyoidosis	Steroid	RT-qPCR	Cough, Fever	moderate	Y	Y
P3	91	M	Vascular	2	HT ; smoker	Y	CHF	-	-	CT-scan	Fever, Dyspnea	mild	Y	Y
P4	74	F	FSGS	1	HT ; DM ; OW	N	-	HIV	-	RT-qPCR	cough	-	N	N
P5	69	M	Diabetic & vascular nephropathy	9	HT ; DM ; smoker	Y	-	-	-	RT-qPCR	UK	-	Y	N
P6	72	F	ANCA vasculitis nephropathy	5	HT	N	-	ANCA vasculitis	MMF	CT-scan	Cough, , Fever	-	Y	Y
P7	28	M	FSGS	<1	-	N	CHF ; COPD	HLH	Steroid ; Etoposide	RT-qPCR	UK		N	N
P8	48	M	Glomerular disease	4	HT	N	-	-	-	RT-qPCR	No symptoms	-	N	N
P9	50	F	Glomerular disease	9	HT	Y	-	-	-	CT-scan	No symptoms	Mild	N	N

PAT. : patient; FSGS : Focal and segmental glomerulosclerosis; HT : Hypertension; DM : Diabetes mellitus ; OW :overweight ; CHF : chronic heart failure ; Vasc: vascular ; Dysf. : dysfunction ;HLH: hemophagocytic lymphohistiocytosis; IS :Immunosuppressive ; O_2 : Oxygen therapy; Y : yes ; N = : No COPD: chronic obstructive pulmonary disease

Supplemental table 3. Clinical characteristics of patients with RT-PCR confirmed diagnosis, according to their initial SARS-CoV-2 IgG anti-NC antibody response

VARIABLE	ALL PATIENTS N = 64	SEROPOS. N = 59	SERONEG. N = 5	P VALUE
Age (years), median (IQR)	65 (21)	65 (22)	66 (33.5)	0.563
Male, n (%)	49 (78)	46 (78)	3 (60)	0.583
Cause of nephropathy				0.093
Diabetes and/or vascular nephropathy, n (%)	41 (64)	39 (66)	2 (40)	-
Glomerular disease, n (%)	12 (19)	9 (15)	3 (60)	-
Other, n (%)	11 (17)	11 (19)	0 (0)	-
Time from dialysis initiation (years), median (IQR)	3 (4)	3 (4.1)	1.2 (2.2)	0.07
Comorbidities				
Diabetes mellitus, n (%)	32 (50)	30 (51)	2 (40)	>0.999
Hypertension, n (%)	61 (95)	57 (97)	4 (80)	0.220
BMI >25 kg/m^2, n (%)	31/58 (53)	29/53 (55)	2/5 (40)	0.656
Coronary disease, n (%)	15 (23)	14 (24)	1 (20)	>0.999
Peripheral artery disease, n (%)	22 (34)	21 (36)	1 (20)	0.652
Chronic heart failure	6 (9)	5 (8)	1 (20)	0.399
COPD/asthma	5 (8)	5 (8)	0 (0)	>0.999
Cirrhosis, n (%)	2 (3)	2 (3)	0 (0)	>0.999
Cancer, n (%)	4 (6)	4 (7)	0 (0)	>0.999
Auto-immune disease, n (%)	4 (6)	2 (3)	2 (40)	**0.028**
Immunocompromised, n (%)	12 (19)	9 (15)	3 (60)	**0.042**
Former kidney transplantation, n (%)	4 (6)	4 (7)	0 (0)	>0.999
Other organ transplantation, n (%)	1 (2)	1 (2)	0 (0)	>0.999
Immunosuppressive treatment, n (%)	9 (14)	7 (12)	2 (40)	0.141
HIV, n (%)	4 (6,)	3 (5)	1 (20)	0.284
RAS inhibitor, n (%)	31 (48)	29 (49)	2 (40)	>0.999
ACE inhibitor, n (%)	11 (17)	10 (17)	1 (20)	>0.999
ARBS, n (%)	20 (32)	19 (33)	1 (20)	>0.999
Characteristics, n (%)				
Clinical presentation				
Asymptomatic, n (%)	8 (13)	7 (12)	1 (20)	0.499
Mild, n (%)	33 (52)	30 (51)	3 (60)	>0.999
Severe, n (%)	23 (36)	22 (37)	1 (20)	0.646
Hospitalized, n (%)	34 (53)	32 (54)	2 (40)	0.659

Severe or mild presentation was defined according to the need of oxygen therapy. ACE: angiotensin converting enzyme, ARB: angiotensin receptor blocker, COPD: chronic obstructive pulmonary disease, HIV: human immunodeficiency virus, RAS: renin angiotensin system

Supplemental Table 4. Multivariable analysis of factors associated with the absence of initial SARS-CoV-2 IgG anti-NC antibody response

VARIABLE	OR (95%CI)	P VALUE
Chronic heart failure		
No	Ref.	
Yes	7.551 (0.920-61.966)	0.060
Immunocompromised status		
No	Ref.	
Yes	**13.8 (2.763-69.126)**	**0.001**

Supplemental Table 5. Patient characteristics according to their long-term SARS-CoV-2 IgG anti-NC antibody response

VARIABLE	ALL PATIENTS N = 60	SEROPOS. N = 45	SERONEG. N = 15	P VALUE
Age (years), median (IQR)	63 (18)	63 (15)	63 (20)	0.925
Male, n (%)	43 (72)	34 (76)	9 (60)	0.324
Cause of nephropathy				
Diabetes and/or vascular nephropathy, n (%)	43 (72)	31 (68)	12 (80)	0.806
Glomerular disease, n (%)	9 (15)	7 (16)	2 (13)	-
Other, n (%)	8 (13)	7 (16)	1 (7)	-
Time from dialysis initiation (years), median (IQR)	3 (3.3)	3.3 (3.2)	2.1 (3.4)	0.522
Comorbidities				
Diabetes mellitus, n (%)	30 (50)	21 (47)	9 (60)	0.371
Hypertension, n (%)	59 (98)	44 (97)	15 (100)	>0.999
BMI >25 kg/m^2, n(%)	32 (59)	24 (57)	8 (60)	>0.999
Coronary disease, n (%)	12 (20)	9 (20)	3 (20)	>0.999
Peripheral artery disease n (%)	18 (31)	11 (24)	7 (47)	0.192
Chronic heart failure	3 (5)	3 (7)	0 (0)	0.566
COPD/asthma	3 (5)	2 (4)	1 (7)	>0.999
Cirrhosis, n (%)	2 (3)	1 (2)	1 (7)	>0.999
Cancer, n (%)	4 (6)	3 (7)	1 (7)	>0.999
Auto-immune disease, n (%)	1 (1)	1 (2)	0 (0)	>0.999
Immunocompromised, n (%)	7 (12)	4 (9)	3 (20)	0.351
Former kidney transplantation, n (%)	3 (5)	1 (2)	2 (13)	0.151
Other organ transplantation, n (%)	1 (11)	1 (13)	0 (0)	>0.999
Immunosuppressive treatment, n (%)	4 (7)	3 (7)	1 (7)	>0.999
HIV, n (%)	3 (5)	2 (4)	1 (7)	>0.999
RAS inhibitor, n (%)	34 (57)	26 (58)	8 (53)	0.764
ACE inhibitor, n (%)	12 (20)	8 (17)	4 (27)	0.479
ARB, n (%)	22 (37)	18 (41)	4 (27)	0.325
Characteristics				
Clinical presentation				
Asymptomatic, n (%)	9 (15)	6 (13)	3 (20)	0.678
Mild, n (%)	33 (55)	24 (53)	9 (53)	0.768
Severe, n (%)	18 (30)	15 (33)	3 (20)	0.517
Hospitalized, n (%)	26 (43)	21 (47)	5 (33)	0.367
IgG pic value (Index S/C), median (IQR)	6.7 (3.8)	7.1 (2.3)	3.44 (1.6)	**<0.0001**
Time from diagnosis(days), median (IQR)	70.5 (54)	71 (68)	70 (35)	0.323
Last follow up				
IgG value (Index S/C), at last Fup, median (IQR)	3.240 (3.79)	4.02 (3.05)	0.97 (0.68)	**<0.0001**
Time from diagnosis (days), median (IQR)	189.5 (14.8)	189 (15)	190 (9)	0.764

Severe or mild presentation was defined according to the need of oxygen therapy. ACE: angiotensin converting enzyme, ARB: angiotensin receptor blocker, COPD: chronic obstructive pulmonary disease, HIV: human immunodeficiency virus, RAS: renin angiotensin system, Fup : Follow up

Supplemental Table 6. Clinical and biological presentation of patients at diagnosis

	ALL PATIENTS N = 83
Clinical presentation	
Asymptomatic, n (%)	12 (14.4)
Fever, n (%)	39 (46.9)
Dyspnea, n (%)	16 (19.2)
Fatigue, n (%)	31 (37.3)
Flu-like symptoms, n (%)	36 (43.3)
Diarrhea, n (%)	12 (14.4)
Anosmia, n (%)	2 (2.40)
Time from symptoms onset (days), median (IQR)	2 (4.5)
Biological presentation	
C-reactive protein (g/l), median (IQR)	57.5 (106.9)
Procalcitonin (ng/ml), median (IQR)	1.3 (2.2)
Hemoglobin (g/dl), median (IQR)	10.25 (2.3)
Leucocytes (G/l), median (IQR)	4.7 (3)
Lymphocytes (G/l), median (IQR)	0.796 (0.71)
Severity assessment	
Oxygen therapy, n (%)	28 (34)
Hospitalization, n (%)	41 (49)