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Monitoring strategy of COVID-19 vaccination in dialysis patients based on a multiplex immunodot method: The CovidDial study

Frédéric Debelle[1,2] | Vo Thanh Phuong Nguyen[3] | Laurence Boitquin[3] | Miguel-Ange Guillen-Anaya[1] | Fabrice Gankam[1] | Anne-Emilie Declèves[2] | on behalf of the CoviDial study group

[1]Department of Nephrology and Dialysis, CH EpiCURA, Baudour, Belgium

[2]Department of Metabolic and Molecular Biochemistry, Research Institute for Health Sciences and Technology, University of Mons, Mons, Belgium

[3]Laboratory of Clinical Biology, CH EpiCURA, Hornu, Belgium

Correspondence
Dr Frédéric Debelle, Department of Nephrology and Dialysis, CH EpiCURA Baudour, Rue Louis Caty 136, 7331 Baudour, Belgium.
Email: frederic.debelle@epicura.be

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Abstract

Introduction: COVID-19 vaccine was demonstrated to be effective in dialysis patients, but boosters are mandatory due to a rapid waning of anti-spike antibodies. A vaccination strategy based on immunologic response might be useful to maintain a favorable risk–benefit balance in this vulnerable population. **Methods:** CoviDial is an observational prospective study enrolling 121 dialysis patients to receive a 3-dose mRNA-1273 vaccine according to a uniform schedule. At baseline, months 1, 3, 6, 9, and 12, anti-spike antibodies against four epitopes (S1, S2, ECD-S1 + S2, RBD) were monitored with a multiplex immunodot enzymatic assay. Potential correlation between initial serologic response and subsequent COVID-19 infection was then assessed. **Results:** Overall, 96.2% and 96.8% of patients had anti-RBD antibodies at 3 and 12 months, respectively. All antibodies titers significantly decreased at month 6 compared to month 3. Booster vaccine induced a robust serologic response at month 9, but with a waning 3 months later, particularly for anti-S2 (37.2 ± 3.3 vs. 61.3 ± 3.0, $p < 0.0001$) and anti-S1 + S2 antibodies (68.4 ± 3.3 vs. 88.4 ± 2.3, $p = 0.0015$). Fifteen patients were later tested positive for SARS-CoV-2. At month 3, mean titers of anti-RBD, anti-S1 + S2, and anti-S2 antibodies were lower in the subsequent SARS-CoV-2 infected cohort (71.57 ± 9.01 vs. 85.79 ± 2.61, $p = 0.0131$; 41.07 ± 7.96 vs. 61.68 ± 3.56, $p = 0.0237$; 13.79 ± 5.03 vs. 39.70 ± 3.86, $p = 0.0096$; respectively). **Conclusion:** Three doses of mRNA-1273 vaccine induce a robust but time-limited immunologic response in dialysis patients. Lower anti-spike antibodies titers after initial vaccination are associated with a higher risk to subsequently contract SARS-CoV-2, even beyond 6 months.

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) is a dramatic medical condition leading to high rates of hospitalization and death, especially in

Collaborators of the CoviDial study group: EpiCURA, Ath, Belgium: Fabrice Gankam, Ahmed Goubella, Olivier Mat. EpiCURA, Baudour, Belgium: Frédéric Debelle, Lidia Ghisdal, Maria Garjau. EpiCURA, Hornu, Belgium: Assma Ballout, Guy Fomegne, Miguel-Ange Guillen-Anaya.

dialysis patients, with a 28-day related mortality of 25%.[1] When multiple severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines were put on the market in early 2021, vaccination program in high-risk populations including end-stage kidney disease (ESKD) patients became a priority for healthcare authorities in many countries.[2] As recommended by the manufacturers, a second dose of mRNA-based vaccines was mandatory 3 (BNT162b2 vaccine) or 4 weeks (mRNA-1273 vaccine) after the first injection to strengthen the humoral protection.[3]

Based on the experience with influenza and hepatitis B vaccines,[4,5] there was concern about the SARS-CoV-2 vaccine effectiveness in ESKD patients since their innate and adaptative immune responses are compromised. This assumption was confirmed in a study showing an insufficient humoral protection with a lower seroconversion rate and a faster waning of antibodies titers when compared to a healthy cohort.[6] Therefore, additional vaccine doses (boosters) were strongly recommended for at-risk populations, without taking into account the circulating anti-spike (S) antibodies levels.[2]

Nevertheless, functional assays revealed that neutralizing anti-S antibodies levels were highly correlated with clinical protection from SARS-CoV-2 infection in healthy participants.[7] In addition, the emergence of variants with numerous spike protein mutations results in a lower efficiency of vaccines[8] along with the humoral immunity waning that significantly increases the risk of COVID-19 related hospitalization or death.[9] This suggests that a reliable follow-up of immunologic response after vaccination is required, and particularly to maintain a favorable risk–benefit balance in vulnerable population.

Therefore, to further refining the vaccine strategy based on individual serological responses to SARS-CoV-2 vaccination, we prospectively monitored four different anti-spike antibodies titers in patients receiving maintenance dialysis. The secondary objective consisted in determining potential correlation between the anti-spike antibodies levels induced by the initial two-dose vaccination regimen and the risk of subsequent COVID-19 infection in dialysis patients.

2 | MATERIALS AND METHODS

2.1 | Study design

The CoviDial study is a 1-year observational prospective study including patients on hemodialysis or peritoneal dialysis who received three doses of mRNA-1273 vaccine (Spikevax® Moderna) for prevention of COVID-19 (Figure S1). The protocol was specifically designed to monitor SARS-CoV-2 antibodies against the nucleocapsid protein (N) and four epitopes of the spike protein (S1, S2, Ectodomain S1 + S2 and Receptor Binding Domain) by using the multiplex D-tek COVIDOT 5 IgG immunodot assay during the vaccination period. In parallel, patients were tested for anti-nucleocapsid and anti-spike IgG antibodies with the clinically available Elecsys® Anti-SARS-CoV-2 immunoassay (Roche®). According to the Belgian health authorities' recommendation for the COVID-19 vaccination schedule in the dialysis population, we started the immunization within our three dialysis units (CH EpiCURA, Ath, Baudour and Hornu, Belgium) in mid-March 2021. A second dose and a third dose of vaccine were administrated in mid-April and in mid-October 2021, respectively. The CoviDial study was conducted following the ethical principles of the Declaration of Helsinki and approved by the central ethical committee of CUB Erasme (Brussels, Belgium) as well as our local ethical committee (CH EpiCURA, Baudour, Belgium) on February 4, 2021 (CCB B4062021000037).

2.2 | Study population

Patients aged >18 years, admitted for chronic dialysis (hemodialysis or peritoneal dialysis) in our three dialysis units and able to give informed consent, were eligible to participate in the CoviDial study. The demographic and clinical data, dialysis-specific parameters, medical comorbidities, COVID-19 infection status, information about medications, laboratory findings, and humoral response against SARS-CoV-2 were recorded at baseline. Patients were reassessed after 1 month (just before the second injection of the vaccine), 3, 6, 9 (before the 3rd injection of the vaccine), and 12 months (Figure S1).

2.3 | Multiplex immunodot enzymatic immunoassay (COVIDOT) for SARS-CoV-2 antibodies detection

At different time points, a serum sample was collected by using a standardized operating procedure and immediately sent to our central lab. The BlueDiver COVIDOT 5 IgG (Alphadia D-tek, Mons, Belgium), a commercially available CE-marked enzyme immunoassay, was used for the semiquantitative detection of IgG antibodies against five main epitopes of the SARS-CoV-2: the nucleocapsid protein (N), the spike (S) protein (ECD, ectodomain, S1 + S2), the S1 subunit of the S-protein, the S2 subunit of the S-protein, and the receptor-binding domain (RBD) of the S1 subunit. The results are expressed as arbitrary units (AU) and range from 0 [negative result] to 100 [high positive result], depending on the color intensity of the enzymatic reaction. Based on a previous study testing the performance of this assay, values ≥10 AU were considered as positive, between 5 to 9 AU as equivocal, and <5 AU as negative.[10] Details about the technique as well as its clinical specificity and sensitivity are published elsewhere.[10]

2.4 | Electrochemiluminescence immunoassay (ECLIA) for SARS-CoV-2 antibodies detection

The Elecsys® Anti-SARS-CoV-2 method (Roche®) which was performed in clinical routine for anti-nucleocapsid and anti-S protein RBD antibodies determination, was used as a comparator. The technique is based on a double-antigen sandwich assay format with a quantification by electrochemiluminescence technique (ECLIA). For

the anti-nucleocapsid antibody assay, a cut-off index ≥1 E/S was considered as positive with a clinical sensitivity of 99.5% (95% confidence interval [CI]: 97%–100%) and specificity of 99.8% (95% CI: 99.69%–99.88%) at 14 days post-PCR confirmation. The results of the SARS-CoV-2 spike protein receptor binding domain antibodies determination were expressed as U/mL and considered to be positive for values ≥0.8 U/mL. According to the manufacturer's product information, clinical sensitivity and specificity were 98.8% (95% CI: 98.1–99.3%) and 99.98% (95% CI: 99.91–100%), respectively.

2.5 | Statistical analysis

Demographic and clinical characteristics of patients were presented as frequencies and proportions for categorical variables. For numerical variables, we calculated the median and interquartile range (IQR) as well as the mean and standard deviation (SD) or standard error of the mean (SEM), as appropriate.

According to the variable distribution, the nonparametric one-way analysis of variance (ANOVA) Friedman test was applied to compare anti-spike antibodies titers at each time-point, followed by Dunn's multiple comparison test. We used the nonparametric Mann–Whitney test to compare anti-spike antibodies titers at month 3 between the subsequent SARS-CoV-2 infected patients versus the noninfected cohort.

All statistical analysis was performed by using GraphPad Prism version 9.5.0 for Windows (GraphPad Software, San Diego, California USA, www.graphpad.com). A p value <0.05 was considered significant.

3 | RESULTS

3.1 | Baseline demographic, clinical and pathological characteristics of the patients

From 187 screened patients, 66 patients were excluded for the following reasons: no serological evaluation available at baseline ($n = 52$), patients not yet on chronic dialysis ($n = 4$), and patients who have already received a dose of vaccine ($n = 10$). Among the 121 participants who fulfilled the inclusion criteria, 102 (84.3%) were treated with hemodialysis (Figure 1).

Male gender was predominant (59.5%) and the mean (±SD) age was 71.3 ± 12.1 years (Table 1). Diabetes, hypertension, and chronic tubulointerstitial nephritis were the causes of the primary renal disease in 22.3%, 17.4%, and 18.2% of patients, respectively. The median (IQR) dialysis vintage was 2.7 years (1.5–5.7). One hundred and five (86.8%) patients had hypertension while half of the participants had diabetes. Previous COVID-19 infection demonstrated by a positive PCR testing was found in 13 patients (10.7%). Steroids and other immunosuppressive medication were prescribed in 14 (11.6%) and nine (7.4%) patients, respectively (Table 1).

During the 12-month follow-up period, 16.5% of patients died ($n = 20$). The cause of death was from unknown origin in four patients, severe sepsis in four patients, cardiac failure in six patients, neoplasia in five patients, and following a surgical procedure in one patient (Figure 1). COVID-19 infections were diagnosed by PCR testing in 15 patients (12.4%), mostly during the time when Omicron variant was predominant in Belgium[11] (10 out of 15 cases). The symptoms were mild or absent, and no patient died.

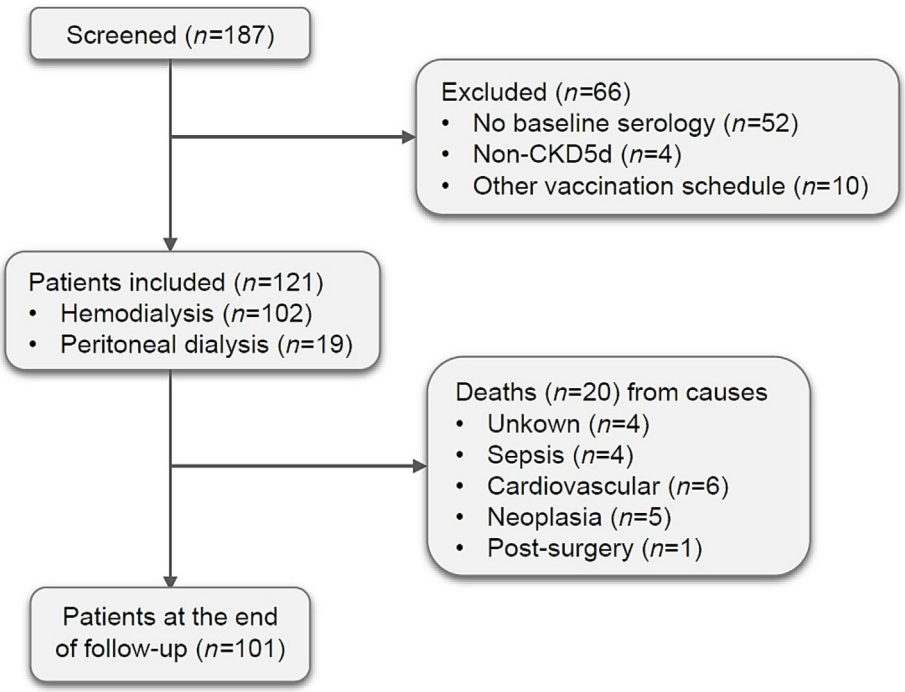

FIGURE 1 Patients flow chart.

TABLE 1 Demographic and clinical characteristics of patients ($n = 121$).

Characteristics	*n* (%)	
Demographics		
Age (years)		
Mean (SD)		71.3 (12.1)
Median (IQR)		72.4 (66.5–80.6)
Gender		
Male	72 (59.5)	
Female	49 (40.5)	
Dialysis modality		
HD/HDF	102 (84.3)	
PD	19 (15.7)	
Dialysis vintage (years)		
Mean (SD)		4.2 (4.5)
Median (IQR)		2.7 (1.5–5.7)
Primary nephropathy		
Diabetic	27 (22.3)	
Hypertensive	21 (17.4)	
Vascular	5 (4.1)	
IgA nephropathy	5 (4.1)	
Autoimmune	13 (10.7)	
ADPKD	3 (2.5)	
Tubulo-interstitial nephritis	22 (18.2)	
Other/unknown	25 (20.7)	
Medical history		
Hypertension	105 (86.8)	
Diabetes mellitus	60 (49.6)	
Obesity	47 (38.8)	
Chronic coronary syndrome	38 (31.4)	
Cerebrovascular disease	22 (18.2)	
Peripheral artery disease	20 (16.5)	
COPD	15 (12.4)	
Solid organ transplantation	6 (5.0)	
Cancer disease	27 (22.3)	
Autoimmune disease	5 (4.1)	
Previous COVID-19	13 (10.7)	
Medication		
ACEi	29 (24)	
ARB	19 (15.7)	
Antiplatelet therapy	73 (60.3)	
Vitamin K antagonist	29 (24.0)	
Steroids	14 (11.6)	
Immunosuppressive therapy	9 (7.4)	
Insulin	35 (28.9)	
Oral hypoglycemic drug	6 (5.0)	

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ADPKD, autosomal dominant polycystic disease; ARB, angiotensin-receptor blocker; COPD, chronic obstructive pulmonary disease; HD, hemodialysis; HDF, hemodiafiltration; IQR, interquartile range; PD, peritoneal dialysis; SD, standard deviation.

3.2 | Anti-SARS-CoV-2 antibodies determination at baseline

Based on the multiplex immunodot enzymatic immunoassay, 97 (80.2%) patients were seronegative for the anti-nucleocapsid antibody while 23 patients (19%) had a positive test. The remaining three patients had an equivocal result with values ranging between 5 to 9 AU. Nine of the 23 patients (39%) with a positive anti-nucleocapsid antibody test had a history of a symptomatic SARS-Cov-2 infection with a mean time interval of 5.3 ± 3.7 months [Min 0.7 – Max 11.7].

At baseline, the IgG antibodies against the RBD, the ectodomain (S1 + S2), the S1 subunit, and the S2 subunit of the S-protein were found in 21.5%, 23.1%, 19.8%, and 21.5% of patients, respectively.

3.3 | The time course of vaccine response

The anti-S protein RBD measured by the Elecsys® Anti-SARS-CoV-2 method was positive in 73.6% patients 1 month after the first vaccine injection and in 98.1% 2 months after the second dose, showing an excellent response to the mRNA-1273 vaccine. At month 6, almost all patients (99%) developed anti-RBD antibodies. Following the Belgian health authorities' recommendation for the COVID-19 vaccination, we administrated a third dose in mid-October 2021 (month 7), regardless of antibody levels. Two and 5 months later (months 9 and 12), 99% and 100% of patients had antibodies against the spike protein.

The anti-RBD antibodies detected by the multiplex immunodot technique were found in 57.9%, 96.2%, 91.8%, 97.1%, and 96.8% of patients at months 1, 3, 6, 9, and 12, respectively. Similar results were observed for the anti-S1 unit of the spike protein. The seroconversion rates were lower for the anti-S (S1 + S2, ECD) and the anti-S2 antibodies in the first months but rose to 97.1% and 95.1% by the ninth month.

3.4 | The time course of anti-SARS-CoV-2 antibodies levels

For the study of vaccination response kinetic, we analyzed the time course of anti-SAR-CoV-2 antibodies levels in 68 patients who received the three vaccine doses and for whom data were available at all time points. One month after the first vaccinal dose, the four different epitopes anti-spike antibodies levels measured by the COVIDOT assay were increased but only significantly for the anti-S1 and anti-RBD antibodies (30.4 ± 4.3 vs. 6.9 ± 2.2, $p = 0.0156$ and 38.7 ± 4.7 vs. 10.1 ± 3.0, $p = 0.0016$, respectively; Figure 2A,D). The second dose significantly boosted the immune response with approximately a two-fold increase of the mean antibodies levels 2 months later (anti-S1: 68.2 ± 3.6 vs. 30.4 ± 4.2, $p < 0.0001$; anti-S2: 32.9 ± 4.2 vs. 18.7 ± 4.4, $p < 0.001$; anti-S1 + S2: 57.0 ± 3.9 vs. 23.6 ± 4.5, $p < 0.0001$ and anti-RBD: 85.6 ± 3.0 vs. 38.7 ± 4.7, $p < 0.0001$). However, this response was not sustained over time as evidenced by the significant decrease of the four different anti-spike antibodies (anti-

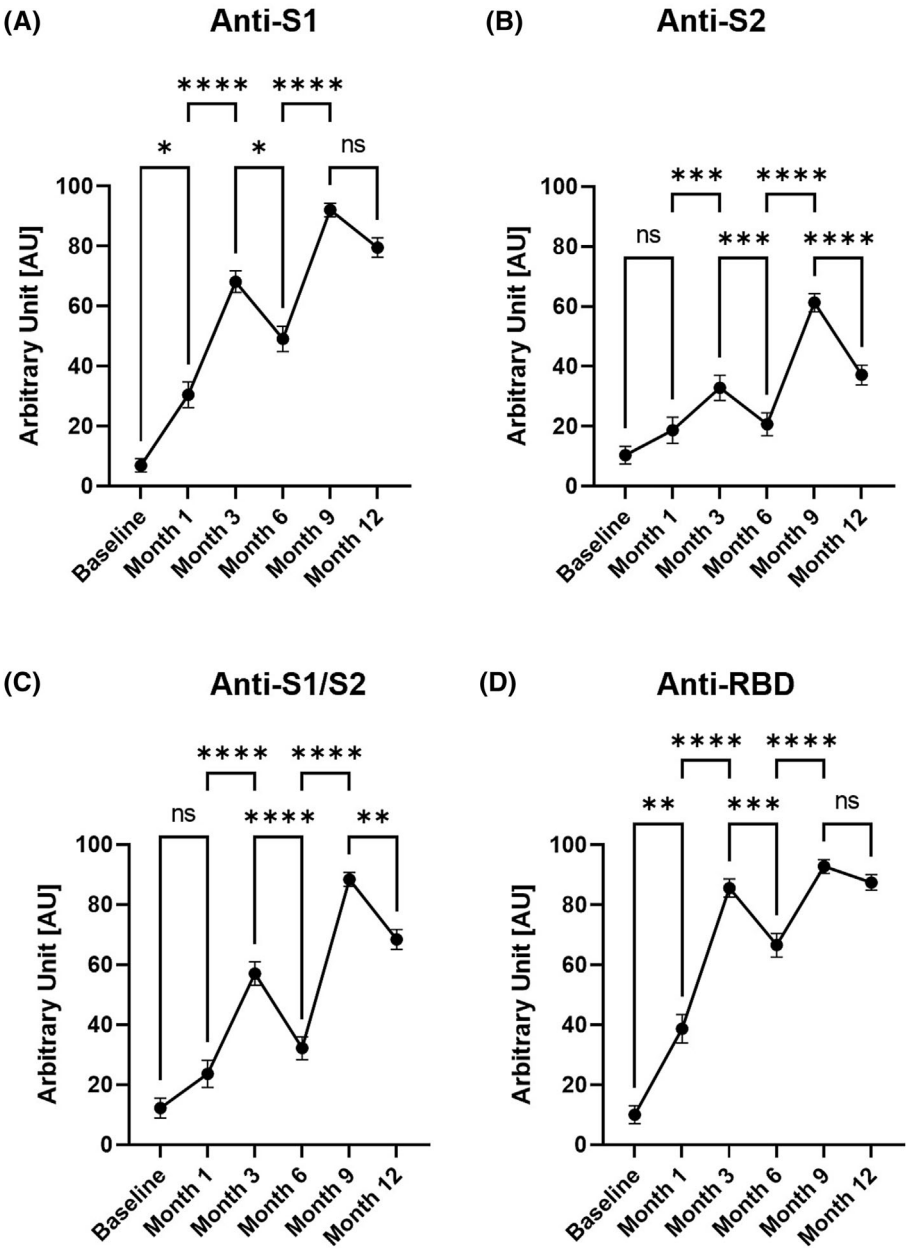

FIGURE 2 Anti-SARS-CoV-2 antibodies kinetics assessed by the multiplex immunodot enzymatic assay. IgG antibodies against (A) the S1 subunit of the S-protein, (B) the S2 subunit of the S-protein, (C) the spike protein (ECD, ectodomain, S1/S2), and (D) the receptor binding domain (RBD) of the S1 subunit. The results are expressed as mean ± SEM (arbitrary unit ranging from 0 to 100). $N = 68$. One-way ANOVA Friedman test, followed by Dunn's multiple comparison test. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$. ns = nonsignificant.

S1: 49.1 ± 4.2 vs. 68.2 ± 3.6, $p = 0.037$; anti-S2: 20.7 ± 3.8 vs. 32.9 ± 4.2, $p < 0.001$; anti-S1 + S2: 32.2 ± 3.8 vs. 57.0 ± 3.9, $p < 0.0001$ and anti-RBD: 66.6 ± 4.0 vs. 85.6 ± 3.0, $p < 0.001$) levels at month 6 (Figure 2A–D). Nevertheless, it is worth to note the anti-spike antibodies levels were still higher than in baseline.

Two months after the third dose of mRNA-1273 vaccine, the mean levels of antibodies against the four epitopes significantly increased (anti-S1: 92.1 ± 2.3 vs. 49.1 ± 4.2, $p < 0.0001$; anti-S2: 61.3 ± 3.0 vs. 20.7 ± 3.9, $p < 0.0001$; anti-S1 + S2: 88.4 ± 2.3 vs. 32.2 ± 3.8, $p < 0.0001$; and anti-RBD: 92.8 ± 2.3 vs. 66.6 ± 4.0, $p < 0.0001$). Compared to month 9, the mean antibodies levels at the end of the study decreased, most notably for the anti-S2 (37.19 ± 3.3 vs. 61.3 ± 3.0, $p < 0.0001$) and anti-S1 + S2 antibodies (68.4 ± 3.3 vs. 88.4 ± 2.3, $p = 0.0015$) (Figure 2A–D). In contrast, no significant decrease of anti-spike protein levels was found with the Elecsys® Anti-SARS-CoV-2 method (240.6 ± 4.8 vs. 241.1 ± 4.6, $p > 0.999$) (Figure 3).

3.5 | Initial vaccination response and further SARS-CoV-2 infection

Self-limited or asymptomatic COVID-19 infections were demonstrated by PCR testing in 15 patients (12.4%), the majority of which (10 subjects) occurred after January 1st, 2022, when the Omicron variant was predominant in Belgium[11] (Figure S2).

Based on the ECLI method for SARS-CoV-2 antibodies detection, a level below the upper limit of quantification (250 U/mL) was found at month 3 in 50% of patients (seven of 14, one patient died before the third month) who later tested positive for SARS-CoV-2 and 26.7% of

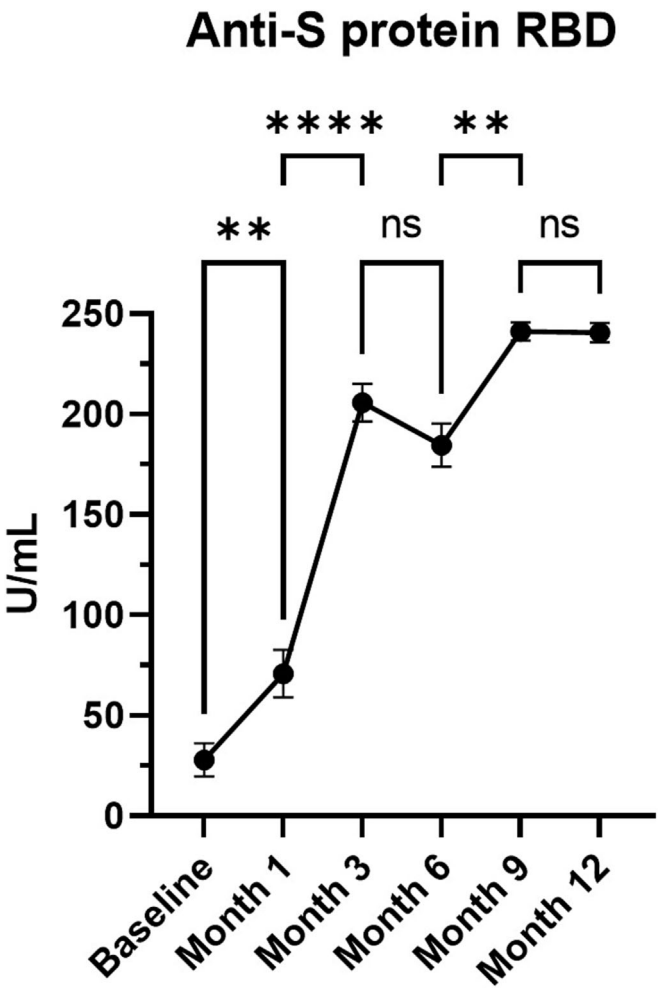

FIGURE 3 Anti-spike (S) protein receptor binding domain (RBD) kinetic assessed by the electrochemiluminescence immunoassay (ECLIA) for SARS-CoV-2 antibodies. The results are expressed as mean ± SEM (U/mL ranging from 0 to 250). $N = 74$. One-way ANOVA Friedman test, followed by Dunn's multiple comparison test. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$, ns = nonsignificant.

patients (24 of 90) considered not to be contaminated by the virus during the 1-year observational period ($p = 0.078$). As shown in the Figure 4A, the mean antibodies level at month 3 was lower in SARS-CoV-2 positive patients compared to SARS-CoV-2 negative cohort, but without being statistically significant (162.3 ± 28.9 vs. 212.4 ± 8.1, $p = 0.059$). In COVIDOT multiplex analyses (Figure 4B), the difference between the two groups was statistically significant for anti-RBD (71.57 ± 9.01 vs. 85.79 ± 2.61, $p = 0.0131$), anti-S1 + S2 (41.07 ± 7.96 vs. 61.68 ± 3.56, $p = 0.0237$), and anti-S2 (13.79 ± 5.03 vs. 39.70 ± 3.86, $p = 0.0096$), but not for the anti-S1 antibody (60.57 ± 8.27 vs. 69.70 ± 3.14, $p = 0.158$).

4 | DISCUSSION

This 1-year observational prospective study demonstrated that the mRNA-1273 anti-SARS-CoV-2 vaccine was highly effective in patients receiving maintenance dialysis with responder rates of 73.6% 1 month after the first injection and 98.1% 2 months after the second dose. A booster dose administrated systematically 5 months later lead to a humoral response in 99% and 100% of patients at months 9 and 12, respectively. Alongside the humoral response, the vaccination resulted in effective clinical protection with a very low rate of SARS-CoV-2 infection accompanied by few or no symptoms. Interestingly, patients who were subsequently infected with SARS-CoV-2 initially had an inefficient humoral response after the primary two-dose vaccine regimen with significant lower titers of anti-RBD, anti-S1 + S2 and anti-S2 antibodies assessed by multiplex immunodot enzymatic assay at month 3.

In line with previously published studies,[12,13] we found a significant waning of anti-spike antibodies titers between months 3 and 6 confirming that the humoral response to the two-dose vaccination scheme is impaired in dialysis populations when compared to healthy patients.[14] In a study evaluating immune response after the second dose of the BNT162b2 COVID-19 mRNA vaccine in 160 dialysis patients (79.4% receiving hemodialysis), Berar Yanay et al. showed a >90%

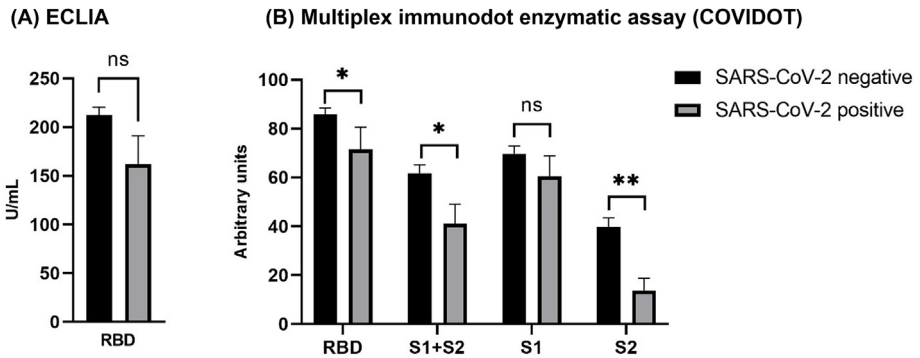

FIGURE 4 Anti-spike antibodies titers assessed by ECLIA (A) and by multiplex immunodot enzymatic assay (B) at month 3 in de novo SARS-CoV-2 infected patients (■, $n = 14$) compared to the noninfected cohort (■, $n = 90$). The results are expressed as mean ± SEM. Nonparametric Mann–Whitney test. $^{*}p < 0.05$, $^{**}p < 0.01$, ns, nonsignificant. ECLIA, electrochemiluminescence assay; RBD, receptor binding domain; S1, spike subunit-1 protein; S2, spike subunit-2 protein; S1 + 2, Ectodomain S1 + S2.

seropositivity in the dialysis cohort, however with significant lower anti–spike antibody levels than in the healthy control group.[15] Our study also brought to light that a third vaccine dose induced an immune response in 97% of patients with a statistically significant rebound of the four different anti-spike antibodies levels detected by the multiplex COVIDOT assay. Using a serologic test detecting IgG antibodies to the RBD of the S1 subunit of SARS-CoV-2 spike protein, Ducloux et al. showed that 93% hemodialysis patients had an antibody titer >50 AU 1 month after the third vaccine dose with a median increase in antibody titers of 580%.[16] But no information was provided about the long-term antibodies kinetic and a possible lowering of antibodies levels as we observed in our prospective study 5 months after the booster vaccine.

Since there are numerous methods and lack of standardization for assessing the humoral and cellular immune response to SARS-CoV-2,[17,18] the comparison of studies is challenging especially to investigate potential relationship between antibodies titers and clinical outcomes. With this in mind, we decided to use two different methods consisting of an electrochemiluminescence immunoassay (Elecsys® Anti-SARS-CoV-2 method) and a multiplex immunodot enzymatic method (COVIDOT). The Elecsys® assay had the advantage to have a very high clinical sensitivity and specificity, but it evaluated only one single epitope with a relatively low upper limit of quantification (250 U/mL), whereas the COVIDOT allowed us to semi-quantify several Anti-SARS-CoV-2 antibodies in a single assay, however, with a lower sensitivity and specificity.

Interestingly, we found a statistically significant correlation between lower anti-spike antibodies titers after the two-dose regimen vaccination and the risk for de novo viral infection, remembering that the majority of infections occurred more than 6 months later when the Omicron variant was predominant. It is worth mentioning that studies with a follow-up longer than 6 months carried out in dialysis patients receiving three vaccine doses are relatively scarce.[19] We can mention Ficiociello's work conducted in 124 hemodialysis patients who received three doses of mRNA-1273 vaccine resulting in a strong humoral response after 250–296 days.[12] However, no relationship between antibody index value and ability to neutralize the virus or fight the infection has been demonstrated.[12]

The limitations of our study are mainly the small sample size attributable to exclusion of one third of the subjects at baseline and missing data regarding the anti-spike antibodies kinetics throughout the 1-year observational period. Conversely, the prospective nature of the protocol, the enrolment of a homogenous dialysis cohort vaccinated according to a uniform schedule with a narrow time range, the assessment of SARS CoV-2 antibodies titers based on an original multiplex immunodot enzymatic assay, and the evaluation of clinical efficacy strengthen the relevance of this study. Another limitation of our study is the lack of a systematic screening of COVID-19 infection, which may have resulted in underestimating its prevalence. According to the protocol applicable in our hospital at that time, SARS-CoV-2 PCR testing was only performed in patients with suspicious symptoms or in case of hospitalization for any reason. It should also be noted that most COVID-19 cases in our study were suspected to be related to the Omicron variant based on Belgian epidemiologic data and not on the virus sequencing (Figure S2). Interestingly, Altarawneh et al. demonstrated that previous mRNA-1273 two-dose regimen vaccination provided a marginal effectiveness against symptomatic Omicron infection whereas a booster vaccine increased the protection up to approximatively 50%.[20] Compared to the initial SARS-CoV-2 virus, the lower protective efficacy of mRNA-based COVID-19 vaccine can be attributed to extensive mutations in the spike proteins, leading to a relative resistance to neutralizing monoclonal antibodies against the receptor-binding domain.[21] Finally, our study did not investigate the potential relationship between in vitro neutralization levels and the anti-SARS-CoV-2 antibodies titers, although such a correlation was demonstrated in healthy subjects.[7]

In conclusion, our study confirms the importance of additional mRNA-based COVID-19 vaccines (boosters) to maintain a sufficient humoral response while ensuring an effective clinical protection in dialysis patients. The multiplex immunodot assay allowed us to highlight the association between a less robust immunization response to the initial vaccination and the risk of ensuing SARS-CoV-2 infection. Assessing circulating IgG antibodies titers against four main epitopes of the viral spike protein could be a valuable tool to personalize COVID-19 vaccine strategy and to maintain a favorable benefit (COVID-19 effective protection)–risk (side effects and vaccine-hesitancy) balance at the individual level. Further studies are required to prospectively validate this strategy in the context of emerging variant with mutations on SARS-CoV-2 spike protein and subsequent new mRNA-based vaccines.

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CONFLICT OF INTEREST STATEMENT

FD declares to hold shares in Moderna. V.T.P.N., L.B., G.-A., F.G. and A.-E.D. have disclosed no conflicts of interest. The results presented in this paper have not been published previously in whole or in part.

DATA AVAILABILITY STATEMENT

The data underlying this research can be made available upon reasonable request to the corresponding author.

ORCID

Frédéric Debelle https://orcid.org/0000-0002-9369-0869

REFERENCES

1. Hilbrands LB, Duivenvoorden R, Vart P, et al. COVID-19-related mortality in kidney transplant and dialysis patients: results of the ERACODA collaboration. *Nephrol Dial Transplant*. 2020;35(11):1973-1983. doi:10.1093/NDT/GFAA261

2. Francis A, Baigent C, Ikizler TA, Cockwell P, Jha V. The urgent need to vaccinate dialysis patients against severe acute respiratory syndrome coronavirus 2: a call to action. *Kidney Int*. 2021;99(4):791-793. doi:10.1016/J.KINT.2021.02.003
3. Baden LR, el Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2020;384(5):403-416. doi:10.1056/NEJMoa2035389
4. Broeders NE, Hombrouck A, Lemy A, et al. Influenza A/H1N1 vaccine in patients treated by kidney transplant or dialysis: a cohort study. *Clin J am Soc Nephrol*. 2011;6(11):2573-2578. doi:10.2215/CJN.04670511
5. Edey M, Barraclough K, Johnson DW. Review article: hepatitis B and dialysis. *Nephrology (Carlton)*. 2010;15(2):137-145. doi:10.1111/J.1440-1797.2009.01268.X
6. Kanai D, Wakui H, Haze T, et al. Improved immune response to the third COVID-19 mRNA vaccine dose in hemodialysis patients. *Kidney Int Rep*. 2022;7(12):2718-2721. doi:10.1016/j.ekir.2022.09.005
7. Khoury DS, Cromer D, Reynaldi A, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med*. 2021;27(7):1205-1211. doi:10.1038/s41591-021-01377-8
8. Ovcar E, Patyna S, Kohmer N, et al. Increasing but insufficient neutralizing activity against Omicron-BA.1 after a second booster dose of mRNA-1273 vaccine in chronic haemodialysis patients. *Clin Kidney J*. 2022;15(12):2346-2348. doi:10.1093/CKJ/SFAC211
9. Nordström P, Ballin M, Nordström A. Risk of infection, hospitalisation, and death up to 9 months after a second dose of COVID-19 vaccine: a retrospective, total population cohort study in Sweden. *Lancet*. 2022;399(10327):814-823. doi:10.1016/S0140-6736(22)00089-7
10. Favresse J, Brauner J, Bodart N, et al. An original multiplex method to assess five different SARS-CoV-2 antibodies. *Clin Chem Lab Med*. 2021;59(5):971-978. doi:10.1515/cclm-2020-1652
11. Sciensano. COVID-19 - Situation épidémiologique. https://covid-19.sciensano.be/fr/covid-19-situation-epidemiologique
12. Ficociello LH, Hymes JL, Willetts J, Mullon C, Johnson C, Anger MS. Full and booster doses of SARS-CoV-2 mRNA-1273 vaccine increase waning antibody levels after completed vaccination among dialysis patients at a large dialysis organization. *Int J Nephrol Renovasc Dis*. 2022;15:319-321. doi:10.2147/IJNRD.S383215
13. Quiroga B, Soler MJ, Ortiz A, et al. Humoral response to third dose of SARS-CoV-2 vaccines in the CKD spectrum. *Clin J am Soc Nephrol*. 2022;17(6):878-876. doi:10.2215/CJN.01770222/-/DCSUPPLEMENTAL
14. Moreno NF, McAdams R, Goss JA, Galvan NTN. COVID-19 vaccine efficacy and immunogenicity in end-stage renal disease patients and kidney transplant recipients. *Curr Transplant Rep*. 2022;9(3):174-184. doi:10.1007/S40472-022-00366-1
15. Berar Yanay N, Freiman S, Shapira M, et al. Experience with SARS-CoV-2 BNT162b2 mRNA vaccine in dialysis patients. *Kidney Int*. 2021;99(6):1496-1498. doi:10.1016/J.KINT.2021.04.006
16. Ducloux D, Colladant M, Chabannes M, Yannaraki M, Courivaud C. Humoral response after 3 doses of the BNT162b2 mRNA COVID-19 vaccine in patients on hemodialysis. *Kidney Int*. 2021;100(3):702-704. doi:10.1016/j.kint.2021.06.025
17. Ikizler TA, Coates PT, Rovin BH, Ronco P. Immune response to SARS-CoV-2 infection and vaccination in patients receiving kidney replacement therapy. *Kidney Int*. 2021;99(6):1275-1279. doi:10.1016/j.kint.2021.04.007
18. Malik SA, Modarage K, Goggolidou P. A systematic review assessing the effectiveness of COVID-19 mRNA vaccines in chronic kidney disease (CKD) individuals. *F1000Res*. 2022;11:909. doi:10.12688/F1000RESEARCH.122820.2
19. Yang X, Zhang H, Bao W, Fu S, Jin H. Immunogenicity rates after SARS-CoV-2 three-dose vaccination in patients under dialysis: a systematic review and meta-analysis. *Vaccines (Basel)*. 2022;10(12):2070. doi:10.3390/VACCINES10122070
20. Altarawneh HN, Chemaitelly H, Ayoub HH, et al. Effects of previous infection and vaccination on symptomatic Omicron infections. *N Engl J Med*. 2022;387(1):21-34. doi:10.1056/NEJMOA2203965
21. Wang P, Nair MS, Liu L, et al. Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. *Nature*. 2021;593(7857):130-135. doi:10.1038/S41586-021-03398-2

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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