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ORIGINAL ARTICLE

Time-dependent evolution of IgG antibody levels after first and second dose of mRNA-based SARS-CoV-2 vaccination in haemodialysis patients: a multicentre study

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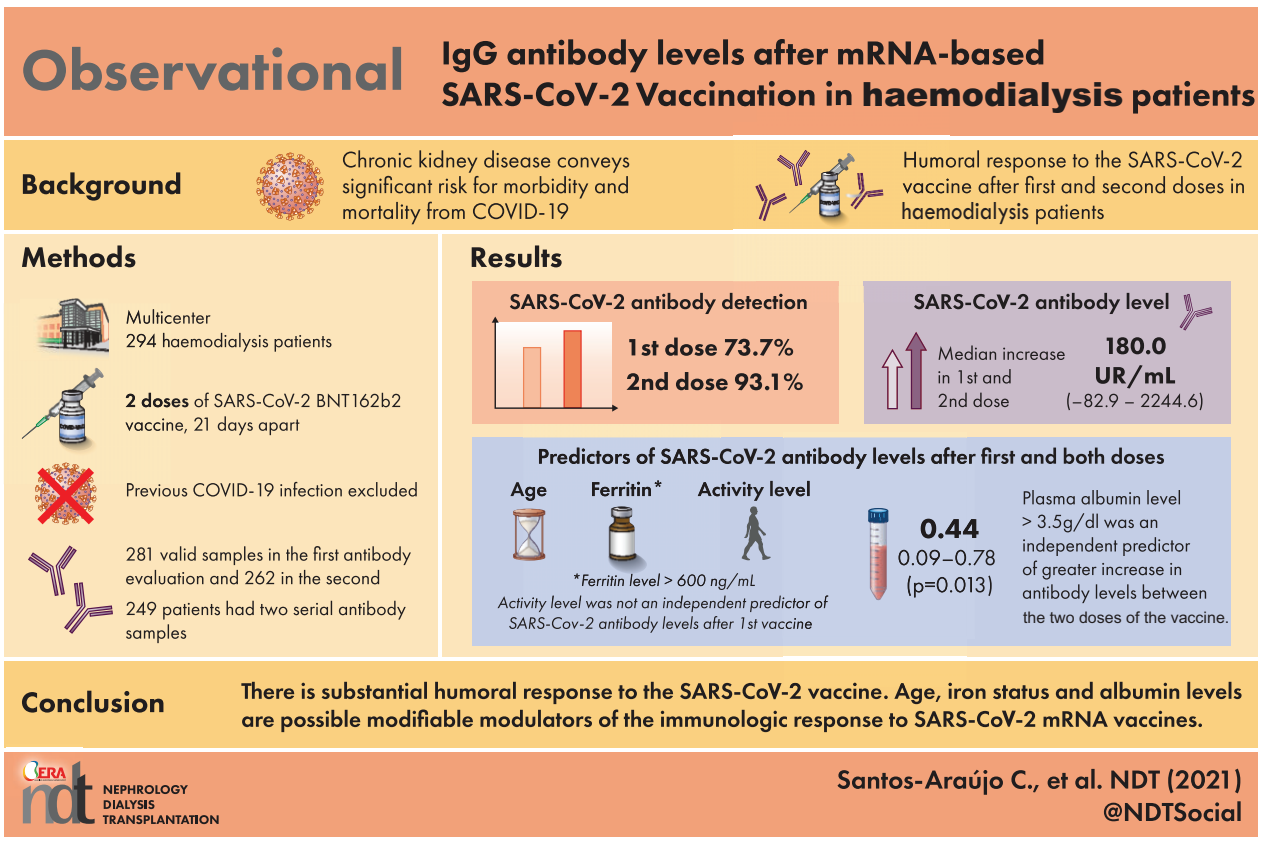
GRAPHICAL ABSTRACT



KEY LEARNING POINTS

What is already known about this subject?

- Chronic kidney disease, and particularly haemodialysis, conveys significant risk for morbidity and mortality from coronavirus disease 2019 (COVID-19).
- mRNA-based severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines represent the mainstay of COVID-19 management and pandemic control.
- Haemodialysis patients frequently develop blunted immunologic reactions to vaccination, but these responses may be enhanced by specific interventions, as shown previously for influenza vaccination.

What this study adds?

- In our cohort of haemodialysis patients, we have documented a substantial humoral response to the SARS-CoV-2 BNT162b2 vaccine, which is more impressive after the second dose and still evident 6 weeks after the last inoculation.
- Vaccination with BNT162b2 vaccine was well tolerated in our cohort, with an overall adverse event incidence of 10.9% and all incidents registered mild and self-limited.
- Younger age and two modifiable factors—higher albumin and ferritin plasma levels—were identified as independent predictors of antibody levels after the first and the second vaccine doses and of a greater increase in antibody levels between doses.

What impact this may have on practice or policy?

- The significant increase in the number of responders from the first to the second vaccine doses may preclude the potential benefit of subsequent exposures of the patient immune system to additional vaccine administrations.
- Early identification of the dialysis population at higher risk of a damped immune response to vaccination may help the implementation of strategies to monitor and take full advantage of seroconversion.
- Some of these strategies may include improving iron status and adjust nutritional support before the vaccination protocol.

ABSTRACT

Background. Vaccination programs are essential for the containment of the coronavirus disease 2019 pandemic, which has hit haemodialysis populations especially hard. Early reports suggest a reduced immunologic response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines in dialysis patients, in spite of a high degree of seroconversion. We aimed to identify risk factors for a reduced efficacy of an mRNA vaccine in a cohort of haemodialysis patients.

Method. In a multicentre study, including 294 Portuguese haemodialysis patients who had received two doses of BNT162b2 with a 3-week interval, immunoglobulin G-class antibodies against the SARS-CoV-2 spike protein were determined 3 weeks after the first dose (M1) and 6 weeks after the second dose (M2). The threshold for seroconversion was 10 UR/mL. Demographic and clinical data were retrieved from a quality registry. Adverse events were registered using a questionnaire.

Results. At M2, seroconversion was 93.1% with a median antibody level of 197.5 U/mL (1.2–3237.0) and a median increase of 180.0 U/mL (−82.9 to 2244.6) from M1. Age [beta −8.9; 95% confidence interval (95% CI) −12.88 to −4.91; $P < 0.0001$], ferritin >600 ng/mL (beta 183.93; 95% CI 74.75–293.10; $P = 0.001$) and physical activity (beta 265.79; 95% CI 30.7–500.88; $P = 0.03$) were independent predictors of SARS-CoV-2 antibody levels after two vaccine doses. Plasma albumin >3.5 g/dL independently predicted the increase of antibody levels between both doses (odds ratio 14.72; 95% CI 1.38 to 157.45; $P = 0.03$). Only mild adverse reactions were observed in 10.9% of patients.

Conclusions. The SARS-CoV-2 vaccine BNT162b2 is safe and effective in haemodialysis patients. Besides age, iron status and nutrition are possible modifiable modulators of the immunologic response to SARS-CoV-2 mRNA vaccines. These data suggest the need for an early identification of populations at higher risk for diminished antibody production and the potential advantage of the implementation of oriented strategies to maximize the immune response to vaccination in these patients.

Keywords: COVID-19, haemodialysis, SARS-CoV-2, SARS-CoV-2 vaccination

INTRODUCTION

Chronic kidney disease (CKD), and particularly dialysis, has emerged as the most prevalent condition conveying risk for both severe disease and death from coronavirus disease 2019 (COVID-19) [1, 2]. Indeed, several studies performed on haemodialysis patients reported significantly higher infection rates when compared with the general population [3, 4], and a short-term mortality rate above 20% [5]. Vaccination, through the reduction in infection rate, mortality and healthcare system burden, has presented for all healthcare groups as one of the cornerstones of COVID-19 management. Despite prior evidence in CKD patients of significant seroconversion with other type of vaccines, the need for larger doses to elicit an adequate immune response had sometimes motivated the adaptation of immunization protocols in this population [6]. Previous studies have reported the presence of SARS-CoV-2 immunoglobulin G (IgG) antibodies around 2 months after

COVID-19 infection in CKD patients [7], but data regarding the safety and efficacy of SARS-CoV-2 vaccines and the time-dependent evolution of antibody titers during the vaccination process in this population are still scarce.

The aim of our work was to evaluate the evolution of the prevalence of SARS-CoV-2 IgG antibodies in a population of haemodialysis patients after the first and second doses of an mRNA-based SARS-CoV-2 vaccine.

MATERIALS AND METHODS

Design, participants and data source

This is a multicentre, prospective, observational study, including patients aged >18 years randomized from a national haemodialysis cohort admitted permanently for dialysis for at least 3 months and submitted to two doses of BNT162b2 vaccine, 21 days apart. The list of participating centres is presented as supplementary material (Supplementary data, Table S1). Patients with a previous diagnosis of COVID-19 or who were unable to give informed consent were excluded. The demographic and clinical data, dialysis-specific parameters and information about medications were obtained from our Renal Information Management System (iRIMS). Baseline laboratory data were obtained from the last month before immunization. Adverse events were also collected through a specific form conceived for this purpose. The study was approved by the Diaverum National Ethics Committee and written informed consent was obtained from all the participants.

SARS-CoV-2 antibody detection

Blood samples were collected using BD Vacutainer R tubes No. 367 955 just before and 6 weeks after the second administration. After centrifugation, serum samples were stored at –20°C until processing. For the quantitative determination of human IgG-class antibodies, an immunoenzymatic method was applied to the S1 domain of the SARS-CoV-2 spike protein [Anti-SARS-CoV-2 Quantivac ELISA (IgG), EUROIMMUN R, ref. no. EI 2606-9601-10 G]. The method was performed according to the manufacturer's recommendations and a cut-off of 10 UR/mL was used to define immunologic response.

Statistical analysis

Sample size was calculated for a sampling error of 3%, a 95% confidence interval (95% CI) and an estimated proportion of patients with protective antibody levels of 95%. For categorical variables, we calculated frequencies and proportions; for numerical variables, we calculated the median and interquartile range. We compared categorical variables by prevalence and level of SARS-CoV-2 spike protein IgG antibodies using the Chi-square test or Fisher's exact test as appropriate. We used the Mann–Whitney test and Kruskal–Wallis test to compare numerical variables. We used multivariable logistic regression models and multivariable linear regression models to determine independent factors that explain the prevalence of responders versus non-responders and the levels of SARS-CoV-2 IgG antibodies (U/mL), respectively. In multivariate analysis, we included all variables with a $P < 0.2$ in the univariate analyses. We considered P-values of <0.05 to be statistically significant. We analysed all data using IBM-SPSS, version 27.0.

RESULTS

Participant characteristics

The study included 294 patients: 281 valid samples were analysed in the first antibody determination and 262 in the second evaluation. In 249 patients, two serial antibody determinations were obtained (Supplementary data, Figure S1). The list of participating centres is listed in Supplementary data, Table S1.

Baseline characteristics of the total population studied are listed in Supplementary data, Table S2.

SARS-CoV-2 antibody detection

We observed a positive antibody response in 73.7% of the patients after the first vaccine dose and in 93.1% after the second. The median SARS-CoV-2 antibody level observed after the first dose was 8.4 UR/mL (0.1–118.0) and after the second dose 197.5 UR/mL (1.2–3237.0). The median increase in SARS-CoV-2 antibody levels between the first and the second dose of the vaccine was 180.0 UR/mL (−82.9 to 2244.6) (Figure 1).

Antibody response to the first vaccination dose

Univariate analysis is described in Supplementary data, Table S2 for responders versus non-responders and in Supplementary data, Table S3 for IgG levels. In multivariate analysis, a plasma albumin level above 3.5 g/dL [odds ratio (OR) 6.12; 95% CI 1.67–22.4; $P = 0.006$] and a leucocyte count above 5.0×10^9/L (OR 1.99; 95% CI 1.07–3.69; $P = 0.029$) were independent predictors of response to the first vaccine dose (Table 1). Younger age (beta –0.66; 95% CI –0.89 to –0.43; $P < 0.0001$) and a ferritin level >600 ng/mL (beta 10.26; 95% CI 4.001–6.53; $P = 0.001$) were independent predictors of SARS-CoV-2 antibody levels (Table 2).

Antibody response to the second vaccination dose

Univariate analysis is described in Supplementary data, Table S2 for responders versus non-responders and in Supplementary data, Table S3 for IgG levels. In multivariate analysis, age (beta −8.9; 95% CI −12.88 to −4.91; P <0.0001), a ferritin level >600 ng/mL (beta 183.93; 95% CI 74.75 to 293.10; $P = 0.001$) and daily physical activity (beta 265.79; 95% CI 30.7–500.88; $P = 0.03$) were independent predictors of SARS-CoV-2 antibody levels (Table 2).

Predictors of SARS-CoV-2 antibody level response increase between the two doses of the vaccine

Univariate analysis is described in Supplementary data, Table S3 for the difference in IgG levels between the two

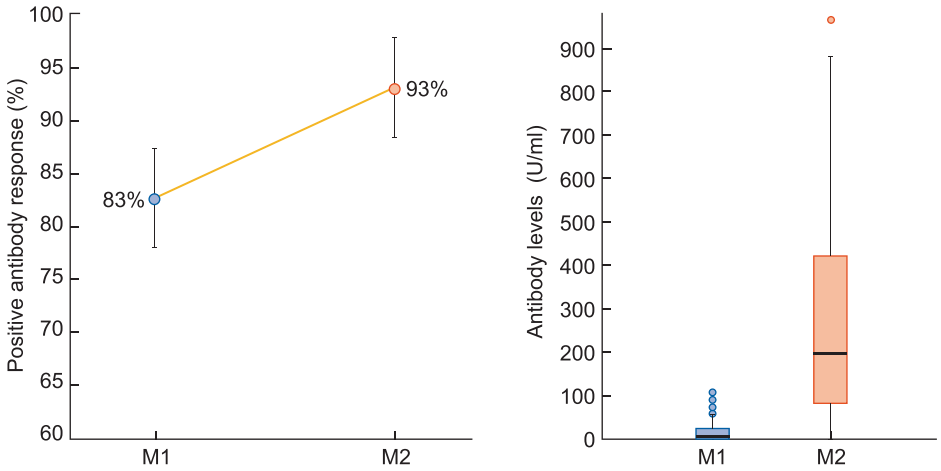


FIGURE 1: Positive IgG spike protein antibody response (%; 95% CI) and antibody levels (Box and Whiskers) after BNT162b2 vaccination of a cohort of haemodialysis patients at two different moments of the study: just before (M1) and six weeks after (M2) de second administration of the vaccine.

Table 1. Independent predictors of a positive serologic response (plasmatic spike protein IgG antibody levels > 10 UR/mL) to BNT162b2 vaccine

	First antibody determination (M1)—Responders			
	Method—Enter		Method—Forward stepwise	
	OR (95% CI)	P	OR (95% CI)	P
Age	0.99 (0.96–1.01)	0.251		
Gender—male	0.51 (0.25–1.00)	0.051	0.46 (0.24–0.88)	0.018
Never smoked	1.46 (0.73–2.92)	0.282		
Pulmonary diseases	0.78 (0.37–1.65)	0.514		
Immunosuppressors	0.43 (0.14–1.33)	0.143		
Albumin ≥3.5 g/dL	4.90 (1.32–18.24)	0.018	6.12 (1.67–22.4)	0.006
Leucocytes ≥5 × 10^9/L	2.41 (1.25–4.65)	0.009	1.99 (1.07–3.69)	0.029
Erythropoietin resistance index	1.04 (0.99–1.09)	0.138		
	Second antibody determination (M2)—Responders			
	Method—Enter		**Method—Forward stepwise**	
	OR (95% CI)	**P**	**OR (95% CI)**	**p**
Age	0.96 (0.88–1.04)	0.320		
Renal vascular disease	0.20 (0.03–1.15)	0.071	0.17 (0.04–0.83)	0.029
Charlson comorbidity index	1.05 (0.71–1.55)	0.802		
Pulmonary diseases	0.28 (0.05–1.59)	0.151	0.18 (0.05–0.71)	0.014
Immunosuppressors	0.11 (0.01–0.90)	0.039	0.07 (0.01–0.55)	0.011
Oral anticoagulants	0.06 (0.01–0.34)	0.002	0.05 (0.01–0.28)	0.001
Antineoplastic agents	0.02 (0.01–0.20)	0.005	0.02 (0.01–0.29)	0.006
Albumin ≥3.5 g/dL	11.17 (0.71–175.56)	0.086		

Multivariate analysis of factors involved in positive serologic response (plasmatic spike protein IgG antibody levels >10 UR/mL) in haemodialysis patients vaccinated with BNT162b2 vaccine at two different moments of the study: M1, just before the second administration and M2, 6 weeks after the second administration of the vaccine. For logistic regression, all variables with P < 0.200 in univariate association were inserted. All models' estimations were done with Enter method and Forward stepwise method. Antineoplastic agents include tamoxifen, thalidomide, bicalutamide and cyproterone.

antibody determinations. In multivariate analysis, a plasma albumin level above 3.5 g/dL was identified as an independent predictor of a greater increase in antibody levels between the two vaccinations (beta 0.44; 95% CI 0.09–0.78; P = 0.013) (Table 2).

Adverse events report to vaccination

Adverse events to BNT162b2 vaccine are reported in Supplementary data, Tables S4 and S5. An overall incidence of 10.9% was documented in our patients, more commonly after the second vaccination dose, compared with the first administration (10.0% versus 2.0%; P < 0.001). Interestingly, a significant association was identified between adverse event occurrence and angiotensin 2 antagonist therapy (26.1% versus 7.3%; P < 0.0001) (Supplementary data, Table S5). All incidents were mild and no hospitalizations were required.

DISCUSSION

In our cohort of haemodialysis patients, we have documented a substantial humoral response to two consecutive doses

Table 2. Independent predictors of the level of plasmatic spike protein IgG antibody levels in response to BNT162b2 vaccine

	First antibody determination (M1)—(UR/mL)			
	Method—Enter		Method—Forward stepwise	
	B (95% CI)	P	B (95% CI)	P
Age	30.32 (−20.77 to 81.42)	0.243	−0.66 (−0.89 to −0.43)	0.000
Daily physical activity	−0.67 (−0.99 to −0.34)	0.000		
Glomerulonephritis	6.97 (−7.15 to 21.09)	0.332		
Renal vascular disease	2.29 (−6.06 to 10.63)	0.589		
Charlson comorbidity index	−3.32 (−11.95 to 5.3)	0.448		
Cardiovascular disease	0.83 (−0.98 to 2.63)	0.366		
Neoplasms	−4.83 (−12.14 to 2.49)	0.195		
Immunosuppressors	2.58 (−5.55 to 10.7)	0.532		
Angiotensin 2 antagonists	−5.62 (−19.14 to 7.9)	0.413		
Oral anticoagulants	5.01 (−3.34 to 13.36)	0.238		
Acetylsalicylic acid	−4.34 (−16.62 to 7.93)	0.486		
Albumin ≥ 3.5 g/dL	−0.6 (−6.94 to 5.74)	0.853		
Ferritin >600 ng/mL	3.06 (−15.51 to 21.63)	0.745	10.26 (4 to 16.53)	0.001
Leucocytes ≥5 × 10^9/L	10.81 (4.31 to 17.31)	0.001		
C reactive protein	4.67 (−2.58 to 11.91)	0.205		
	Second antibody determination (M2)—(UR/mL)			
	Method—Enter		**Method—Forward stepwise**	
	B (95% CI)	**P**	**B (95% CI)**	**P**
Age	−8.05 (−13.62 to −2.47)	0.005	−8.9 (−12.88 to −4.91)	0.000
Daily physical activity	245.6 (9.67 to 481.53)	0.041	265.79 (30.7 to 500.88)	0.027
Glomerulonephritis	−51.39 (−186.48 to 83.7)	0.454		
Renal vascular disease	−121.05 (−267.3 to 25.2)	0.104		
Charlson comorbidity index	−4.24 (−33.56 to 25.09)	0.776		
Cardiovascular disease	−9.96 (−135.85 to 115.93)	0.876		
Immunosuppressors	−57.85 (−292.17 to 176.47)	0.627		
Oral anticoagulants	−179.89 (−393.26 to 33.48)	0.098		
Acetylsalicylic acid	−44.42 (−152.13 to 63.29)	0.417		
Antineoplastic agents	−484.17 (−1010 to 41.65)	0.071		
Albumin ≥3.5 g/dL	72.8 (−257.4 to 403)	0.664		
Ferritin >600 ng/mL	185.95 (76.23 to 295.67)	0.001	178.6 (69.9 to 287.3)	0.001
	M2–M1 (UR/mL)			
	Method—Enter		**Method—Forward stepwise**	
	B (95% CI)	**P**	**B (95% CI)**	**P**
Age	0.00 (−0.01 to 0.00)	0.435		
Glomerulonephritis	−0.03 (−0.19 to 0.13)	0.705		
Renal vascular disease	−0.08 (−0.25 to 0.09)	0.339		
Charlson comorbidity index	0.00 (−0.03 to 0.04)	0.940		
Cardiovascular disease	0.00 (−0.14 to 0.15)	0.970		
Immunosuppressors	−0.09 (−0.34 to 0.17)	0.502		
Oral anticoagulants	−0.19 (−0.43 to 0.06)	0.138		
Acetylsalicylic acid	0.02 (−0.1 to 0.15)	0.700		
Albumin ≥3.5 g/dL	0.38 (0.02 to 0.74)	0.041	0.44 (0.09 to 0.78)	0.013
Ferritin >600 ng/mL	0.00 (−0.01 to 0.01)	0.435		

Multivariate analysis of factors involved in the serologic response (plasmatic anti-spike IgG antibody levels in UR/mL) in haemodialysis patients vaccinated with BNT162b2 vaccine at two different moments of the study: M1, just before the second administration and M2, 6 weeks after the second administration of the vaccine. For linear regression all variables with P < 0.200 in univariate association were inserted. All models' estimations were done with Enter method and Forward stepwise method. Antineoplastic agents include tamoxifen, thalidomide, bicalutamide and cyproterone.

of the SARS-CoV-2 BNT162b2 vaccine. Younger age and higher albumin and ferritin plasma levels were identified as independent predictors of antibody levels after both the first and the second vaccine doses.

The potency of approved SARS-CoV-2 vaccines in immune-compromised individuals is currently unknown, as patients with significant underlying medical conditions, including CKD, have been excluded from the efficacy studies performed so far [8]. This is particularly relevant if we consider that a reduced immune response to infection or vaccination has repeatedly been described in haemodialysis patients [9–11]. In fact, this finding served as a rationale for dose or schedule changes in several vaccination programs for this population in the past [12]. In our cohort, a significant humoral response was observed, with 93.1% of the patients presenting SARS-CoV-2 antibody levels above the defined

threshold of 10 UR/mL, 6 weeks after the administration of the second dose of the vaccine. The median antibody level was almost 20-fold above the threshold. This finding is in accordance with previous reports and confirms the efficacy of vaccination in this subgroup of patients [13–15]. However, this humoral response may be inferior to that observed in the general population [16, 17], which may justify in these patients, in the near future, adaptations to the vaccination schedule, like a vaccine boost several months after the second dose or a more intensive induction vaccination plan with higher vaccine doses. In our study, we have confirmed a significant higher humoral response to SARS-CoV-2 BNT162b2 vaccine after the second dose, when compared with the humoral response after the first dose (73.7% versus 93.1%), supporting the importance of repetitive immune challenge in the development of a robust serologic response to SARS-CoV-2. In accordance to this, a recent study has reported that a third dose of SARS-CoV-2 BNT162b2 vaccine enhanced the humoral response in a group of haemodialysis patients, even in those patients with significant SARS-CoV-2 antibody levels after the two doses of the vaccine [18]. Further studies evaluating the long-term antibody persistence after the vaccination may help to elucidate this point.

In our study, patients with a plasma albumin concentration above 3.5 g/dL and a ferritin level above 600 ng/mL were more likely to respond to the first vaccination dose and to have a higher antibody increase between administrations. Additionally, and in agreement with other reports [16, 17], a negative correlation was observed in our group between age and SARS-CoV-2 antibody levels. Plasma albumin is related to the patient nutritional status and reduced levels may be associated with decreased antibody response to immunization in dialysis patients [12, 19]. Our study is the first report of an association of increased plasma ferritin with an improved immune response to SARS-CoV-2 vaccine in haemodialysis patients, which is in line with previous findings with influenza vaccination [20]. Iron status is a modulator of immune reactivity [21] and iron supplementation may improve vaccination response [22]. Improving nutritional status can be challenging in dialysis patients, particularly in the elderly, but the early identification of the dialysis population exposed at the higher risk of a damped immune response to vaccination may help to implement strategies to monitor and take full advantage of seroconversion. Some of these strategies may include improving iron status and adjusting nutritional support before the vaccination protocol.

Vaccination with BNT162b2 vaccine was well tolerated in our cohort, with an overall adverse event incidence of 10.9%. This is in accordance with previous descriptions in this population [23, 24]. Despite the significantly higher report rate after the second administration when compared with the first vaccine dose, all incidents registered were mild and self-limited. Additionally, we had no hospitalizations related to the vaccination process and almost all patients recovered. Interestingly, a significant association was observed between adverse event occurrence and therapy with angiotensin 2 antagonists. As far as we know, this is the first time that this association has been described and further evaluation is needed.

Our study had several limitations. Despite the fact that all patients with a previous history of COVID-19 were excluded, no antibody determination was performed before the administration of the first dose of the vaccine and we cannot affirm with certainty that all the serologic responses were in fact due to vaccination. However, our patients were routinely screened with SARS-CoV-2 PCR tests, whenever a positive contact was identified. Additionally, no control group was included and we cannot compare the efficacy and amplitude of serologic response with patients without terminal kidney disease.

In conclusion, our study demonstrates that BNT162b2 vaccine is safe and effective in a cohort of multicentre haemodialysis patients. Besides increased age, modifiable risk factors for a reduced vaccine efficacy, such as low albumin and ferritin levels, were identified, suggesting an impact of malnutrition and iron status on the incidence and amplitude of the immunologic response to the vaccine. These data suggest the need for an early identification of populations at higher risk for diminished antibody production and the potential advantage of the implementation of oriented strategies to maximize the immune response to vaccination in these patients.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

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AUTHORS' CONTRIBUTIONS

C.S.-A. and F.M. developed the research questions. C.S.-A., F.M., C.L., M.Haarhaus and M.Haase participated in development of study design and analysis plan. M supervised the sample collection. M.J.S. and M.L.D. performed antibody determination. C.S.-A. supervised data collection. P.M.V. performed the statistical analyses. C.S.-A. and P.M.V. drafted the article. C.S.-A. wrote the final version of the article. F.M. supervised the study. All authors contributed to the interpretation of data and read and approved the final manuscript. All authors had unrestricted access to all data in the study.

CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this paper have not been published previously in whole or part.

DATA AVAILABILITY STATEMENT

This paper complies with Data Availability Policies and all data are available as supplementary data.

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