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Decreased response to the mRNA anti-SARS-CoV-2 vaccine in hepatitis B vaccine non-responders and frail patients treated with peritoneal dialysis

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Vaccination is the pivotal tool for protection against severe coronavirus disease-2019 (COVID-19). Numerous studies have shown dialysis patients to respond insufficiently to other vaccines, e.g. hepatitis B virus (HBV) [1] or influenza [2], with quantitatively lower and shorter-lived titers. Although there may be a better immune function due to less chronic inflammation and preservation of residual renal function [3–5] in peritoneal dialysis (PD) patients, the response to HBV vaccination was not different from that in patients treated with haemodialysis (HD) [6].

In a recent study on the response to COVID-19 vaccination in dialysis patients, there was a superior humoral response in patients treated with PD compared with HD [7]. In another study, which observed a serological response in 62.5% after the first dose and 97% after the second dose of an mRNA vaccine, there was no difference in baseline characteristics between responders and non-responders [8]. In comparison with healthy individuals, patients treated with PD have lower antibodies against the subunit S1 of the spike protein, with a median anti-S1 IgG index of 21.8 (interquartile range 5.8–103.9) versus 134.9 (23.8–283.6) [9].

The present study aimed to determine the serological response to the mRNA severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) vaccine (Spikevax, Moderna, MA, USA) in patients with chronic PD, as assessed by the Roche Elecsys Anti-SARS-CoV-2 S (Roche, Basel, Switzerland) which detects antibodies against the SARS-CoV-2 virus, as well as associations with baseline and clinical characteristics.

After obtaining ethical approval (EC number: 33–391 ex 20/21), we retrospectively screened 36 patients who had received routine SARS-CoV-2 vaccination for study inclusion. Four patients had positive nucleocapsid antibodies and were excluded due to prior SARS-CoV-2 infection; one patient was lost to follow-up after the first vaccination. Results are presented for the remaining 31 patients.

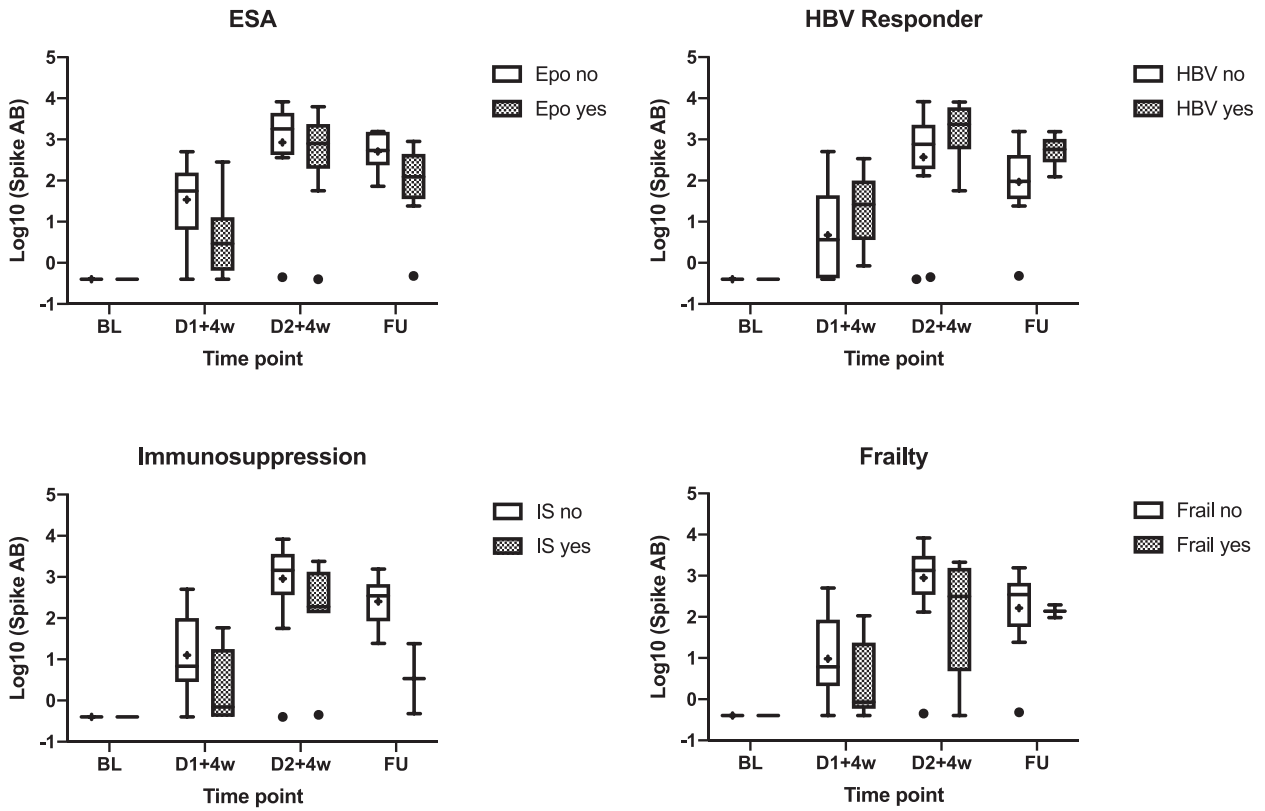
Baseline characteristics are provided in Supplementary data, Table S1, total and stratified by response [i.e. binding antibody unit (BAU) ≥15/mL] after the first dose of vaccination. P-values were obtained via the Fisher's exact test, the *t*-test or the Mann–Whitney *U*-test.

There were no differences between responders and non-responders apart from significantly more non-responders receiving treatment with erythropoiesis-stimulating agents (ESAs) and a better residual renal function.

A total of 28 days after the first dose, 25 (80.6%) test results with the Roche Elecsys Anti-SARS-CoV-2 S were reactive, while 6 were negative (19.4%). A serological response, defined as BAU ≥15/mL was observed in 12 subjects (38.7%). Four weeks after the second dose, assays were reactive in 28 samples (93.3%). A serological response was observed in 28 patients (93.3%; Supplementary data, Table S1). At extended follow-up (mean 202.5 ± 6.2 days; $n = 19$), 18 samples were reactive (94.7%) and the response was maintained in 94.7% as well. Levels of spike antibodies and the logarithmic concentration of spike antibodies are shown in Supplementary data, Table S2 and Figure S1.

A cut-off of 2000 BAU/mL has been suggested to increase the positive predictive value for a high titer of neutralizing antibodies [10]. When using this cut-off, only 40% showed a response 4 weeks after the second dose and none at follow-up ($n = 19$) (Supplementary data, Table S2).

Influence of baseline characteristics on levels of spike antibodies were explored by mixed models, including log10 concentrations as outcome, and the timepoints, the baseline parameter and time–parameter interaction as fixed effects. Results are back transformed and presented as geometric



BL=baseline, D1+4w= 4 weeks after the first vaccination, D2+4w= 4weeks after the second vaccination, FU= follow up, Epo= Erythropoietin

FIGURE 1: Influence of baseline characteristics on anti-SARS-CoV-2 spike protein antibodies.

mean concentrations and ratios (GMRs). Significantly lower responses (i.e. GMR < 1) were observed for patients treated with immunosuppression, treated with ESA, for HBV low or non-responder and frail patients (Supplementary data, Table S3; Figure 1).

This study shows that patients treated with chronic PD have a serologic response to the mRNA vaccine, with a sustained response >200 days (Supplementary data, Table S2).

Besides the underlying renal disease, patients on PD have a high prevalence of a number of conditions that predispose them to adverse outcomes in the case of COVID-19. Thus, while routine SARS-CoV-2 serology is as of yet not recommended after vaccination, the knowledge of which patients are more prone to show an insufficient response to the SARS-CoV-2 vaccination is likely to be clinically relevant. This is of special interest when considering the current emergence of SARS-CoV-2 variants that are less efficiently neutralized even after complete immunization.

We found a significant association with current ESA treatment. This might be due to the pro-inflammatory environment in chronic kidney disease, which leads to functional iron deficiency and requires the initiation of ESA treatment for anaemia. Also, patients with a higher frailty score showed a significantly worse response in terms of GMR, which was not dependent on age.

The immunomodulating properties of erythropoietin have been a subject of investigation over the past years, but a recent meta-analysis concluded that there is no impact on the response to the HBV vaccine [11].

Cut-offs (as medical decision limits for acquired immunity) are still not sufficiently validated due to uncertainties regarding the contribution of humoral immunity against SARS-CoV-2. The manufacturer recommends a cut-off of 15 BAU/mL to increase the positive predictive value (>99%) for the presence of neutralizing antibodies. So far, this cut-off has only been evaluated in natural infections but not for vaccinations. It has been shown, however, that serological assays reliably reflect B-cell action [12].

Limitations include the small sample size and the lack of information on neutralizing antibodies. In addition, while the definition of serological response has been chosen to reflect the presence of neutralizing antibodies, it is still unknown whether this translates to clinically meaningful protection against adverse clinical outcomes from COVID-19 and especially against new variants of concern. Furthermore, the comparability of different SARS-CoV-2 antibody assays is very limited because of lacking analytical harmonization. Even those assays which

are mathematically aligned to the international reference material by the World Health Organization (NIBSC 20/136) exhibit severe disagreement when applied on the same samples [13, 14].

In conclusion, we show a good serological response to the SARS-CoV-2 vaccination in PD patients. Patients with frailty or those treated with ESA or immunosuppression exhibit significantly poorer antibody production, as is the case for HBV vaccine low- and non-responders. This knowledge may help in identifying candidates for earlier or additional boostering or more aggressive treatment, including monoclonal antibody therapy in the case of infection.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

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AUTHORS' CONTRIBUTIONS

M.K., R.R., A.R.R. and A.H.K. conceived and designed the study and drafted the manuscript. W.R., A.-M.M., M.K. and B.B. acquired patients' data. T.N. performed the laboratory analysis. R.R. performed the statistical analysis. All authors (M.K., R.R., W.R., A.R.R., A.H.K., A.-M.M. and B.B.) contributed to the acquisition and interpretation of the data and provided critical revision of the manuscript for important intellectual content.

CONFLICT OF INTEREST STATEMENT

This work has not been published previously and is not being considered for publication elsewhere. All authors declare that they have no conflicts of interests for this manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author, A.H.K.

REFERENCES

1. Gasim GI, Bella A, Adam I. Immune response to hepatitis B vaccine among patients on hemodialysis. *World J Hepatol* 2015; 7: 270–275
2. Mastalerz-Migas A, Gwiazda E, Brydak LB. Effectiveness of influenza vaccine in patients on hemodialysis—a review. *Med Sci Monit* 2013; 19: 1013–1018
3. Dhondt A, Vanholder R, Van Biesen W *et al.* The removal of uremic toxins. *Kidney Int Suppl* 2000; 76: S47–S59
4. Girndt M, Sester M, Sester U *et al.* Molecular aspects of T- and B-cell function in uremia. *Kidney Int Suppl* 2001; 78: S206–S211
5. Ducloux D, Legendre M, Bamoulid J *et al.* ESRD-associated immune phenotype depends on dialysis modality and iron status: clinical implications. *Immun Ageing* 2018; 15: 16
6. Fabrizi F, Dixit V, Bunnapradist S *et al.* Meta-analysis: the dialysis mode and immunological response to hepatitis B virus vaccine in dialysis population. *Aliment Pharmacol Ther* 2006; 23: 1105–1112
7. Tylicki L, Piotrowska M, Biedunkiewicz B *et al.* Humoral response to COVID-19 vaccination in patients treated with peritoneal dialysis: the COViNEPH Project. *Pol Arch Intern Med* 2021; 131
8. Rodriguez-Espinosa D, Broseta JJ, Maduell F *et al.* Humoral response of the mRNA-1273 SARS-CoV-2 vaccine in peritoneal dialysis patients. *Kidney Int* 2021; 100: 476–477
9. Speer C, Schaier M, Nusshag C *et al.* Longitudinal humoral responses after COVID-19 vaccination in peritoneal and hemodialysis patients over twelve weeks. *Vaccines (Basel)* 2021; 9: 1130
10. Meschi S, Matusali G, Colavita F *et al.* Predicting the protective humoral response to a SARS-CoV-2 mRNA vaccine. *Clin Chem Lab Med* 2021; 59: 2010–2018
11. Fabrizi F, Dixit V, Martin P *et al.* Erythropoietin use and immunogenicity of hepatitis B virus vaccine in chronic kidney disease patients: a meta-analysis. *Kidney Blood Press Res* 2012; 35: 504–510
12. Mrak D, Tobudic S, Koblischke M *et al.* SARS-CoV-2 vaccination in rituximab-treated patients: B cells promote humoral immune responses in the presence of T-cell-mediated immunity. *Ann Rheum Dis* 2021; 80: 1345–1350
13. Giavarina D, Carta M. Improvements and limits of anti SARS-CoV-2 antibodies assays by WHO (NIBSC 20/136) standardization. *Diagnosis* 2021; 10.1515/dx-2021-0126
14. Microbiology—infectious diseases including COVID 19. *Clin Chem Lab Med* 2021; 59: s564–s646

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