

## LETTER TO THE EDITOR

# The effect of COVID-19 vaccination on kidney function and HLA antibody formation in patients with end-stage kidney disease and on kidney replacement treatment

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To the Editor,

COVID-19 vaccination in patients with kidney disease has generally been stated not to cause accelerated eGFR decline or an increase in proteinuria [1]. However, from the observational studies that have been performed thus far, no firm conclusions can be drawn, as no comprehensive longitudinal analyses were performed. Here, we report, to our knowledge, the first data on longitudinal kidney function before and after COVID-19 vaccination in patients with end-stage kidney disease and after kidney transplantation. Additionally, we studied proteinuria and the formation of HLA antibodies after COVID-19 vaccination.

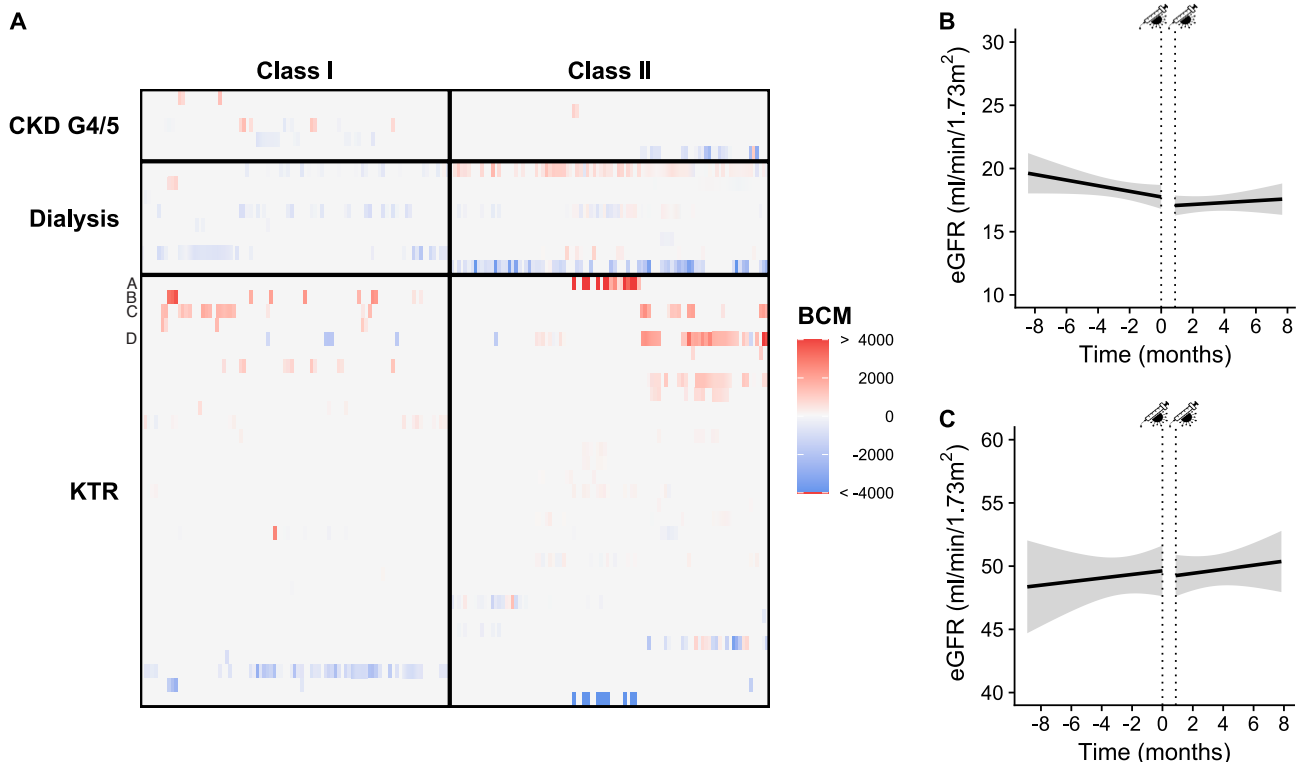
For this study, we included patients with chronic kidney disease grade 4/5 (CKD G4/5), on dialysis and kidney transplant recipients (KTR) who received two mRNA-1273 COVID-19 vaccinations in the context of a clinical trial investigating the im-

mune response after COVID-19 vaccination in kidney patients [2, 3]. A subset of KTR who did not seroconvert after two vaccinations continued in a subsequent randomized clinical trial investigating different vaccination strategies where they received a third COVID-19 vaccination [4]. Estimated GFR slopes were compared in 169 CKD G4/5 and 294 KTR six months pre- and post-vaccination (Table S1). Of these KTR, 53 were included for eGFR slope comparison after a third vaccination. In a subset of the eGFR cohort (CKD G4/5  $n = 92$ , KTR  $n = 167$ ), urine protein creatinine ratios were available (Table S2). Additionally, we selected 21 CKD G4/5, 26 dialysis patients, and 55 KTR to determine HLA antibody status pre- and post-vaccination (Table S3) (see Figs. S1 and S2 for a patient flowchart). A detailed description of the methods can be found in the Supplementary Methods.

After two vaccinations, no *de novo* HLA antibodies were detected in each group. In KTR with pre-existing HLA antibodies,

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**Figure 1:** Kidney-related outcomes after COVID-19 vaccination. (a) Heatmap with changes in specific HLA antibodies of positive patients per patient group and class. Alphabetic letters are the individuals whose characteristics are presented in Table S6. Estimated GFR slope before and after mRNA-1273 COVID-19 vaccination in (b) CKD G4/5 patients and (c) KTR. Change in eGFR slope was calculated by segmented mixed effects linear regression. Dotted lines represent the first and second vaccination. BCM, background corrected mean fluorescence intensity.

some individuals had considerable changes (Fig. 1A; Table S4). One KTR with a substantial rise in donor-specific HLA antibodies had an increase in urine protein creatinine ratio and a decline in eGFR. The kidney biopsy showed chronic active antibody-mediated rejection, and consequently, this patient received a higher dosage of mycophenolate mofetil (Patient A in Fig. 1A). Combining our data with other published studies on HLA antibody formation after COVID-19 vaccinations, a total of 642 KTR and 583 waitlisted patients were investigated.<sup>S1–S16</sup> Of these patients, 12 (1.9%) KTR and 6 (1.0%) waitlisted patients developed *de novo* HLA antibodies. The reported 1%–2% of patients with *de novo* HLA antibody formation after COVID-19 vaccination seems to be in line with the incidence reported during regular follow-up with an interval of eight months between measurements after kidney transplantation [5].

The rate of eGFR loss over time was less steep in CKD G4/5 patients after two vaccinations ( $\beta_{\text{before}} -3.65$  (CI:  $-7.3, -1.83$ ) versus  $\beta_{\text{after2}} -1.46$  (CI:  $-3.29-0.37$ ) ml/min/1.73 m<sup>2</sup> per year;  $P = 0.01$ ; Fig. 1a). Results were not different for various subgroups (Table S5). In KTR, there was no change in the annual rate of eGFR loss after two vaccinations ( $\beta_{\text{before}} 1.10$  (CI:  $-0.37-2.56$ ) vs.  $\beta_{\text{after2}} 0.73$  (CI:  $-0.37-2.19$ ) ml/min/1.73 m<sup>2</sup> per year;  $P = 0.83$ ; Fig. 1b) nor after three vaccinations ( $\beta_{\text{after3}} -0.99$  (CI:  $-2.58-0.59$ ) vs.  $\beta_{\text{before}} -0.92$  (CI:  $-4.69, 2.84$ ) ml/min/1.73 m<sup>2</sup> per year;  $P = 0.99$ ). No changes in proteinuria were observed in both groups [CKD G4/5 86.6 (31.7–178.4) vs. 86.1 (36.1–174.2) mg/mmol;  $P = 0.73$  and KTR 14.3 (9.5–36.5) vs. 16.7 (10.0–40.0) mg/mmol;  $P = 0.35$ ], or according to subgroups (Table S6).

In conclusion, we did not observe changes in kidney-related outcomes longitudinally assessed in kidney patients before and after mRNA-1273 COVID-19 vaccination. Neither did we observe a change in the development of *de novo* HLA antibodies. These findings imply that the COVID-19 vaccination is safe and does not worsen kidney damage or function in patients with end-stage kidney disease and kidney transplantation recipients.

## SUPPLEMENTARY DATA

Supplementary data are available at [ckj](#) online.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

## AUTHORS' CONTRIBUTIONS

R.G. and J.S. designed the study protocol. M.R., D.B., F.B., R.M., R.v.d.M., D.D., E.R., R.V., and L.H. contributed to the protocol design. C.I. participated in the performance of the research. C.I., A.M., and L.B. participated in data analysis. C.I., A.M., R.G., and J.S. participated in the writing of the paper. F.B., M.R., and L.H. contributed to the intellectual content.

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## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, upon reasonable request. Research proposals can be submitted to the Consortium members via the corresponding author.

## CLINICAL TRIAL NOTATION

NCT04741386 and NCT05030974 (clinicaltrials.gov).

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