Vaccine 44 (2025) 126544

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

COVID-19 vaccine responses are influenced by distinct risk factors in naive and SARS-CoV-2 experienced hemodialysis recipients

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ARTICLE INFO

Keywords:
COVID-19
Hemodialysis
Hybrid immunity
mRNA vaccination
Systems immunology

ABSTRACT

Background: Clinical risk factors of deficient immune responses to COVID-19 mRNA vaccination in SARS-CoV-2 naive hemodialysis recipients (HDR) have already been identified. Clinical factors influencing hybrid immunity induced by SARS-CoV-2 infection and vaccination in HDR have not been reported.

Methods: A comprehensive analysis of antibody (Ab) and T cell responses to two doses of BNT162b2 mRNA vaccination was performed in 103 HDR, including 75 SARS-CoV-2 naive and 28 experienced patients, and in 106 healthy controls (HC) not undergoing HD, including 40 SARS-CoV-2 naive and 66 experienced subjects. Clinical risk factors associated with lower humoral and cellular immunity were analyzed in SARS-CoV-2 naive and experienced HDR by univariate and multivariate analyses.

Results: Naive HDR had lower neutralizing and non-neutralizing antibody responses to vaccination than naive HC; lower vaccine responses were correlated with previous transplantation, immunosuppressive treatment, corticosteroid treatment, hypoalbuminemia, older age, hypertension, and negative response to hepatitis B vaccination. In contrast, vaccine responses of SARS-CoV-2 experienced HDR were similar to those of HC and were correlated with time between infection and vaccination and with previous transplantation, but not with the other risk factors associated with lower vaccine responses in naive HDR.

Abbreviations: ADCD, antibody-dependent complement deposition; ADCP, antibody-dependent cellular phagocytosis; AVF, arteriovenous fistula; BAU, binding antibody unit; BLI, biolayer interferometry; *E*-HC, SARS-CoV-2 experienced healthy control; E-HDR, SARS-CoV-2 experienced hemodialysis recipient; ELISA, enzyme-linked immunosorbent assay; ESRD, end-stage renal disease; HBV, hepatitis B virus; HC, healthy control; HDR, hemodialysis recipient; MFI, median fluorescence intensity; mRNA, messenger ribonucleic acid; nAb, neutralizing antibody; N-HC, SARS-CoV-2 naive healthy control; N-HDR, SARS-CoV-2 naive hemodialysis recipient; PC, principal component; PCA, principal component analysis; PICOV, prior infection with SARS-CoV-2; RBD, receptor binding domain; S, SARS-CoV-2 spike protein; S1, SARS-CoV-2 spike protein subunit S1; S2, SARS-CoV-2 spike protein subunit S2; WT, wild type; Wuhan NT50, SARS-CoV-2 Wuhan 50 % neutralizing antibody titer.

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https://doi.org/10.1016/j.vaccine.2024.126544
Received 12 September 2024; Received in revised form 28 October 2024; Accepted 17 November 2024
Available online 29 November 2024

Conclusion: COVID-19 vaccine responses are influenced by distinct risk factors in SARS-CoV-2 naive and experienced HDR. These observations have important implications for the understanding of vaccine-induced immunity and for the management of this vulnerable patient population.

1. Introduction

During the first wave of the coronavirus disease 2019 (COVID-19) pandemic, hemodialysis recipients (HDR) were at higher risk of severe COVID-19 and death as compared to the general population [1]. This higher risk was attributed to chronic kidney disease-induced immunosuppression and to comorbidities [2]. Previous studies have shown that HDR also developed lower humoral and cellular immune responses to primary COVID-19 vaccination as compared to healthy individuals and were at higher risk of breakthrough infections [3–6]. In these early reports, reduced COVID-19 vaccine responses were associated with clinical characteristics such as age, time in dialysis, immunosuppressive treatment, response to hepatitis B vaccination, lymphocyte count and albuminemia [7–11]. Booster vaccinations, pre-exposure prophylaxis with monoclonal antibodies, and bivalent variant-adapted vaccination have been proposed to non-responders to protect against the different variants of SARS-CoV-2 [12–14].

The increased susceptibility of HDR to severe COVID-19 and their lower response to COVID-19 vaccination as compared to the general population were not surprising as these patients also have increased susceptibility to other respiratory pathogens and poor responses to other vaccines [15]. Several strategies have been used to improve vaccine-induced immunity in HDR, including higher doses of vaccine [16], use of adjuvants [17], and booster immunizations [18]. Yet, understanding of the mechanisms underlying defective vaccine responses in HDR remains limited. Identifying conditions under which these vulnerable patients can develop high vaccine responses has therefore important implications for protection against endemic and epidemic pathogens.

Previous SARS-CoV-2 infection has been reported to increase binding antibody and IFNγ-producing cell responses to COVID-19 mRNA vaccination in HDR, as is also observed in immunocompetent individuals [3,5,9,19]. Although the mechanisms underlying the induction of such hybrid immunity remain incompletely understood, these observations suggest that it may overcome the immunosuppression associated with end-stage renal disease (ESRD) and hemodialysis.

In this study, we explored the clinical factors correlating with the magnitude of the response to COVID-19 mRNA vaccination in a prospective cohort of SARS-CoV-2 naive and SARS-CoV-2 experienced HDR. To gain insight into the factors influencing the diverse components of vaccine responses, we performed a comprehensive analysis of neutralizing and non-neutralizing functions of SARS-CoV-2 spike (S) protein-specific antibodies as well as S-specific CD4 and CD8 T cell responses.

2. Materials and methods

2.1. Study design and participant characteristics

The study was designed to prospectively evaluate the immune responses to BioNTech/Pfizer BNT162b2 mRNA (Comirnaty®) vaccination in COVID-19 naive (N) and experienced (E) HDR and healthy controls (HC). All participants were above 18 years and provided written informed consent. Patients with active cancer were excluded from the study. Participants were enrolled before COVID-19 vaccination and then received two doses of the BNT162b2 vaccine 21 days apart, following the Belgian national vaccination program. HDR were recruited from the departments of Nephrology of Erasme Hospital, Brussels, and of Civil Hospital Marie Curie, Charleroi, Belgium. HC were healthcare workers recruited from two Belgian nursing homes, as previously reported [20]. Both studies were approved by the Ethics Committee of Erasme Hospital, Brussels, Belgium (P2020/312, A2021/127, B4062020000134) and by the Belgian Federal Agency for Medicines and Health Products (EudraCT 2021–000461-33 and 2021–000401-24).

Previous SARS-CoV-2 infection status was established as previously described [21] (see supplementary methods). The first vaccine dose was administered to HC between 21/01/ 2021 and 28/01/2021, and to HDR between 01/03/2021 and 23/03/2021. The second vaccine dose was administered to HC between 11/02/2021 and 18/02/2021, and to HDR between 22/03/2021 and 22/04/2021. Blood was collected to assess humoral and cellular immunity to SARS-CoV-2 just prior to the first vaccine dose (day 0) as well as four weeks after the second dose (day 49).

2.2. Humoral immune responses

Levels of total IgG specific for the Wuhan SARS-CoV-2 Receptor Binding Domain (RBD) were measured using an enzyme-linked immunosorbent assay; avidity of Wuhan SARS-CoV-2 RBD-specific IgG was measured with Biolayer Interferometry (BLI); titers of antibodies neutralizing Wuhan SARS-CoV-2 were measured using a live virus microneutralization assay; levels of SARS-CoV-2-specific antibody isotypes, subclasses, and FcγR-binding IgG and antibody-dependent complement deposition (ADCD) were measured using a customized multiplexed immunoassay, antibody-dependent cellular phagocytosis (ADCP) was assessed by flow cytometry, as previously described [20,22–27]. Detailed methods are provided in Supplementary Methods.

2.3. Cellular immune responses

SARS-CoV-2 Wuhan S1 and S2 specific T cell frequencies were measured in peripheral blood mononuclear cells (PBMC) by flow cytometry following intracellular cytokine staining (BD Fastimmune, BD-Beckton Dickinson and Company-Biosciences, San Jose, CA), as previously described [28,29], and analysis was performed using FlowJo V10.8.1. Detailed methods are provided in Supplementary Methods.

2.4. Statistical analyses

Demographic characteristics of HDR and HC are presented as median (first quartile Q1 – third quartile Q3) for continuous variables and n (%) for categorical variables. Comparisons of categorical and continuous variables were made with the $\chi 2$ test, or Fisher's exact test when appropriate, and the 2-tailed Mann-Whitney *U* test, or Kruskal-Wallis test followed by a Dunn's test with Bonferroni correction for multiples comparisons, respectively. Spearman correlation analysis was used for single continuous variate correlation analyses. Associations between immune variables and continuous clinical categorical variables were explored by univariate and multivariate linear regressions. Principal component analysis (PCA) was applied to the entire cohort on the one hand, and in N-HDR and *E*-HDR separately on the other hand. Statistical analyses were performed using GraphPad Prism 10.1.1 (GraphPad Software, San Diego, CA, USA), R version 4.2.0 and Rstudio version 1.3.1073 with R version 4.2.1 [30,31]. Detailed methods are provided in Supplementary Methods.

3. Results

3.1. Cohorts and participant characteristics

One hundred and three HDR were enrolled in the study, including 75 SARS-CoV-2 naive (N)-HDR and 28 SARS-CoV-2 experienced (*E*)-HDR. Two N-HDR and one *E*-HDR were excluded because a SARS-CoV-2

infection was diagnosed between the two doses of COVID-19 vaccine. Demographic and clinical characteristics were similar between N-HDR and *E*-HDR except for sex and ethnicity (Table 1).

One hundred and six healthcare workers were included as healthy controls (HC), with 40 N-HC and 66 E-HC, respectively. Detailed characteristics of naive and SARS-CoV-2 experienced HDR and HC are shown in **Table S1**. HC were younger than HDR with a higher proportion of females. HDR had a higher proportion of comorbidities as compared to HC and 15,5 % of HDR were under immunosuppressive treatment. SARS-CoV-2 infections among experienced participants were more commonly symptomatic among *E*-HDR, who required more oxygen and included a higher proportion of patients hospitalized in intensive care unit than E-HC.

3.2. E-HDR have higher antibody responses to COVID-19 mRNA vaccination as compared to N-HDR

SARS-CoV-2 spike (S) RBD-specific binding IgG were not detected at baseline in N-HDR and N-HC, whereas most previously experienced participants had detectable antibodies (Fig. 1A). *E*-HDR had comparable levels of SARS-CoV-2 RBD-specific binding IgG and neutralizing antibodies (nAb) (Fig. 1A and C) as well as IgG subclasses (Fig. 2A) and even higher levels of RBD-specific IgG avidity (Fig. 1B) as compared to *E*-HC. Following vaccination, N-HDR had markedly lower levels of RBD binding IgG and nAb as compared to N-HC (Fig. 1A and C), as previously reported [4,5,32]. In contrast, high antibody responses to vaccination were detected in both *E*-HC and E-HDR. At day 49, E-HDR had markedly higher levels of RBD binding IgG, IgG avidity and nAb (Fig. 1A, B and C) as well as IgG1 and IgA (Fig. 2B) than N-HDR. Antibody levels in vaccinated E-HDR reached similar levels to those detected in *E*-HC. The higher level of RBD-specific IgG avidity detected at baseline in E-HDR as compared to E-HC was no longer significant after vaccination (Fig. 1B).

3.3. E-HDR develop higher IgG Fc-dependent effector responses to mRNA vaccination than N-HDR

To understand how prior SARS-CoV-2 infection influences vaccine-induced antibody Fc-dependent effector functions among HDR, we first measured the binding of RBD, S1 and S2 subunit-specific IgG to human Fc-receptors. At baseline, levels of SARS-CoV-2 S-specific antibody binding to FcγRIIa and FcγRIIIa levels were similar in *E*-HDR and E-HC. Consistent with binding IgG responses to vaccination, S-specific antibody binding to Fcγ receptors was higher in *E*-HDR as compared to N-HDR and was comparable to those detected in E-HC (Fig. 3). To determine whether these FcγR-binding profiles translated to increased IgG effector functions, we measured antibody-dependent complement deposition (ADCD) of RBD, S1 and S2-specific IgG and antibody-dependent cellular phagocytosis (ADCP) activities of RBD-specific IgG. At baseline and post-vaccination, *E*-HDR had similar levels of ADCD and ADCP as compared to E-HC, confirming data obtained in Fcγ receptor binding assays (Fig. 4).

3.4. CD4 and CD8 T cell responses to mRNA vaccination in E-HDR and N-HDR

To assess the impact of previous SARS-CoV-2 infection on cellular immunity of HDR, we explored T cell responses to SARS-CoV-2 S1 and S2 subunits by flow cytometry. Before vaccination, *E*-HDR had similar frequencies of CD4 T cells expressing CD154 and IFNγ and higher frequencies of CD4 T cells expressing IL2 in response to both S1 and S2 as compared to *E*-HC (Fig. 5A). Post-vaccination, E-HDR had similar frequencies of CD4 T cells expressing CD154 and IL2 in response to both S1 and S2 and higher frequencies of CD4 T cells expressing IFNγ in response to S1 as compared to N-HDR (Fig. 5B). Frequencies of S1 and S2-specific CD4 T cells expressing IL2 and S1-specific CD4 T cells expressing IFNγ were higher in E-HDR than in E-HC. In contrast, CD8 T cell responses to

Table 1
Comparison of baseline characteristics between SARS-CoV-2 naive and SARS-CoV-2 experienced HDR.

N (%) or median [Q1 - Q3]	N-HDR	*E*-HDR	*P-value*[*]
	N = 75	*N* = 28	
Age in years	67 [60.0–77.0]	67.5 [54.0–74.5]	*0.446*
Female sex	21 (28.0)	15 (53.6)	***0.021***
Body mass index in kg/m^2	26 [22.8–30.4]	27.5 [23.2–32.8] [a]	*0.378*
Ethnicity			
Caucasian	65 (86.7)	13 (46.4)	***<0.001***
Asiatic	1 (1.3)	0	
North African	7 (9.3)	4 (14.3)	
Subsharian African	2 (2.7)	11 (39.3)	
Active smoking	24 (35.8) [b]	4 (18.2) [c]	*0.186*
Dialysis Mode			
Conventional hemodialysis	60 (80.0)	24 (85.7)	*0.582*
Self-care in-center hemodialysis	15 (20.0)	4 (14.3)	
Dialysis access, avf	28 (38.4) [d]	9 (32.1)	*0.648*
Mean KT/V (one session)	1.46 [1.27–1.52] [e]	1.5 [1.40–1.64] [f]	*0.158*
Mean KT/V (three sessions) + urinary KT/V	4.08 [3.64–4.33] [g]	4.46 [4.12–4.82] [h]	*0.068*
Comorbidities			
Arterial hypertension	64 (85.3)	25 (89.3)	*0.753*
Diabetes	36 (48.0)	18 (64.3)	*0.184*
Ischemic cardiopathy	45 (60.0)	14 (50.0)	*0.38*
Chronic respiratory disease	18 (24.0)	4 (14.3)	*0.42*
History or inactive cancer	16 (21.3)	3 (10.7)	*0.27*
History of transplantation (kidney, lung or heart)	12 (16.0)	4 (14.3)	*>0.99*
History of transplantation (other than kidney)	4 (5.3)	1 (3.6)	*>0.99*
Immunosuppression			
Corticosteroids	10 (13.3)	4 (14.3)	*>0.99*
Mycophenolate mofetil	1 (1.3)	1 (3.6)	*0.472*
Azathioprine	1 (1.3)	0	*>0.99*
Tacrolimus	5 (6.7)	1 (3.6)	*>0.99*
Cyclosporin A	2 (2.7)	1 (3.6)	*>0.99*
Lenalidomide	1 (1.3)	0	*>0.99*
Number of chronic immunosuppressive treatment			
None	63 (84.0)	24 (85.7)	*0.89*
One	6 (8.0)	2 (7.1)	
Two	5 (6.7)	1 (3.6)	
Three	1 (1.3)	1 (3.6)	
Time between HD and RNA vaccination in months	22 [8.6–51.3]	35.4 [12.3–71.5]	*0.323*
Biological data			
Hemoglobin in g/dL	10.7 [10.1–11.4]	10.85 [9.7–11.6]	*0.676*
Absolute white blood cell count in / mm^3	7390 [5850–8590]	7535 [5575–9858]	*0.599*
Absolute neutrophil count in /mm^3	4780 [3510–5930]	5185 [3460–6548]	*0.438*
Absolute lymphocyte count in /mm^3	1380 [810–1840]	1470 [1185–1818]	*0.361*
Absolute monocyte count in /mm^3	640 [530–840]	650 [505–848]	*0.806*
Serum albumin in g/L	38 [34.4–40.0]	38.6 [35.6–42.0]	*0.115*
Serum prealbumin in g/L	0.26 [0.22–0.31]	0.28 [0.24–0.33]	*0.293*
C-reactive protein in mg/L	4.6 [2.0–9.0]	5.9 [2.3–8.1]	*0.867*
Serum phosphorus in mmol/L	1.54 [1.23–1.96]	1.52 [1.23–1.77]	*0.574*
Serum ferritin in µg/L	293 [164–458]	288 [114–429]	*0.525*
Hepatitis B vaccine response			
Negative <10 mIU/mL	26 (34.7)	6 (21.4)	*0.408*
Intermediate 10–200 mIU/mL	28 (37.3)	14 (50.0)	
Positive >200 mIU/mL	21 (28.0)	8 (28.6)	
SARS-CoV-2 infection			
Time between SARS-CoV-2 infection and COVID-19 mRNA vaccination in days	NA	145 [129–318][i]	*NA*
Asymptomatic	NA	5 (17.9)	*NA*

(*continued on next page*)

Table 1 (*continued*)

N (%) or median [Q1 - Q3]	N-HDR	*E*-HDR	*P-value**
	N = 75	*N* = 28	
Need for supplemental oxygen	NA	11 (39.3)	*NA*
Intensive care requirement	NA	3 (10.7)	*NA*

Continuous variables are expressed as median [Q1 - Q3] and categorical variables as frequency (%).
HDR: hemodialysis recipient; HD: hemodialysis; AVF: arteriovenous fistula; RNA: ribonucleic acid; NA: not applicable or not available.
[a] 27 values; [b] 67 values; [c] 22 values; [d] 72 values; [e] 29 values; [f] 19 values; [g] 43 values; [h] 8 values; [i] 23 values.
* Qualitative variables were compared using a Fisher's Exact or chi-square test and quantitative variables were compared using a Mann-Whitney U test.

S1 and S2 were similar in SARS-CoV-2 experienced HDR and HC at baseline and post-vaccination. Frequencies of S1-specific CD8 T cells expressing IFNγ were significantly higher in E-HC than in N-HC.

3.5. Integrated analysis of immune response to mRNA vaccination in naive and SARS-CoV-2 experienced HDR and HC

To visualize and characterize differences in immune response features across individuals and groups, dimensionality reduction was performed using principal component analysis (PCA) [33]. PCA resulted in two components with eigenvalues greater than one that described relationships between immunological parameters following mRNA vaccination. The two major components, PC1 and PC2, accounted for 53.8 % of the total variance (Fig. 6A). SARS-CoV-2 experienced and naive subjects formed distinct clusters, whether HDR or HC. PC1 was significantly different between SARS-CoV-2 experienced and naive subjects, both in HDR and in HC (Fig. 6B). PC2 was significantly different between HDR and HC, both SARS-CoV-2 experienced and naive. As shown in Fig. 6C, humoral immune response features dominated the main principal component, PC1, whereas cellular immune features, specifically CD4 T cell responses, contributed most to PC2. Together, these analyses indicate that N-HDR and *E*-HDR have unique vaccine response profiles across multiple different immune effectors. Moreover, the potential contribution of clinical factors to the different profiles between N-HDR and E-HDR was assessed by multivariate analyses. As shown in Table 1, *E*-HDR included higher proportions of female sex and lower proportions of Caucasians than N-HDR. Multivariate linear regression showed that previous SARS-CoV-2 infection was the only significant variable determining the differences of neutralizing and non-neutralizing functions of antibody response features between both groups (**Table S2**).

3.6. Associations between immune response to mRNA vaccination and clinical characteristics are different in N-HDR and E-HDR

The contrast between the low responses to mRNA vaccination in N-HDR and the potent hybrid immunity acquired in E-HDR suggests differing regulation of vaccine responses in the two study groups. Univariate and multivariate linear regressions were used to explore correlations between demographic, clinical, and biological factors and the immune response features that differed most between N-HDR and E-HDR.

In N-HDR, levels of RBD binding IgG, RBD-specific IgG avidity and titers of nAb were correlated with multiple clinical factors in univariate analyses (Table 2, **Table S3, Table S4, Table S5**). In multivariate analysis, levels of RBD binding IgG were significantly correlated with previous transplantation and with response to HBV vaccination (Table 2 **and Table S3**). RBD-specific IgG avidity was significantly correlated with response to HBV vaccination (**Table S4**). Titers of nAb were significantly correlated with older age, levels of albumin and response to HBV vaccination (**Table S5**). Clinical parameters associated with RBD binding antibody, RBD-specific avidity and nAb levels were also correlated with non-neutralizing functions of S specific antibodies such as FcγRIIa-binding (**Table S6**), FcγRIIIa-binding (**Table S7**), ADCD (**Table S8**) and ADCP levels (**Table S9**). In multivariate analyses, negative correlations with previous transplantation and immunosuppressive treatment and positive correlations with response to HBV vaccination were observed (**Table S6, Table S7, Table S8 and Table S9**). Several clinical and biological parameters were correlated with S1-specific CD4 T cell responses in univariate analyses (**Table S10,**

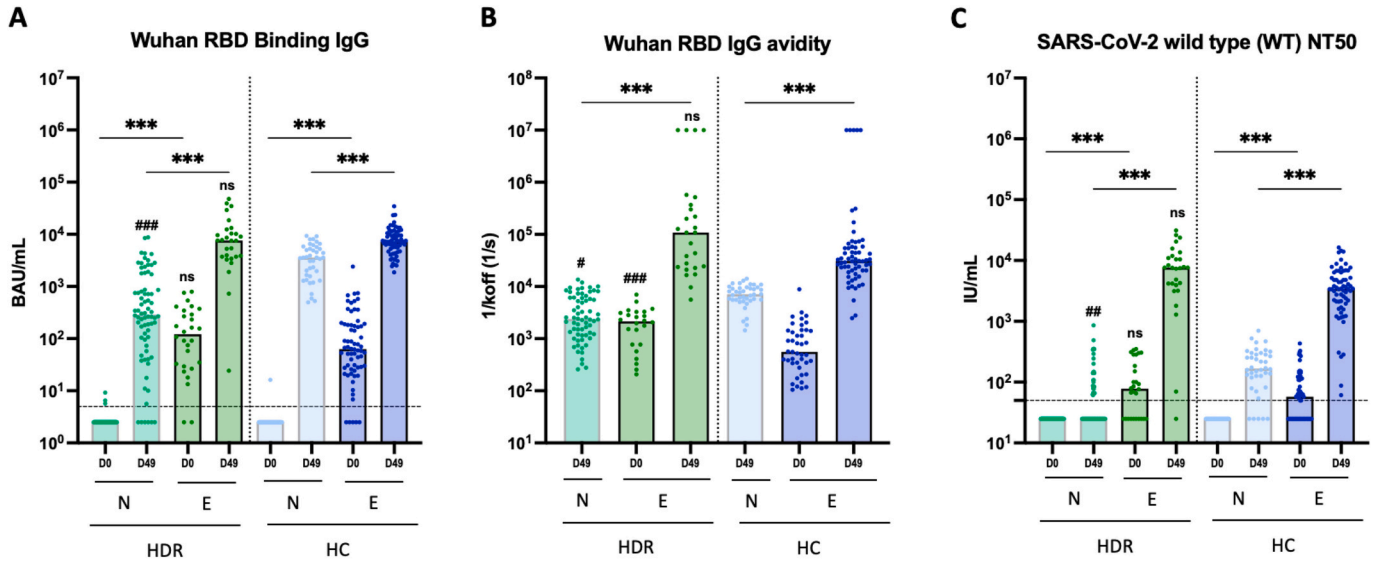

Fig. 1. Binding IgG, RBD IgG avidity and neutralizing antibody responses to SARS-CoV-2 mRNA vaccination in naive and experienced HDR and HC. Serum levels of SARS-CoV-2 receptor binding domain (RBD) specific binding IgG (BAU: binding antibody units), RBD specific IgG avidity (k_{off}: dissociation rate constant) and titers of neutralizing antibodies (NT50: 50 % neutralization titer) were measured before vaccination (D0) and 1 month after 2 doses of mRNA vaccine (D49) in naive hemodialysis recipients (N-HDR, light green), experienced (E-)HDR (dark green), naive healthy controls (N-HC, light blue) and experienced (E-)HC (dark blue). Bars indicate median values. Horizontal dashed lines indicate a technical negative signal (blank). Dunn's test results using Bonferroni correction are shown as followed: for within HC or HDR comparisons, ns: not significant; *:$p < 0.05$; **:$p < 0.01$; ***:$p < 0.001$; for comparisons between HC and HDR, ns: not significant; #: $p < 0.05$; ##:$p < 0.01$; ###:$p < 0.001$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

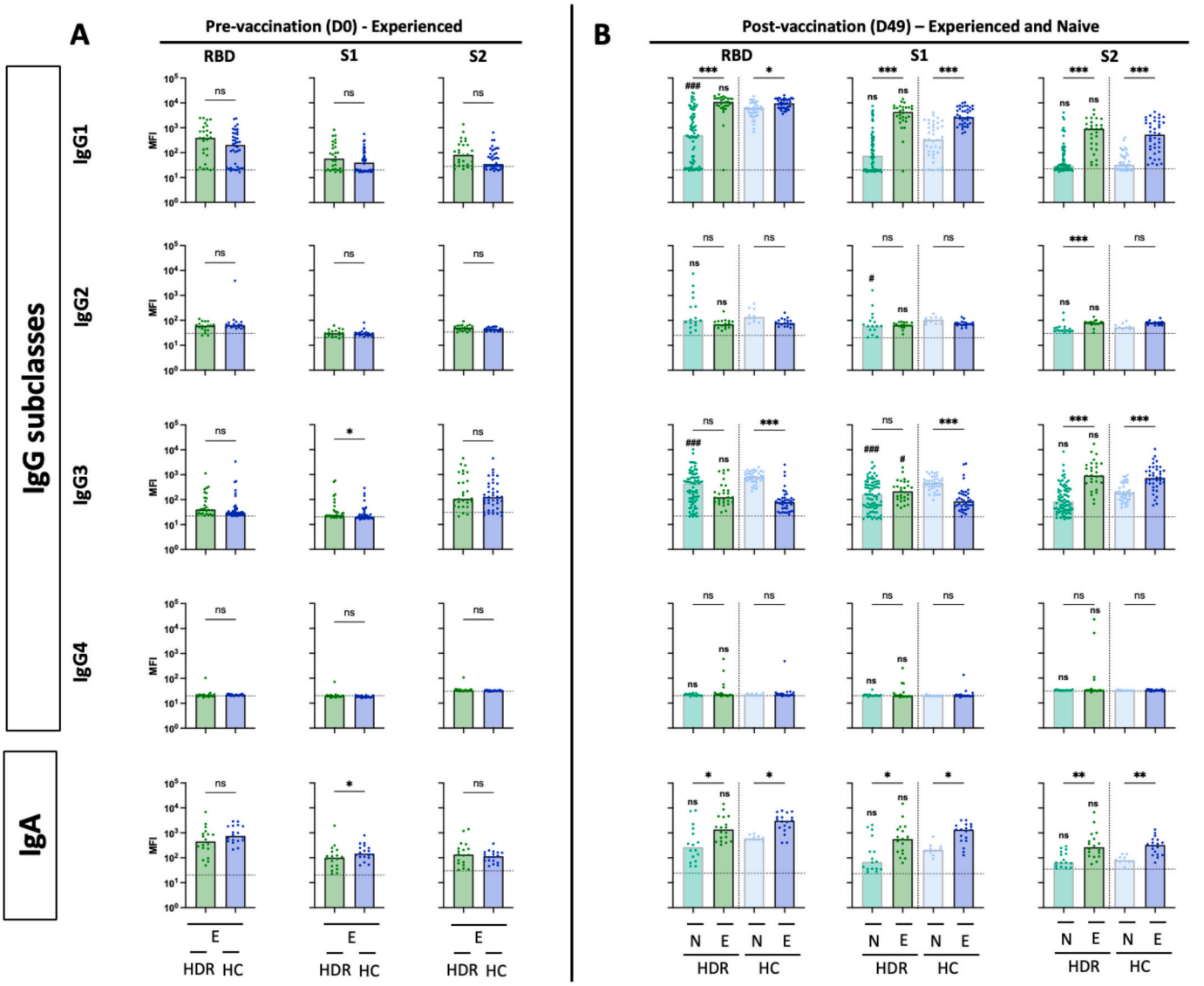

Fig. 2. IgG Subclasses and IgA responses to SARS-CoV-2 mRNA vaccination in naive and experienced HDR and HC. Serum levels of SARS-CoV-2 Receptor Binding Domain (RBD) specific, spike S1 subunit specific, and spike S2 subunit specific IgG1, IgG2, IgG3, IgG4 and IgA were measured before vaccination (D0, panel A) and 1 month after vaccination (D49, panel B) in naive hemodialysis recipients (N-HDR, light green), experienced (E-)HDR (dark green), naive healthy controls (N-HC, light blue) and experienced (E-)HC (dark blue). MFI: median fluorescent intensity. Bars indicate median values. Horizontal dashed lines indicate a technical negative signal (blank). Dunn's test results using Bonferroni correction are shown as followed: for within HC or HDR comparisons, ns: not significant; *:p < 0.05; **:$p < 0.01$; ***:$p < 0.001$; for comparisons between HC and HDR, ns: not significant; #:p < 0.05; ##:p < 0.01; ###:$p < 0.001$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table S11 and Table S12). In multivariate analyses, levels of albumin and intermediate response to HBV vaccination were positively correlated with frequencies of S1-specific CD4 T cells expressing IFNγ (**Table S10**); corticosteroid treatment negatively correlated and levels of albumin and response to HBV vaccination positively correlated with S1-specific CD4 T cells expressing CD154 (**Table S11**); and hypertension negatively correlated and levels of albumin and response to HBV vaccination positively correlated with S1-specific CD4 T cells expressing IL2 (**Table S12**). Together, these results indicate that several parameters correlated with low immune response in N-HDR, including previous transplantation, chronic immunosuppressive treatment, low levels of albumin, older age, hypertension, and a low response to HBV vaccination.

Distinct factors influenced vaccine responses in *E*-HDR (Table 2 **and Table S13 to S20**). In multivariate analysis of risk factors in E-HDR, time between infection and vaccination was positively correlated with levels of RBD binding IgG, RBD IgG avidity, nAb, S1 FcγRIIa-binding IgG, S1 FcγRIIIa-binding IgG, RBD ADCP, as well as frequencies of S1-specific CD4 T cells expressing IFNγ (Table 2**, Table S13, Table S14, Table S15, Table S16, Table S17, Table S19, Table S20**). Previous transplantation was negatively correlated with levels of S1 FcγRIIa-binding IgG (**Table S16**), S1 FcγRIIIa-binding IgG (**Table S17**) and S1 ADCD (**Table S18**). Body mass index was positively correlated with frequencies of S1-specific CD4 T cells expressing IFNγ (**Table S20**). Inactive cancer or history of cancer were negatively correlated with frequencies of S1-specific CD4 T cells expressing IL2 (**Table S22**).

To further explore the role of demographic and clinical factors in immune response features in N-HDR and *E*-HDR, we performed PCA, and we analyzed their correlations with dominant PCs (**Fig. S2 and Fig. S3**). In line with multivariate regression analyses, in N-HDR, PC1 was correlated with levels of hemoglobin, levels of albumin, positive response to HBV vaccination, previous transplantation, and immunosuppressive treatment particularly with corticosteroids and tacrolimus. PC2 was correlated with ethnicity and time between hemodialysis

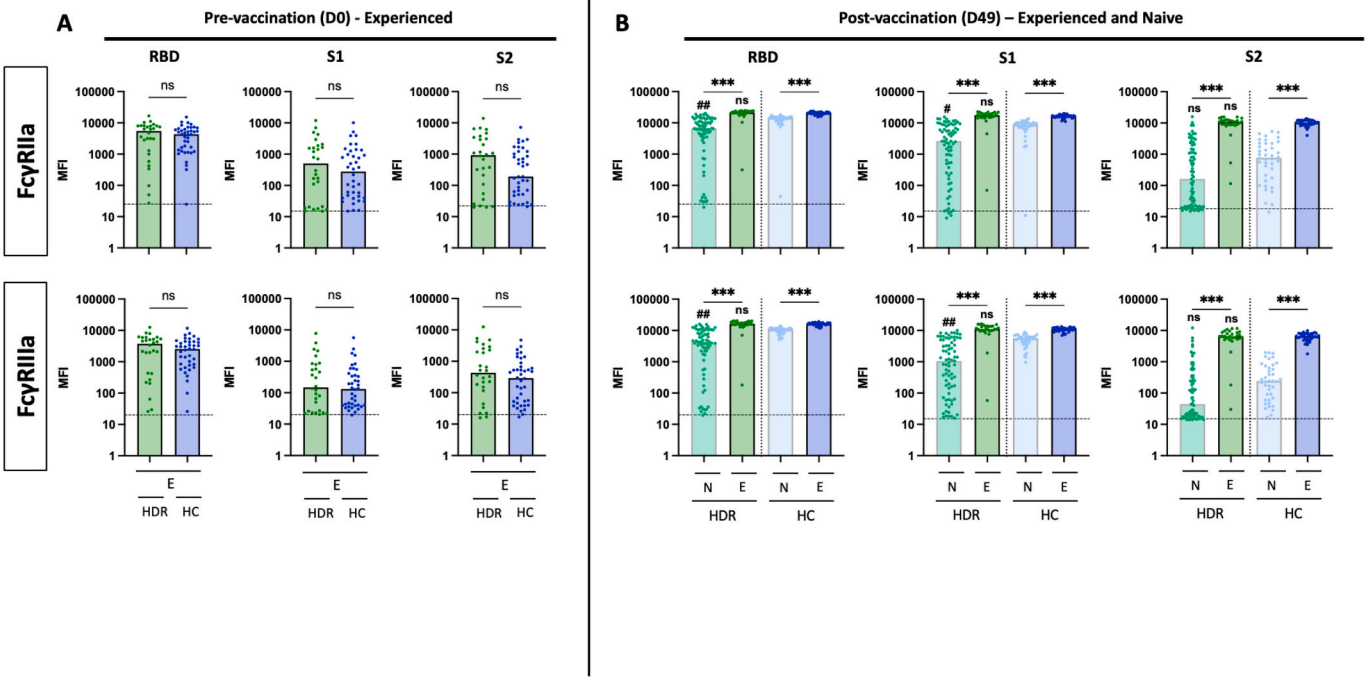

Fig. 3. Fcγ receptors binding antibody responses to SARS-CoV-2 mRNA vaccination in naive and experienced HDR and HC. Serum levels of SARS-CoV-2 Receptor Binding Domain (RBD) specific, spike S1 subunit specific, and spike S2 subunit specific antibodies binding the Fcγ receptors FcγRIIa and FcγRIIIa were measured before vaccination (D0, panel A) and 1 month after vaccination (D49, panel B) in naive hemodialysis recipients (N-HDR, light green), experienced (E-)HDR (dark green), naive healthy controls (N-HC, light blue) and experienced (E-)HC (dark blue). MFI: median fluorescent intensity. Bars indicate median values. Horizontal dashed lines indicate a technical negative signal (blank). Dunn's test results using Bonferroni correction are shown as followed: for within HC or HDR comparisons, ns: not significant; *:$p < 0.05$; **:$p < 0.01$; ***:$p < 0.001$; for comparisons between HC and HDR, ns: not significant; #:$p < 0.05$; ##:$p < 0.01$; ###:$p < 0.001$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

initiation and vaccination (**Table S23**). In E-HDR, PC1 was correlated with time between infection and vaccination, and PC2 was correlated with KT/V and ischemic cardiopathy (**Table S24**). Together, these data further support the observation that distinct factors are associated with low vaccine responses in N-HDR and in *E*-HDR.

4. Discussion

Defective immune response to vaccination has long been a concern for the prevention of severe infections in HDR. The high burden of morbidity and mortality associated with COVID-19 and the lower immune responses to SARS-CoV-2 mRNA vaccination have highlighted the need to develop more effective approaches to protect this vulnerable population from emerging pathogens. The observation that HDR can acquire high levels of hybrid immunity when infected with SARS-CoV-2 before COVID-19 mRNA vaccination has provided a proof of principle that effective immunity can be induced in these patients [3,5,9,19]. In this study, we comprehensively assessed vaccine-induced humoral and cellular immunity in HDR and demonstrated that distinct factors influence vaccine responses in *E*-HDR and N-HDR.

At baseline, high levels of polyfunctional antibody and T cell responses to SARS-CoV-2 spike protein were observed after SARS-CoV-2 infection in E-HDR, even higher regarding some immune parameters, confirming previous reports [34]. Anft et al. reported that HDR may have higher T cell responses to SARS-CoV-2 infection as compared to patients with normal renal function [34]. The combination of higher IgG avidity and IL2-producing CD4 T cell responses in E-HDR as compared to E-HC suggests qualitatively different interactions between T cells and B cells between the two groups [35,36]. Survival bias, more severe COVID-19, and prolonged viral shedding in *E*-HDR as compared to E-HC could contribute to the differences in immune responses observed between the two groups [37–42].

As previously reported, N-HDR had lower RBD binding and neutralizing antibody responses to the spike protein following mRNA vaccination as compared to N-HC [4,32,43]. We now show that this difference extends to Fcγ receptor binding and ADCD responses. In contrast, ADCP as well as CD4 and CD8 T cell responses to vaccination were not significantly different between the two groups. These data indicate that in SARS-CoV-2 naive HDR, T cell and some functional IgG responses are less affected by ESRD and hemodialysis-associated immune suppression.

Previous SARS-CoV-2 infection enhanced polyfunctional antibody responses to mRNA vaccination in HDR, as observed in HC. The higher humoral responses, including binding IgG and IgA, neutralizing antibody and Fcγ receptor-dependent responses, and higher frequencies of S1-specific CD4 T cells expressing IFNγ in *E*-HDR as compared to N-HDR following vaccination are consistent with previous reports [3,5,8,10] showing higher binding IgG and IFNγ responses to mRNA vaccination in SARS-CoV-2 convalescent as compared to naive HDR and show that hybrid immunity involves enhanced humoral and cellular immune responses in these patients. Previous studies reported a dampened CD8 T cell response to COVID-19 vaccination in subjects previously infected with SARS-CoV-2 [44,45]. Our data in *E*-HDR or E-HC do not show such altered CD8 T cell responses but confirm the differential impact of hybrid immunity on CD4 and CD8 T cell responses to SARS-CoV-2 spike protein. Although the mechanisms underlying hybrid immunity remain incompletely understood, the efficient priming of memory B cells and CD4 T cells, boosted by mRNA vaccination, likely plays a central role

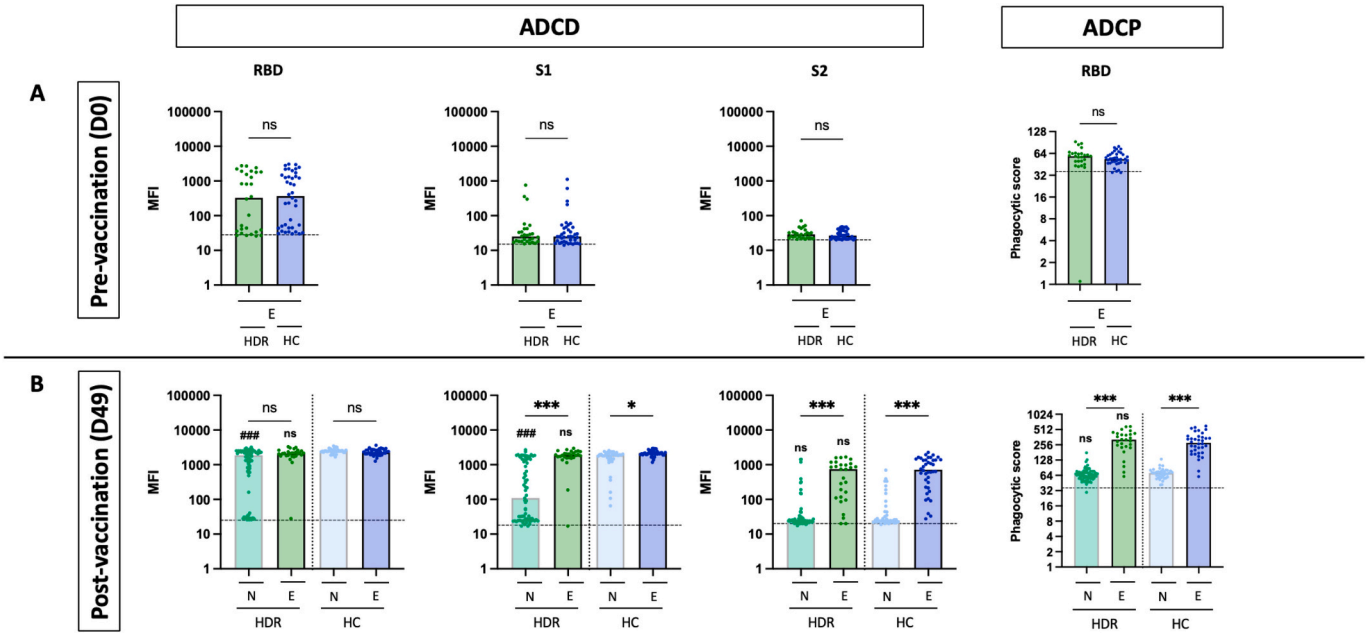

Fig. 4. IgG-dependent complement deposition and phagocytosis responses to SARS-CoV-2 mRNA vaccination in naive and experienced HDR and HC. Serum levels of SARS-CoV-2 Receptor Binding Domain (RBD) specific, spike S1 subunit specific, and spike S2 subunit specific IgG promoting complement deposition (ADCD) and cellular phagocytosis (ADCP) were measured before vaccination (D0, panel A) and 1 month after vaccination (D49, panel B) in naive hemodialysis recipients (N-HDR, light green), experienced (E-)HDR (dark green), naive healthy controls (N-HC, light blue) and experienced (E-)HC (dark blue). Levels of ADCD are expressed as MFI: median fluorescent intensity. Levels of ADCP are expressed as phagocytic score (see methods). Bars indicate median values. Horizontal dashed lines indicate a technical negative signal (blank). Dunn's test results using Bonferroni correction are shown as followed: for within HC or HDR comparisons, ns: not significant; *:$p < 0.05$; **:$p < 0.01$; ***:$p < 0.001$; for comparisons between HC and HDR, ns: not significant; #:$p < 0.05$; ##:$p < 0.01$; ###:$p < 0.001$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

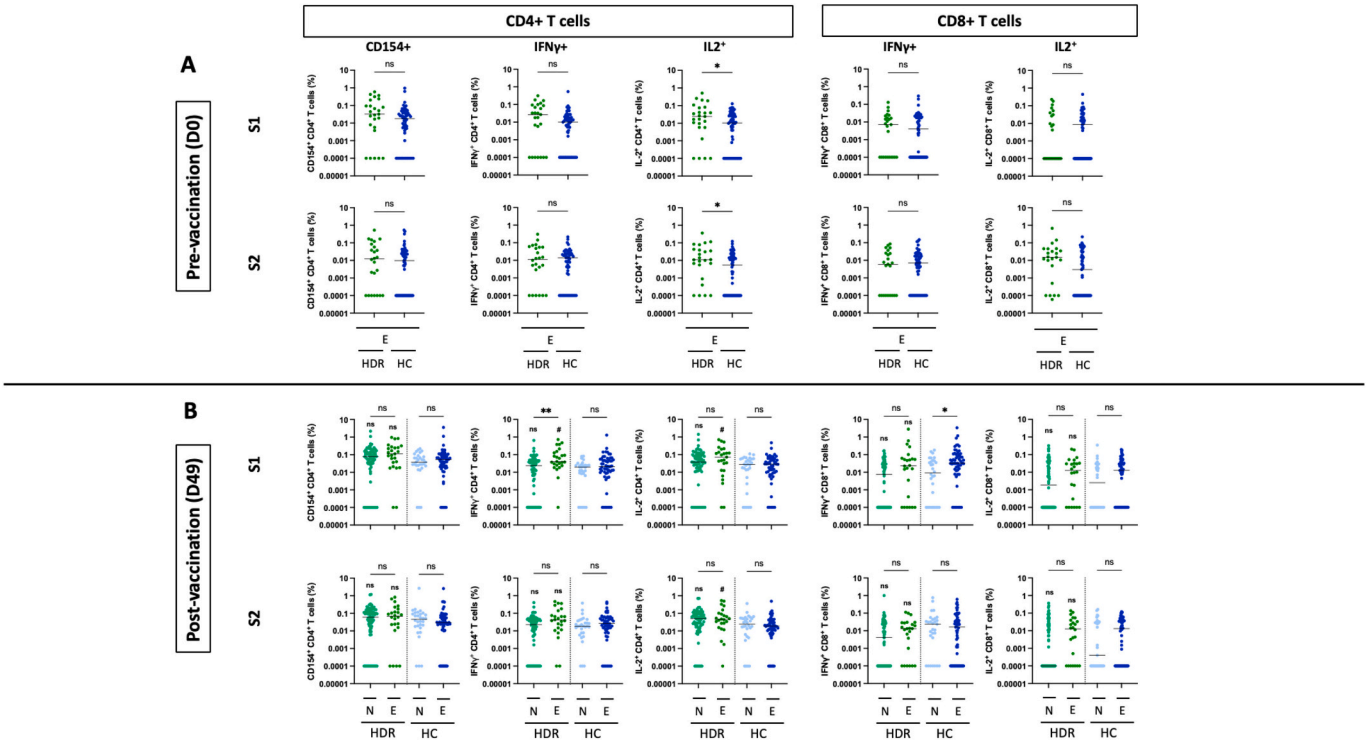

Fig. 5. CD4 and CD8 T cell responses to SARS-CoV-2 mRNA vaccination in naive and experienced HDR and HC. Percentage of SARS-CoV-2 spike S1 subunit and spike S2 subunit specific CD4 T cells expressing CD154, IFNγ and IL2, and of CD8 T cells expressing IFNγ and IL2 were measured in peripheral blood before vaccination (D0, panel A) and 1 month after vaccination (D49, panel B) in naive hemodialysis recipients (N-HDR, light green), experienced (E-)HDR (dark green), naive healthy controls (N-HC, light blue) and experienced (E-)HC (dark blue). Bars indicate median values. Dunn's test results using Bonferroni correction are shown as followed: for within HC or HDR comparisons, ns: not significant; *:$p < 0.05$; **:$p < 0.01$; ***:$p < 0.001$; for comparisons between HC and HDR, ns: not significant; #:$p < 0.05$; ##:$p < 0.01$; ###:$p < 0.001$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

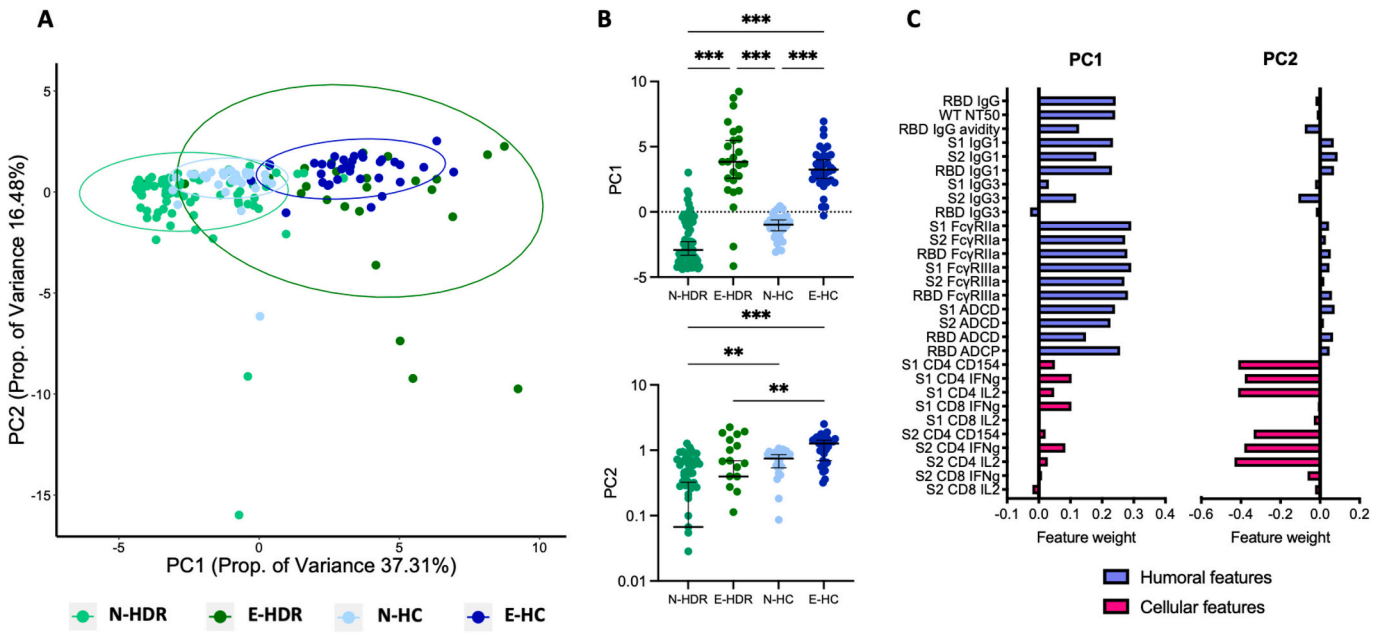

Fig. 6. Principal component analysis of immune responses to SARS-CoV-2 mRNA vaccination in naive and experienced HDR and HC. A. Scatter plot of principal component analysis (PCA) including all immune response parameters except IgG2, IgG4 and IgA measured 1 month after vaccination (D49) in naive hemodialysis recipients (N-HDR, light green), experienced (E-)HDR (dark green), naive healthy controls (N-HC, light blue) and experienced (E-)HC (dark blue). Colored ellipses (size determined by a 0.95 probability level) show the observances grouped by the marked class. B. Comparison of PC1 and PC2 values between groups by Dunn's test results using Bonferroni correction with $p < 0.05$. *:p < 0.05; **:p < 0.01; ***:p < 0.001. C. Relative weighting of individual immune response parameters in PC1 and PC2. PC: principal component. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Univariate and multivariate linear regressions related to RBD binding IgG response after mRNA vaccination in N-HDR and *E*-HDR.

RBD Binding IgG		Univariate linear regression			Multivariate linear regression		
		Estimate (B)	95 % CI	*P-value*	Estimate	Standard error	*P-value*
N-HDR	Kidney or other organ transplantation	−0.92	−1.5, −0.38	***0.001***	−0.57	0.25	***0.024***
	Chronic immunosuppressive treatment	−1,1	−1.6, −0.61	***<0.001***			
	Corticosteroids	−1.1	−1.7, −0.51	***<0.001***			
	Tacrolimus	−1.2	−2.0, −0.40	***0.004***	−0.67	0.36	*0.068*
	Serum albumin	0.08	0.04, 0.13	***<0.001***	0.04	0.02	*0.074*
	Serum ferritin	0.00	0.00, 0.00	***0.027***	−0.00	0.00	*0.051*
	Positive hepatitis B vaccine response	1.2	0.79, 1.7	***<0.001***	0.48	0.11	***<0.001***
	Time between SARS-CoV-2 infection and COVID-19 mRNA vaccination	/	/	/	/	/	/
E-HDR	Kidney or other organ transplantation	−0.21	−0.91, 0.49	0.5			
	Chronic immunosuppressive treatment	−0.29	−0.99, 0.40	0.4			
	Corticosteroids	−0.29	−0.99, 0.40	0.4			
	Tacrolimus	/	/	/	/	/	/
	Serum albumin	−0.02	−0.09, 0.04	0.5			
	Serum ferritin	0.00	0.00, 0.00	0.5			
	Positive hepatitis B vaccine response	−0.62	−1.3, 0.06	0.071			
	Time between SARS-CoV-2 infection and COVID-19 mRNA vaccination	0.00	0.00, 0.01	**0.003**	0.00	0.00	***0.003***

Significant ($p < 0.05$) univariate and multivariate linear regressions with log(10) RBD Binding IgG after vaccination in N-HDR and E-HDR, respectively. For the univariate analyses, all variables that were significant ($p < 0.05$) in N-HDR and/or E-HDR are reported for both groups. A multivariate analysis per group was then done, including only the variables ($p < 0.05$) significant in its own group. Of note, significant variables in univariate analysis with less than 3 subjects per category were not included in the multivariable analysis.
E-HDR: SARS-CoV-2 experienced hemodialysis recipients; N-HDR: SARS-CoV-2 naive hemodialysis recipients.

[46,47].

In N-HDR, all antibody response and CD4 T cell response parameters were positively correlated with the response to previous hepatitis B vaccination. This observation suggests that hemodialysis alters common immune pathways that are involved in the response to different types of vaccines. Importantly, immunogenicity of hepatitis B vaccination is improved by the addition of an adjuvant [17]. The use of adjuvants to enhance the immunogenicity of mRNA vaccines has been proposed but has not yet been evaluated in HDR [48]. The absence of correlation with the response to previous hepatitis B vaccination in *E*-HDR suggests that priming of the immune system by SARS-CoV-2 infection compensates for immune pathways alterations associated with defective vaccine responses. Moreover, the association between several clinical factors, such as hypoalbuminemia, older age, and hypertension, with reduced immune responses to COVID-19 vaccination observed in N-HDR, but not in *E*-HDR, further supports the notion that previous SARS-CoV-2 infection compensates the immunodeficiency associated with several clinical factors in HDR.

Intriguingly, the association between immunosuppressive therapy with reduced humoral and cellular responses to mRNA vaccination was

observed in N-HDR only whereas previous organ transplantation was associated with reduced humoral responses in both N-HDR and E-HDR, suggesting that current use of immunosuppressive drugs does not significantly reduce the immune priming induced by SARS-CoV-2 infection, whereas previous organ transplantation is associated with a prolonged alteration of immune pathways involved in the induction of antibody response to vaccination. The nature of such alteration remains to be defined but likely involves changes in the programming of immune cells or immune cell progenitors.

The positive correlation of time between SARS-CoV-2 infection and vaccination in E-HDR with humoral and cellular responses to mRNA vaccination confirms previous studies in healthy adults, and suggests the intriguing notion that immunological memory primed by SARS-CoV-2 infection improves with time post-infection [49]. How long after infection a plateau may be reached has not been established.

Together, our observations indicate that previous SARS-CoV-2 infection primes B and CD4 T cell responses and increases responses to mRNA vaccination in HDR, as it does in healthy adults. Identifying the immune pathways involved could provide a basis for improved vaccination of this vulnerable population against emerging pathogens. Systems biology has been successfully applied to identify immune pathways promoting responses to vaccination, including COVID-19, in healthy adults but has not yet been used to identify predictors of vaccine responses in HDR [50].

An important strength of this study is that HDR and HC were recruited before the administration of the first dose of COVID-19 vaccine and were included in parallel studies with standardized protocols and procedures. One of the limitations of our work is its relatively small sample size. Nevertheless, our study was able to confirm differences in vaccine responses between groups and risk factors associated with low vaccine responses in N-HDR that were previously reported in larger studies. Further studies of hybrid immunity in other HDR populations are needed to validate our observations. Other limitations include the lack of follow-up of the study population and the focus of the analysis on the immune response to the Wuhan strain. The study was focused on the response to primary immunization as it offered the best model to compare vaccine-induced immunity and their determinants independently of post-vaccination exposure to SARS-CoV-2 variants.

In conclusion, distinct factors influence humoral and cellular immune responses to COVID-19 mRNA vaccination in naive and previously SARS-CoV-2 infected HDR. Understanding the cellular and molecular bases of hybrid immunity in HDR has the potential to help the development of optimized vaccination strategies against emerging pathogens for this vulnerable population.

Funding

This study was co-funded by the Belgian Federal Government through Sciensano, Belgium, by the Fonds de la Recherche Scientifique, F.R.S.-FNRS, Belgium, and by the Fonds Erasme, Belgium. N.G. received a PhD studentship from the Fonds Erasme and from the F.R.S- FNRS. D. K. received a PhD studentship from the Fonds Erasme and from the F.R.S- FNRS. A.M. is Research Director of the F.R.S.-FNRS. This study was supported in part by the US NIAID (grants R56AI165448 and P01AI162242).

CRediT authorship contribution statement

Nicolas Gemander: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Delphine Kemlin:** Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Stéphanie Depickère:** Software, Resources. **Natasha S. Kelkar:** Formal analysis. **Shilpee Sharma:** Supervision, Formal analysis. **Pieter Pannus:** Supervision, Methodology. **Alexandra Waegemans:** Formal analysis. **Véronique Olislagers:** Supervision, Formal analysis. **Daphnée Georges:** Formal analysis. **Emilie Dhondt:** Formal analysis. **Margarida Braga:** Formal analysis. **Leo Heyndrickx:** Formal analysis. **Johan Michiels:** Formal analysis. **Anaïs Thiriard:** Supervision, Formal analysis. **Anne Lemy:** Data curation. **Thomas Baudoux:** Data curation. **Marylène Vandevenne:** Formal analysis. **Maria E. Goossens:** Funding acquisition. **André Matagne:** Supervision. **Isabelle Desombere:** Supervision. **Kevin K. Ariën:** Supervision. **Margaret E. Ackerman:** Supervision. **Alain Le Moine:** Funding acquisition, Conceptualization. **Arnaud Marchant:** Writing – original draft, Visualization, Validation, Supervision, Resources, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Nicolas Gemander reports financial support was provided by Sciensano. Margaret Ackerman reports financial support was provided by US NIAID (grants R56AI165448 and P01AI162242). Margaret Ackerman reports financial support was provided by NIH NIGMS. Margaret Ackerman reports financial support was provided by Bill and Melinda Gates Foundation. Margaret Ackerman reports financial support was provided by SD Ireland Foundation. Margaret Ackerman reports equipment, drugs, or supplies was provided by Johns Hopkins Universities. Margaret Ackerman reports article publishing charges was provided by Elsevier. Margaret Ackerman reports financial support was provided by Seromyx systems. Margaret Ackerman reports financial support was provided by Keystone Conferences. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We acknowledge the contribution of the Robotein platform of the BE Instruct-ERIC Centre for providing access to the Octet HTX and the Microlab STAR liquid handling workstation. We thank all the staff members of Department of Nephrology, Dialysis and Transplantation at Erasme Hospital to conduct the clinical study and all the staff members of European Plotkin Institute for Vaccinology (ULB) to conduct experiments and data analysis. Particularly, we thank Sorya Fagnoul and Emilie Navaux for the help in the recruitment of patients. Maria Spanu, Anne Gillardin and Sophie Verhofstadt for the sampling and the follow-up of patients. Inès Vu Duc, Fatima Gjemajli, Sara Cuman, Robin Van Naemen, Florian Ballieu, Vianney Nana Tchouta, Marie-Annick Ottou Eyenga and Caroline Rodeghiero for technical assistance. The authors thank the Fonds Erasme for their support. Last, we thank all the patients and the healthcare workers for participation in this clinical study. Graphical abstract was created with BioRender.com.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2024.126544.

Data availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request, following material transfer agreement.

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