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Original Article

ORIGINAL ARTICLE

Longitudinal SARS-CoV-2 neutralization of Omicron BA.1, BA.5 and BQ.1.1 after four vaccinations and the impact of breakthrough infections in haemodialysis patients

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ABSTRACT

Background. Individuals on haemodialysis (HD) are more vulnerable to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection than the general population due to end-stage kidney disease–induced immunosuppression.
Methods. A total of 26 HD patients experiencing SARS-CoV-2 infection after a third vaccination were matched 1:1 with 26 of 92 SARS-CoV-2-naïve patients by age, sex, dialysis vintage and immunosuppressive drugs receiving a fourth vaccination with a messenger RNA–based vaccine. A competitive surrogate neutralization assay was used to monitor vaccination success. To determine infection neutralization titres, Vero-E6 cells were infected with SARS-CoV-2 variants of concern (VoCs), Omicron sublineage BA.1, BA.5 and BQ.1.1. The 50% inhibitory concentration (IC50, serum dilution factor 1:x) was determined before, 4 weeks after and 6 months after the fourth vaccination.

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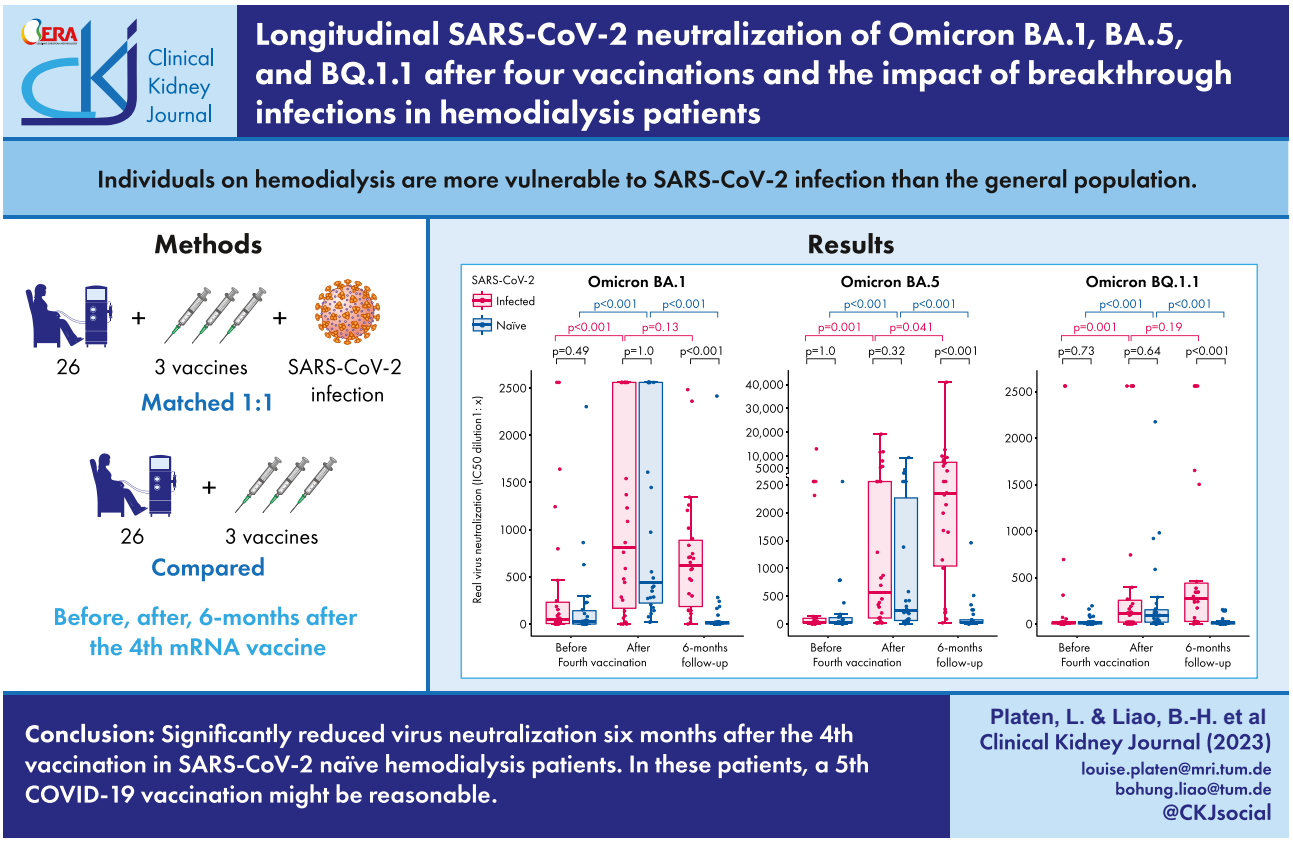
Results. A total of 52 HD patients received four coronavirus disease 2019 (COVID-19) vaccinations and were followed up for a median of 6.3 months. Patient characteristics did not differ between the matched cohorts. Patients without a SARS-CoV-2 infection had a significant reduction of real virus neutralization capacity for all Omicron sublineages after 6 months ($P < .001$ each). Those patients with a virus infection did not experience a reduction in real virus neutralization capacity after 6 months. Compared with the other Omicron VoC, the BQ.1.1 sublineage had the lowest virus neutralization capacity.

Conclusions. SARS-CoV-2-naïve HD patients had significantly decreased virus neutralization capacity 6 months after the fourth vaccination, whereas patients with a SARS-CoV-2 infection had no change in neutralization capacity. This was independent of age, sex, dialysis vintage and immunosuppression. Therefore, in infection-naïve HD patients a fifth COVID-19 vaccination might be reasonable 6 months after the fourth vaccination.

LAY SUMMARY

Haemodialysis (HD) patients are a vulnerable patient group when infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Immunity after vaccination is less pronounced and diminishes more quickly in these patients when compared with healthy individuals. We matched and compared 26 HD patients experiencing a SARS-CoV-2 breakthrough infection after full vaccination with 26 virus-naïve patients and followed them up for 6 months after the fourth vaccination. We found rapidly decreasing immunity in the form of virus neutralization capacity for the current Omicron variants BA.5 and BQ.1.1 in SARS-CoV-2-naïve patients 6 months after the fourth vaccination, whereas in convalescents from infection, relatively stable titres in real-virus neutralization assays were observed. Overall, the recent Omicron BQ.1.1 sublineage showed the highest immune escape capacity, arguing for a booster vaccination with an adapted vaccine in SARS-CoV-2-naïve HD patients.

GRAPHICAL ABSTRACT



Keywords: BA.1, BA.5, BQ.1.1, COVID-19 vaccination, haemodialysis

INTRODUCTION

Due to their impaired immune systems, haemodialysis (HD) patients are known to be at high risk for severe courses of coronavirus disease 2019 (COVID-19) [1]. It has been observed that the currently available vaccinations against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) significantly reduce the mortality of COVID-19 in HD patients [2]. Nevertheless, a lower humoral response to vaccination in HD patients

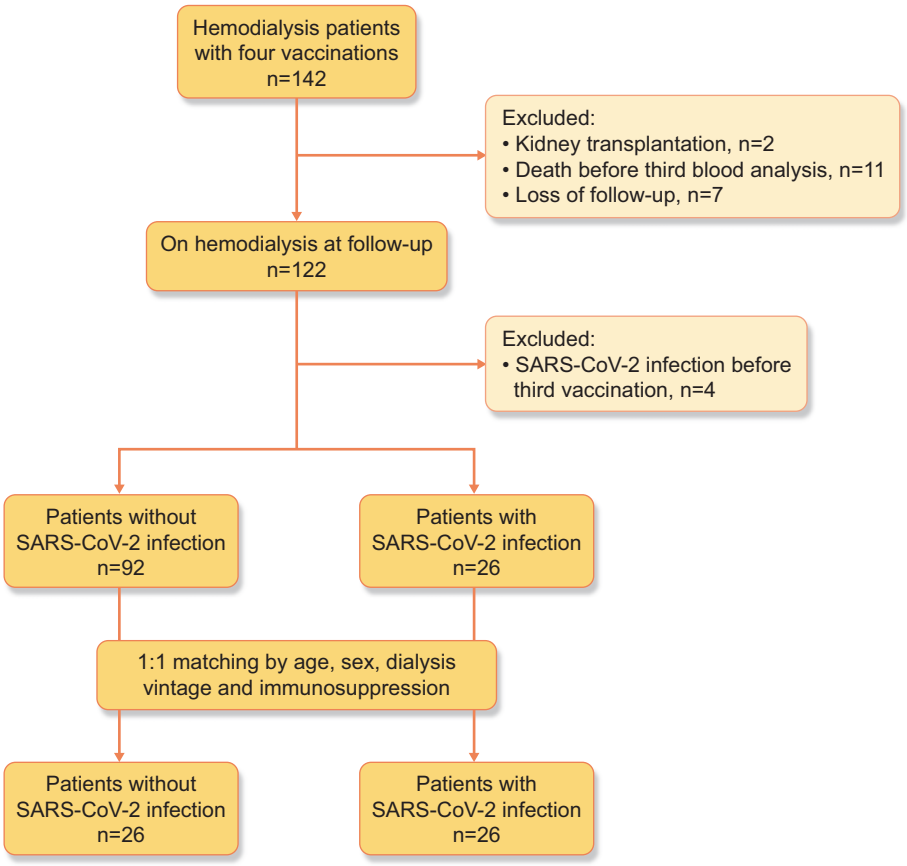


Figure 1: Flow chart of the study cohort. A cohort of 142 HD patients received a fourth COVID-19 vaccination. A total of 122 patients on HD who could be followed up for 6 months (median 191 days) after a fourth vaccination were enrolled in this study. At the end of follow-up, 30 of 122 patients (24.5%) had experienced a SARS-CoV-2 breakthrough infection. Of these, 26 patients were selected who experienced a SARS-CoV-2 infection after the third vaccination and were matched to SARS-CoV-2-naïve patients.

compared with healthy controls has been reported as well as a significant decline in antibody levels and seropositivity over time [3–5]. Meanwhile, the continuous emergence of new variants and subvariants with immune-evasive properties [6] leads to an increased rate of breakthrough infections and necessitates research on the immune capacity generated by the initial wild-type-specific vaccinations.

HD patients are advised by German health authorities to perform a basic immunization consisting of three vaccinations followed by booster shots at least 3 months after the last immunization. Since homogeneous data on the impact of infections on immunity in HD patients are limited, there are no clear recommendations for patients after SARS-CoV-2 infections [7].

An Omicron breakthrough infection in HD patients may induce higher Omicron-specific antibody titres and fewer non-responders than vaccination only. A primary variant of concern (VoC) BA.1 or BA.2 infection seems to mainly generate variant-specific humoral immunity [8, 9]. In older healthy adults, breakthrough infections seem to generate a more durable humoral immunity than vaccinations alone [10].

The aim of this study was to investigate the course of the immune response in infection-naïve compared with recently infected HD patients after the fourth vaccination over 6 months independent of age, sex, dialysis vintage and immunosuppressive medication in an observational matched cohort study. Here we present the results of the live-virus infection neutralization of SARS-CoV-2 VoC Omicron BA.1, BA.5 and BQ.1.1 and antibody-mediated immunity shortly before, 4 weeks after and 6 months after the fourth COVID-19 vaccination in a matched cohort of 52 HD patients.

MATERIALS AND METHODS

Study design

The COVIIMP study (German: 'COVID-19-Impfansprechen immunsupprimierter Patient*innen') is an observational cohort. The study design has been described previously [11]. In brief, the immune status and COVID-19 infections of HD patients and other immunocompromised patients are observed. The study conforms to the ethical guidelines of the Helsinki Declaration and has been approved by the local ethics committee (ethic vote 163/21 S-SR, 19 March 2021, Medical Ethics Committee of the Klinikum rechts der Isar of the Technical University of Munich) and was reported (NIS592) to the Paul Ehrlich Institute. All study participants provided written informed consent.

Study population

A total of 142 HD patients who had received four COVID-19 vaccinations through 20 March 2022 were recruited from four dialysis centres (Kidney Center Eifeldialyse, Mechernich, Germany; KfH Kidney Center München-Harlaching, Munich,

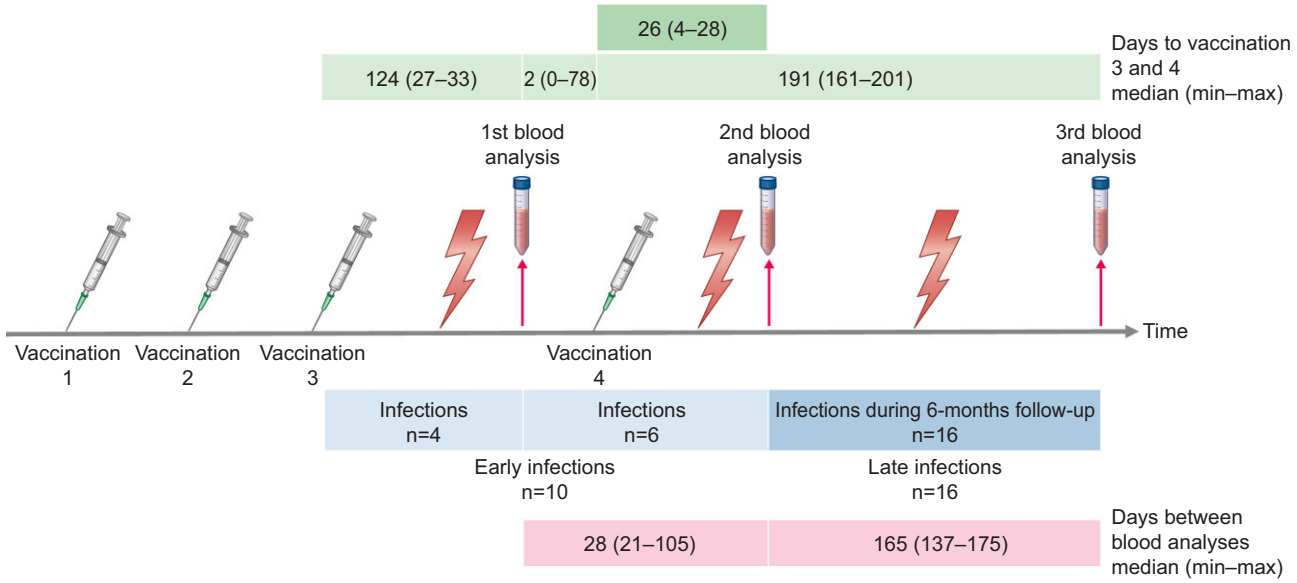


Figure 2: Timing of SARS-CoV-2 breakthrough infections. Patients with a SARS-CoV-2 infection after the third vaccination but before the second blood sample taken a median of 26 days after the fourth vaccination were defined as early infections ($n = 10$). Patients with an infection during the follow-up period, i.e. after the second blood sample taken a median of 26–191 days after the fourth vaccination were defined as late infections ($n = 16$). vac: vaccination; min: minimum; max: maximum.

Germany; KfH Kidney Center Traunstein, Traunstein, Germany; Klinikum rechts der Isar München, Munich, Germany). All patients were vaccinated by their treating physicians according to German guidelines. Twenty patients were lost to follow-up and four patients were excluded because they experienced a SARS-CoV-2 breakthrough infection before the third vaccination, resulting in a cohort of 118 patients. Twenty-six of the 118 patients experienced a SARS-CoV-2 breakthrough infection after the third vaccination and in the remaining 92 patients, no history of SARS-CoV-2-infection was verifiable. Propensity score matching was carried out for the variables age, sex, dialysis vintage and presence of immunosuppressive medication using the MatchIt package in R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) to match these 26 patients with a history of SARS-CoV-2 infection to 26 of 92 SARS-CoV-2-naïve patients (Fig. 1).

Blood analysis was performed three times in the 52 included participants between February and September 2022. The time of analysis was a median of 124 days [interquartile range (IQR) 103–124; minimum 27, maximum 133] after the third vaccination and 26 days (IQR 26–26; minimum 6, maximum 28) and 191 days (IQR 191–192; minimum 161, maximum 201) days after the fourth vaccination.

Dialysis data including total ultrafiltration, dialysis duration, patients' weight before and after dialysis as well as dry weight as defined by the local physician and the dialysis modality was collected at three time points [time of the fourth vaccination, time of the second blood draw and time of the third blood draw (±1 week)]. The percentage above the dry weight was calculated as follows: dry weight = [(weight before dialysis − dry weight) ÷ dry weight] × 100% [12].

SARS-CoV-2 infections

SARS-CoV-2 infections were defined by a reported polymerase chain reaction (PCR)-confirmed infection or by a new positive N-specific immunoglobulin G (IgG) level in the blood analysis. SARS-CoV-2 infections before the second blood sample were defined as early infection and breakthrough infections during the follow-up period were defined as late infections (Fig. 2). Data on the severity of all clinically apparent SARS-CoV-2 infections were collected and categorized into mild, moderate and severe disease using the World Health Organization (WHO) score [13].

SARS-CoV-2 IgG assay

Two types of SARS-CoV-2-specific IgG-type antibodies were measured by chemiluminescent immunoassays (CLIAs) using magnetic particle–based detection on an iFlash 1800 CLIA Analyzer (YHLO Biotechnology, Shenzen, China) as described previously [11]. The 2019-nCoV IgG kit (YHLO) was employed for the detection of SARS-CoV-2 nucleocapsid-specific antibodies (anti-N IgG) and considered positive at ≥10 AU/ml. The assay has a high specificity for SARS-CoV-2 of 99.3% (95% CI 98.3–99.7) as reported previously [14]. Thus false positive results, e.g. by detection of cross-reactive antibodies against seasonal coronaviruses, are very unlikely but cannot be completely excluded. Anti-S antibodies were determined using the SARS-CoV-2 IgG II Quant Assay on the Architect platform (Abbott, Wiesbaden, Germany). SARS-CoV-2 receptor-binding domain (RBD)-specific neutralizing antibodies (NAbs) were measured using a surrogate neutralization assay (2019 nCOV NAb kit; YHLO) that determines NAb titres preventing the binding of recombinant RBD (Wuhan strain) to the SARS-CoV-2 receptor ACE-2 protein. Titres were determined according to the WHO standard and are given in BAU/ml. Lower and upper limits of detection for NAbs were 4 and 800 BAU/ml, respectively. For values exceeding the upper limit of quantification, a value of 801 AU/ml was used in the statistical models.

SARS-CoV-2 infection neutralization assay

The method for analysis of patients' serum neutralization capacity of several SARS-CoV-2 strains has been described in detail

elsewhere [15]. Briefly, SARS-CoV-2 isolates of VoC Omicron BA.1 (B.1.1.529, GISAID EPI ISL: 7808190), VoC Omicron BA.5 (GISAID EPI-ISL: 15942298) and BQ.1.1 (GISAID EPI ISL: 15812430) were obtained from nasopharyngeal swabs of infected individuals. Vero E6 cells were incubated with the respective variants in Dulbecco's Modified Eagle Medium for 2–3 days and high-titre virus stock was gained by collecting and centrifuging the supernatant. The viral stock was aliquoted and stored at −80°C. Virus titres were determined by plaque assay before the start of analysis and viral strains were confirmed by next-generation sequencing.

The patient's sera were diluted 1:20 to 1:2560 and incubated for 1 hour with a defined multiplicity of infection of 0.03 plaque-forming units (PFU)/cell (450 PFU/15 000 cells/well) at 37°C. Then the inoculum was incubated for 1 hour on Vero E6 cells seeded into 96-well plates before removing the virus inoculum and washing the cells. After 24 hours, cells were fixed and permeabilized with 4% paraformaldehyde and 0.5% saponin buffer, blocked with 10% goat serum and stained with a primary anti-SARS-CoV-2-N antibody (40143-T62; Sino Biological, Beijing, China). Afterwards, a colorimetric, quantitative analysis was performed by an in-cell enzyme-linked immunosorbent assay using goat anti-rabbit IgG2a-horseradish peroxidase secondary antibody (12-348; EMD Millipore, Shanghai, China) and adding substrate tetramethybezidine.

After implementation of non-linear regression, the serum 50% inhibitory concentration (IC50) was defined as the dilution factor at which 50% infection inhibition was obtained. As described before [11], patients were classified as responders if the IC50 value of the infection neutralization was >1:20. Non-responders were defined for sera with a neutralizing IC50 value ≤1:20. Extremely strong responders exceeded the maximum detection range when diluted up to 1:40 960 ($n = 16$). GraphPad Prism 9.5.1 (GraphPad Software, San Diego, CA, USA) was used for calculations.

Analysis of neutralization capacity for VoC Omicron BA.1 before and after the fourth vaccination was performed and described previously [11] with the same protocol. Remaining samples were analysed concurrently for BA.1 and analyses for BA.5 and BQ1.1 strains were added for all time points. Serum samples were stored at −80°C after blood collection and were thawed and refrigerated at 4°C until analysis.

Statistical analysis

Variables are presented as frequencies and percentages and as mean ± standard deviation (SD) or median and interquartile range (IQR), as appropriate. The χ^2 test or Fisher's test was used for group differences and the *t*-test and Mann–Whitney U test were applied to continuous variables. Paired samples were tested with the McNemar or Wilcoxon test, as appropriate. For correlation analysis, Spearman correlation was used. *P*-values <.05 were considered significant; tests were two-sided. Statistical analysis was carried out with R version 4.2.2 (R Foundation for Statistical Computing).

RESULTS

Patient characteristics

Overall, 52 HD patients were included in the study (Fig. 1). Patients were followed up for a median of 6.3 months (IQR 6.3–6.3) after the fourth vaccination. Patients had a median age of 71.4 years (IQR 60.2–81.9) and 9/52 patients (17.3%) were female. The median dialysis vintage was 51.7 months (IQR 24.2–94.9), the median relative ultrafiltration was 4.6 ml/kg/h and the median absolute ultrafiltration was 1.8 L/session at the time of the fourth vaccination (Table 1, Supplemental Table 1). One individual in each group received immunosuppressive medication, due to a history of lung transplantation in the infection group (tacrolimus, mycophenolate mofetil, prednisolone) and due to anterior ischaemic optic neuropathy (prednisolone) in the control group (Table 1). The matching variables age, sex, dialysis vintage and immunosuppressive medications did not differ between patients with a SARS-CoV-2 breakthrough infection compared with SARS-CoV-2-naïve patients (Table 1). Except for one patient in the infection group and two patients in the infection-naïve group receiving haemodiafiltration, all patients received HD. No correlation was present between the relative ultrafiltration at the time of the fourth vaccination and the neutralization capacity of the VoCs Omicron BA.1 ($P = .10$, $\rho = 0.24$), BA.5 ($P = .82$, $\rho = 0.03$) and BQ1.1 ($P = .41$, $\rho = 0.12$) at the second blood analysis, i.e. 4 weeks after the fourth vaccination.

Vaccinations

Vaccinations were administered using messenger RNA (mRNA) vaccines (BNT162b2 by BioNTech-Pfizer or mRNA-1273 by Moderna) in 49 (94.2%) individuals. Overall, the administered vaccines in the two groups (naïve and infected) were comparable. The infected group received a total of 2 AZD1222 (by AstraZeneca), 95 BNT162b2 and 7 mRNA-1273 vaccinations, while the naïve group received 2 AZD1222, 96 BNT162b2 and 6 mRNA-1273 vaccinations. Three patients received a heterologous vaccination scheme (two patients received one AZD1222 by AstraZeneca and three mRNA vaccines and one patient received two AZD1222 by AstraZeneca and two mRNA vaccines). Vaccination regimes did not differ between the two groups ($P = 1.0$; Table 1).

Group comparisons between patients vaccinated with BNT162b2 ($n = 46$) and mRNA-1273 ($n = 6$) as the fourth vaccination were difficult due to low numbers of patients vaccinated with mRNA-1273 (Supplemental Fig. 1). However, directly after the fourth vaccination the neutralization capacity of Omicron BA.5 was significancy higher in the mRNA-1273 group when compared with the BNT162b2 group (Supplemental Fig. 1).

SARS-CoV-2 infections

SARS-CoV-2 breakthrough infections were detected in 26 patients after the third vaccination. Of these cases, 15 (57.7%) infections were PCR confirmed and 11 (42.3%) infections were identified by N-specific IgG-positivity only. Two patients were infected twice. In both cases the first infection occurred before the first vaccination.

In 10 of the 26 infected patients, the breakthrough infection occurred before the second blood analysis, i.e. before or until 26 days after the fourth vaccination. Of these, four (15.4%) patients were infected before the first blood analysis (taken a median of 4 months after the third and 2 days before the fourth vaccination). Two of these infections were PCR confirmed and occurred 96 and 103 days before the first blood examination. In the other six individuals (23.1%) the infection occurred after the first and before the second blood examination taken a median of 2 days before and 26 days after the fourth vaccination; the PCR-confirmed infections ($n = 4$) occurred a median of 7.5 days after the fourth vaccination.

Of the 26 infected patients, 16 (61.5%) had a SARS-CoV-2 breakthrough infection during the follow-up period, i.e. 26 days–

Table 1: Patient characteristics.

Characteristics	Total (N = 52)	History of SARS-CoV-2-infection		P-value
		Yes (n = 26)	No (n = 26)	
Age (years), median (IQR)	71.4 (60.2–81.0)	71.4 (59.4–80.8)	72.6 (65.1–82.1)	.47
Female, n (%)	9 (17.3)	5 (19.2)	4 (15.4)	1.00
Dialysis vintage (months), median (IQR)	51.7 (24.4–94.9)	45.3 (22.3–91.1)	56.2 (29.5–103.8)	.58
Immunosuppressive medication present, n (%)	2 (3.8)	1 (3.8)	1 (3.8)	1.0
Vaccines, n (%)				1.0
mRNA and vector vaccine	3 (5.8)	1 (7.7)	2 (7.7)	
Only mRNA vaccine	49 (94.2)	25 (96.2)	24 (92.3)	
Days between vaccination and blood analysis, median (IQR)				
Vaccine 3 and blood analysis 1	124 (103–124); min 27, max 133	124 (103–124); min 93, max 126	124 (103–124.8); min 27, max 133	.45
Vaccine 4 and blood analysis 2	26 (26–26); min 6, max 28)	26 (26–26); min 6, max 28)	26 (26–26); min 10, max 28	.63
Vaccine 4 and blood analysis at the 6-month follow-up	191 (191–192; min 161, max 201	191 (191–191.8); min 161, max 194)	191 (191–191.8); min 161, max 201	.98
Ultrafiltration (ml/kg/h), median (IQR)				
At the fourth vaccination	4.6 (2.7–7.1)	3.0 (2.3–6.1)	5.4 (4.2–7.2)	**.027**
4 weeks after the fourth vaccination (blood analysis 2)	5.1 (3.4–6.9)	4.2 (2.4–6.0)	6.3 (4.3–7.1)	.087
6-month follow-up (blood analysis 3)	4.9 (3.4–6.2)	4.5 (3.3–5.8)	5.2 (3.8–6.7)	.29
History of kidney transplantation, n (%)	5 (9.6)	3 (11.5)	2 (7.7)	1.0
Charlson Comorbidity Index, median (IQR)	5.0 (4.0–7.0)	4.5 (4.0–7.0)	6.0 (4.0–7.0)	.75
Renal diagnosis, n (%)				
Glomerulopathy	5 (10.0)			
Diabetic nephropathy	12 (24.0)			
Hypertensive nephropathy	7 (14.0)			
Congenital or cystic renal disease	5 (10.0)			
Tubulointerstitial disease	1 (2.0)			
Reflux nephropathy	1 (2.0)			
Other	5 (10.0)			
Nephropathy of unknown origin	14 (28.0)			
N-specific IgG before fourth vaccination, median (IQR)	0.5 (0.3–0.9)	0.7 (0.2–1.8)	0.5 (0.3–0.7)	
N-specific IgG after fourth vaccination, median (IQR)	0.8 (0.4–1.6)	1.6 (0.6–9.6)	0.5 (0.4–0.8)	
N-specific IgG at follow-up, median (IQR)	1.0 (0.0–13.2)	13.5 (4.2–37.0)	0.0 (0.0–1.0)	

P-values present the results of group-wise comparisons of SARS-CoV-2-infected and -naïve patients.
min: minimum; max: maximum.
Values in bold are statistically significant.

6 months after the fourth vaccination (Fig. 2). PCR-confirmed infections (n = 9) occurred a median of 51 days before the 6-month follow-up blood analysis or a median of 140 days after the fourth vaccination.

In line with this, N-specific IgG-type antibodies were detectable in the infection group at the time of the second blood examination after the fourth vaccination and in the follow-up analysis (Table 1). Interestingly, no difference in serum neutralization titres after the third and before the fourth vaccination (i.e. at the first blood examination) between naïve individuals and those experiencing a breakthrough infection were observed (Table 2). This indicates that the overall relatively low infection neutralization titres against the Omicron VoCs BA.1, BA.5 and BQ.1.1 after three vaccinations are not sufficient to protect from infection with these VoCs.

Of the 26 reported infections in the matched cohort of 52 individuals, 11 infections were clinically undetected, 4 cases were detected but asymptomatic (WHO score 1) and 8 cases were mild ambulatory cases (WHO score 2). In three cases a moderate disease necessitated hospitalization; two of the three patients did not receive oxygen therapy (WHO Score 4) and in one of these three cases mild oxygen therapy was necessary (WHO score 5).

Table 2: Group-wise comparison of immunity of HD patients with and without a recent SARS-CoV-2 infection.

Variables	Total (N = 52)	History of SARS-CoV-2 infection		P-value
		Yes (n = 26)	No (n = 26)	
Neutralizing antibodies				
Before fourth vaccination (BAU/ml)	717.5 (203.8–≥800)	761.5 (165.5–≥800)	455.0 (245.8–≥800)	.73
After fourth vaccination (BAU/ml)	≥800 (≥800–≥800)	≥800 (≥800–≥800)	≥800 (≥800–≥800)	.92
6-month follow-up (BAU/ml)	≥800 (417.2–≥800)	≥800 (≥800–≥800)	505.5 (232.8–≥800)	**<.001**
Omicron BA.1 infection neutralization capacity				
Before fourth vaccination (IC50)	30.0 (0.0–195.8)	48.5 (5.0–231.0)	27.0 (0.0–141.2)	.49
After fourth vaccination (IC50)	570.5 (198.0–2560.0)	811.5 (167.0–2560.0)	444.5 (222.2–2560.0)	1.0
6-month follow-up (IC50)	141.6 (20.0–663.6)	619.2 (185.3–887.4)	20.0 (0.0–20.0)	**<.001**
Omicron BA.5 infection neutralization capacity				
Before fourth vaccination (IC50)	20.0 (20.0–116.1)	22.5 (20.0–101.9)	20.0 (20.0–113.7)	1.0
After fourth vaccination (IC50)	365.6 (76.1–2560.0)	572.8 (107.6–2560.0)	249.7 (62.7–2265.5)	.32
6-month follow-up (IC50)	238.7 (20.0–2329.5)	2339.0 (1041.5–7494.2)	20.0 (20.0–74.9)	**<.001**
Omicron BQ.1.1 infection neutralization capacity				
Before fourth vaccination (IC50)	20.0 (0.0–21.3)	20.0 (0.0–20.0)	20.0 (0.0–23.9)	.73
After fourth vaccination (IC50)	99.0 (20.0–219.4)	116.7 (20.0–255.7)	89.1 (20.0–153.4)	.64
6-month follow-up (IC50)	25.1 (20.0–266.3)	270.0 (27.9–440.0)	20.0 (0.0–20.0)	**<.001**

P-values present the results of group-wise comparisons of SARS-CoV-2-infected and -naïve patients.
Values in bold are statistically significant.

We did not report any COVID-related deaths in the 26 infected individuals during our observation period.

In two individuals, duplicate infections occurred. The first infections occurred before the first vaccination in both cases and were of mild (WHO score 1) and moderate (WHO score 5) disease severity.

Impact of a SARS-CoV-2 infection on immunity

All patients showed a significant increase in neutralizing antibody levels and neutralization capacity for the VoCs Omicron BA.1, BA.5 and BQ.1.1 after a fourth vaccination (Fig. 3, Table 2). However, no significant differences were seen between the two groups with or without a breakthrough infection, not at the first blood analysis before or at the second blood analysis in a median of 26 days after the fourth vaccination (Table 2).

At the follow-up 6 months after the fourth vaccination, SARS-CoV-2-naïve patients had significantly lower virus neutralization capacities for all VoCs ($P < .001$) and significantly lower neutralizing antibody titres ($P < .001$) (Table 2, Fig. 3). Similar results were present when looking at the response rates (Fig. 4). This indicates that a breakthrough infection confers a significant additional level of protection even against newly emerging VoCs like BQ.1.1.

Comparing the virus neutralization capacity between the Omicron variants in the whole cohort, we found significantly lower neutralization capacity of the Omicron BQ.1.1 variant compared with Omicron BA.1 or BA.5 directly after the fourth vaccination ($P < .001$) (Fig. 5). At the 6-month follow-up, neutralization capacity of Omicron BQ.1.1 and BA.1 was significantly lower compared with Omicron BA.5 ($P = .001$ and $P = .013$) (Fig. 5). Stratification of virus-naïve and infected patients showed similar results for both groups (data not shown).

Next, we compared HD patients early versus late SARS-CoV-2 infections (Table 3, Fig. 6). Fig. 6 depicts serum neutralization titres against the different Omicron VoCs and Table 3 displays the medians and IQRs of the respective time points and provides a group comparison. Shortly after infection, i.e. at the second blood analysis time point for those with an early infection, we found a significantly increased serum neutralization capacity for all VoCs compared with those who had not yet (late infection) or not at all (naïve) experienced a SARS-CoV-2 breakthrough infection (Table 3, Fig. 6). Patients with a later infection showed significantly improved neutralization capacity at the 6-month follow-up for Omicron variants BA.5 ($P < .001$) and BQ.1.1 ($P = .002$). Patients with an earlier infection had significantly decreasing serum neutralization capacity for Omicron BA.1 ($P = .004$) and by trend slightly decreasing neutralization capacities for BA.5 ($P = .08$) and BQ.1.1 ($P = .06$) at the 6-month follow-up time point (Fig. 6). However, despite this decrease, neutralization titres remained significantly higher than in SARS-CoV-2-naïve HD patients (Table 3, Fig. 6).

DISCUSSION

This prospective matched observational study demonstrates that virus neutralization capacity for all current VoCs decreased significantly in SARS-CoV-2-naïve HD patients compared with SARS-CoV-2-infected patients 6 months after the fourth vaccination, independent of age, sex, dialysis vintage and immunosuppression. The strength of our study is the examination of the live-virus infection neutralization capacity of patients' sera for different SARS-CoV-2 Omicron VoCs. Compared with the other Omicron VoCs BA.1 and BA.5, the neutralization capacity of the late Omicron BQ.1.1 variant was the lowest. This was true directly after the fourth vaccination as well as at the 6-month follow-up. These findings are highly important, because Omicron BA.5 has been the predominant VoC in Germany during the follow-up period of this study and Omicron BQ.1.1 is currently (as of February 2023) the most frequent VoC in Germany with increasing prevalence [16]. It will therefore be important to closely monitor new variants that might escape the immune system or erase the effectiveness of established antibody treatments [6].

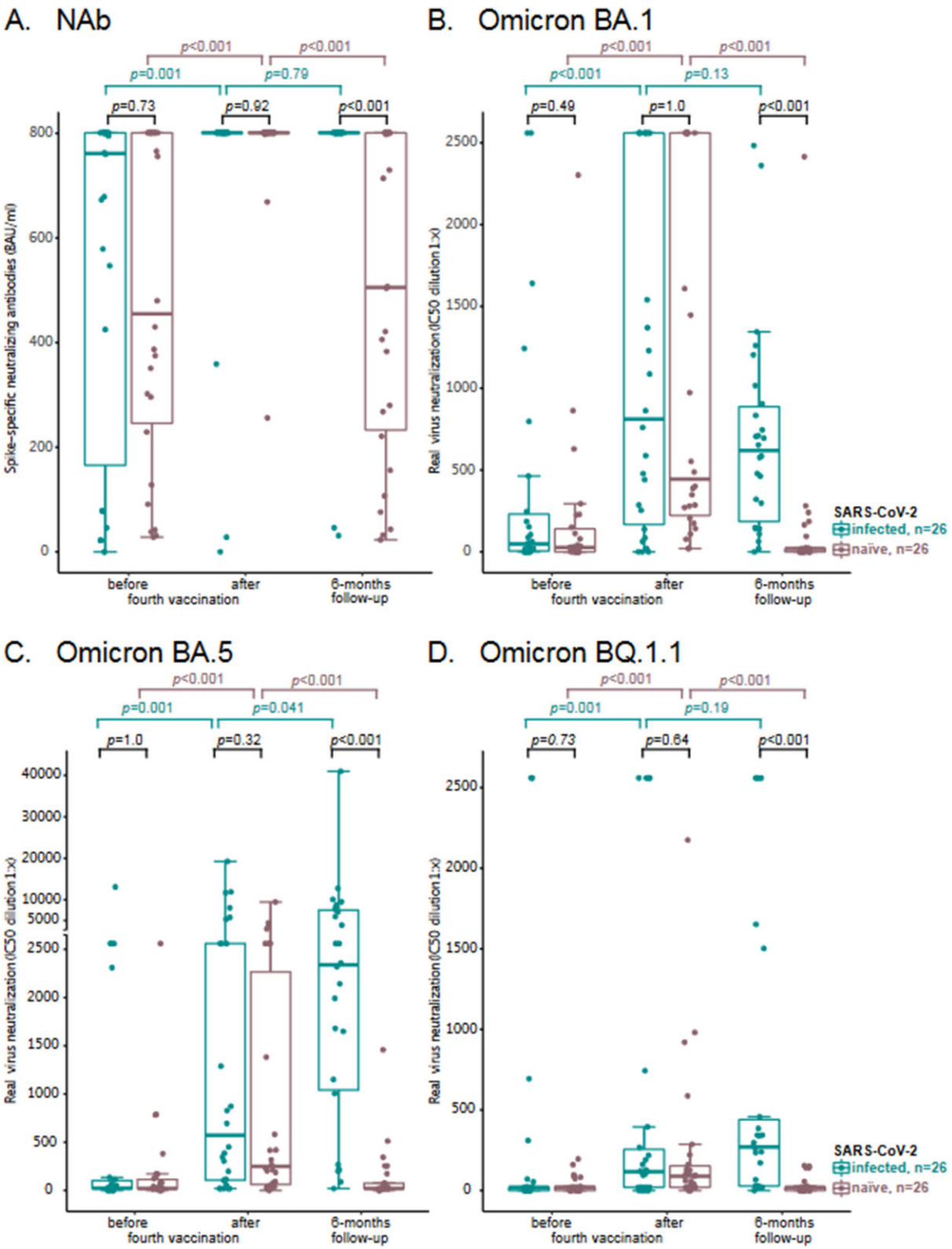


Figure 3: NAb titres before and after the fourth vaccination and at the 6-month follow-up. HD patients who had experienced a breakthrough infection after the third vaccination (infected) were compared with those without (naïve). **(A)** BAU/ml according to the WHO standard using a competitive, surrogate NAb assay. **(B–D)** The IC50 titres in a real-virus neutralization assay with SARS-CoV-2 Omicron VoC **(B)** BA.1, **(C)** BA.5 and **(D)** BQ.1.1. Green and brown indicate neutralizing immunity of infected and infection-naïve patients, respectively. Statistical analysis was performed using a paired-samples Wilcoxon test. *P*-values indicate statistical significance between groups. For better comparability, the y-axis changes its linear scale at 2700 in (C).

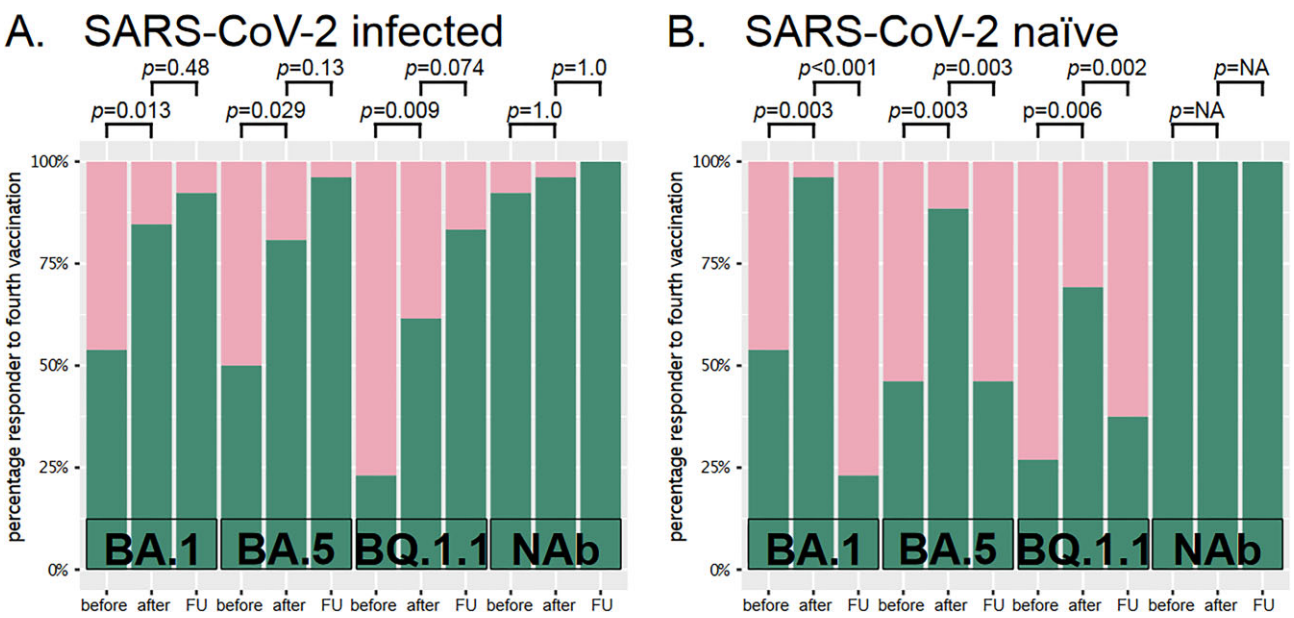


Figure 4: Percentage of vaccine responders before, after the fourth vaccination and at the 6-month follow-up. **(A)** A total of 26 HD patients who had a SARS-CoV-2 breakthrough infection after the third vaccination were compared with **(B)** 26 matched individuals which did not experience an infection. A responder was defined by Omicron BA.1, BA.5 or BQ.1.1 virus infection neutralization of ≥1:20 and as NAbs ≥10 BAU/ml. Green and red indicate the percentages classified as responder and non-responder, respectively. Statistical analysis was done using the McNemar test for paired samples. NA: not applicable; FU: follow-up.

We previously showed that by administration of a fourth vaccine dose, a significant increase of the virus neutralization capacity can be achieved for VoC Delta and Omicron BA.1 [11]. With this work we add that this also holds true for VoC Omicron BA.5 and BQ.1.1. As we found significantly decreasing virus neutralization capacity in the SARS-CoV-2-naïve group for all observed Omicron variants during the follow-up period of 6 months, we assume that the humoral immunity provided by the vaccines that were designed for the original SARS-CoV-2 wild-type strain is rapidly waning over time and in their ability to neutralize current Omicron VoCs. In SARS-CoV-2-naïve HD patients, a fifth vaccination 6 months after the last vaccination could be a reasonable approach—ideally using an adapted vaccine. During the observation period of our study a specific Omicron-adjusted vaccine was not available. Today, an Omicron-specific vaccine has become available that could further improve the immune response [17]. Nevertheless, the effect of another vaccination may not be completely comparable to exposure to the virus itself. As described previously, 'hybrid immunity' achieved by the combination of vaccination and natural infection may lead to a stronger and more sustained immune response than vaccination alone [18].

In SARS-CoV-2-infected patients, no decreased neutralization capacity was observed at the 6-month follow-up for VoC BA.1 and BQ.1.1, and we found a significantly higher neutralization capacity for Omicron BA.5. This might be explained by the fact that most patients in our cohort were infected when the Omicron BA.5 VoC was by far the dominant variant. However, it remains open if the number of exposures to the viral spike protein or the type of spike involved in the booster was the relevant difference. In our study, the infected patients had five exposures while SARS-CoV-2-naïve patients had only four and were exposed to only first-generation vaccines. Alternatively, exposure to a different type of spike protein during breakthrough infection with the current Omicron variants could be the key for a broader immunity against the latest VoC. However, the effect of time has to be considered, since the follow-up analysis in patients with a late infection was closer to the virus exposure than in patients with an early infection or no history of infection. When comparing patients with an early infection with those without a history of infection, we still found an improved neutralization capacity at the follow-up in infected patients, indicating that patients might benefit from a fifth exposure to an Omicron spike protein independent of time (Table 3, Fig. 6). The increased breadth of immunity observed would argue for using an Omicron BA.5-adapted vaccine.

Overall, we were surprised that only 25% of our HD cohort had a SARS-CoV-2 infection until the end of the observation period. The infection was asymptomatic in 42% of the cases and diagnosed by N-specific IgG positivity only. This high rate of asymptomatic infections could be explained by the fact that all patients had received at least three COVID-19 vaccinations at the time of the SARS-CoV-2 infection. However, it has to be taken into account that despite the high specificity of our N-specific antibody assay (99.3% [14]), the detection of e.g. antibodies cross-reactive against seasonal coronaviruses cannot be completely excluded. We did not record the variants; however, as most infections occurred after mid-March, Omicron infections are most likely since initially Omicron BA.1 and BA.2 and from June onwards Omicron BA.5 were the predominant variants in Germany [16, 19, 20]. Interestingly, in patients with late infections (after the second blood examination), a significantly increasing neutralization capacity could only be found for VoC BA.5 and BQ.1.1 during the follow-up period. This could be due to a relevant proportion of patients who might have been infected with the VoC BA.5 during the follow-up period. A breakthrough infection with BA.5 might therefore also positively impact and broaden immunity against the currently

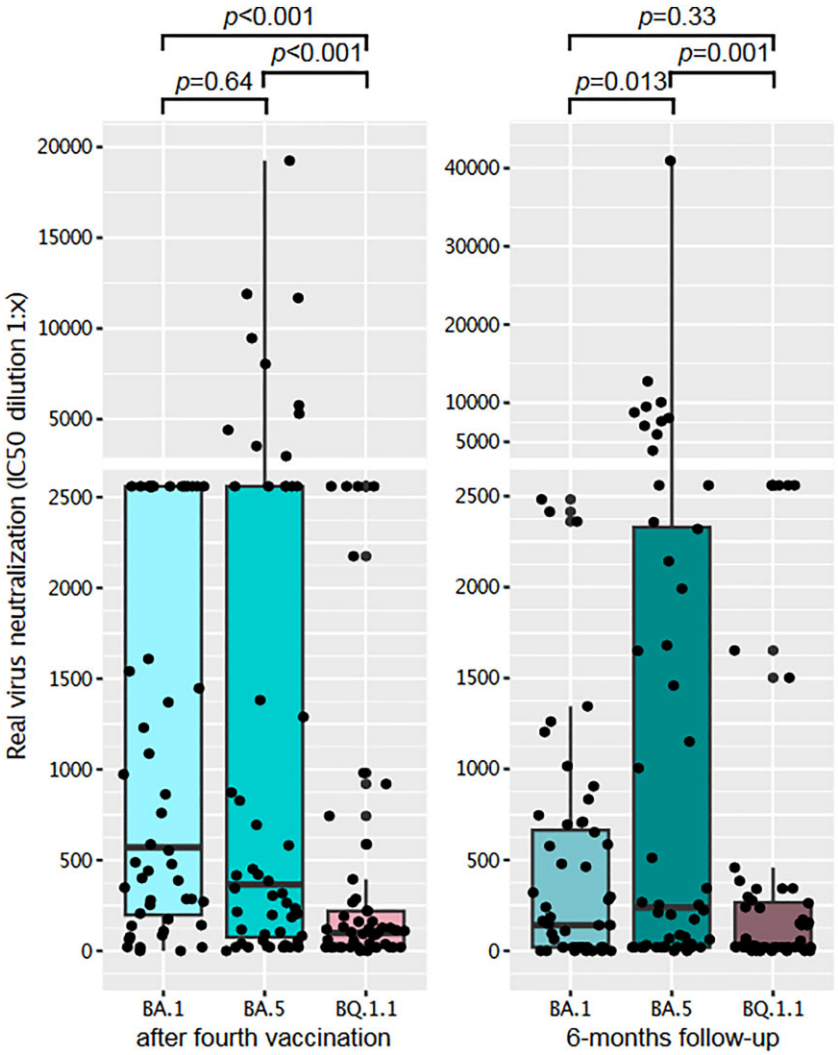


Figure 5: Comparison of neutralization capacity of Omicron variants BA.1, BA.5 and BQ1.1 in the whole cohort [infected and naïve patients ($n = 52$)]. Comparison of neutralization capacity after the fourth vaccination (left side) and at the 6-month follow-up (right side). After the fourth vaccination, neutralization capacity of the Omicron variant BQ.1.1 was significantly lower than for BA.1 and BA.5. At the 6-month follow-up, neutralization capacity for BA.5 was significantly higher for BA.5 compared with BA.1 and BQ.1.1. Statistical analysis was performed using a Wilcoxon test. *P*-values indicate statistical significance between groups.

predominant variant BQ.1.1, which is a variant that was not present in Germany during the study period, while it does not seem to impact immunity against Omicron BA.1. Furthermore, it argues for using an Omicron BA.5-adapted vaccine for booster vaccinations.

Low serum anti-spike concentrations have been associated with an increased risk of breakthrough infections in HD patients [21, 22]. We detected high surrogate NAb titres against the original Wuhan strain in all our patients, although absolute NAb values were significantly decreasing in SARS-CoV-2-naïve patients during the follow-up. It is unknown which NAb level might be an appropriate surrogate cut-off level to evaluate if a patient needs a COVID-19 booster vaccination, especially when these surrogate NAb measurements are designed to detect wild-type-specific antibodies.

In search of factors affecting immunity in HD patients unlike reported previously, we did not find an association between fluid overload and neutralization capacities in our matched cohort [23]. A recent publication showed that the preservation of anti-SARS-CoV-2 antibody titres in HD patients may also depend on the patients' dialysis modality [24]. In our cohort, however, no reliable statement could be made on this subject, as 49 patients (94%) received HD and only 3 patients received haemodiafiltration. The previously observed higher humoral immunity in HD patients receiving mRNA-1273 compared with BNT162b2 could be seen in our cohort for neutralization of Omicron BA.5 after the fourth vaccination [25]. Due to the low numbers of patients vaccinated with mRNA-1273, this result should be interpreted very carefully. We tried to approach immunosuppressive medication, as a well-known factor of reduced immunity in HD patients, with matching and therefore an even distribution between the two groups.

Due to the low numbers of patients with immunosuppression (one in each group) we did not perform separate correlation analyses of these two patients. Supplementary Table 2 provides values for the immunocompromised patients

Table 3: Group-wise comparison of NAbs and neutralization capacity between SARS-CoV-2 infection-naïve, early and late-infected individuals.

Variables	SARS-CoV-2 naïve	Time of SARS-CoV-2 infection		Group-wise comparison		
		Early	Late	*P*-value naïve versus early	*P*-value naïve versus late	*P*-value early versus late
Neutralizing antibodies						
Before fourth vaccination (BAU/ml)	455.0 (245.8–≥800)	740.0 (153.2–≥800)	761.5 (338.5–≥800)	.93	.68	1.0
After fourth vaccination (BAU/ml)	≥800 (≥800–≥800)	≥800 (≥800–≥800)	≥800 (≥800–≥800)	1.0	.87	.89
6-month follow-up (BAU/ml)	505.5 (232.8–≥800)	≥800 (≥800–≥800)	≥800 (≥800–≥800)	**.001**	**.006**	.28
Omicron BA.1 infection neutralization capacity						
Before fourth vaccination (IC50)	27.0 (0.0–141.2)	86.5 (5.0–1541.5)	48.5 (15.0–126.0)	.40	.72	.50
After fourth vaccination (IC50)	444.5 (222.2–≥2560)	≥2560 (1667.5–≥2560)	363.5 (80.2–919.0)	**.046**	.16	**.005**
6-month follow-up (IC50)	20.0 (0.0–20.0)	391.8 (143.2–558.6)	707.8 (506.9–980.0)	**<.001**	**<.001**	.18
Omicron BA.5 infection neutralization capacity						
Before fourth vaccination (IC50)	20.0 (20.0–113.7)	35.8 (20.0–2560.0)	22.5 (20.0–57.0)	.44	.58	.33
After fourth vaccination (IC50)	249.7 (62.7–2265.5)	2560.0 (943.1–6672.2)	251.4 (48.5–739.2)	**.026**	.83	**.021**
6-month follow-up (IC50)	20.0 (20.0–74.9)	2067.5 (1173.8–2348.5)	4922.0 (930.2–8946.8)	**<.001**	**<.001**	.25
Omicron BQ.1.1 infection neutralization capacity						
Before fourth vaccination (IC50)	20.0 (0.0–23.9)	37.1 (5.0–250.6)	0.0 (0.0–20.0)	.25	.17	.055
After fourth vaccination (IC50)	89.1 (20.0–153.4)	243.3 (122.3–2018.7)	20.0 (20.0–129.6)	**.027**	.34	**.021**
6-month follow-up (IC50)	20.0 (0.0–20.0)	204.1 (40.3–257.0)	364.6 (25.1–1879.0)	**<.001**	**<.001**	.13

P-values present the results of group-wise comparisons of naïve and early, naïve and late and early and late SARS-CoV-2-infected HD patients. Early infection is defined as a SARS-CoV-2 infection before the second blood sample (i.e. after the fourth vaccination) and late infection is defined as an infection during the 6-month follow-up (i.e. after the second blood sample).
Values in bold are statistically significant.

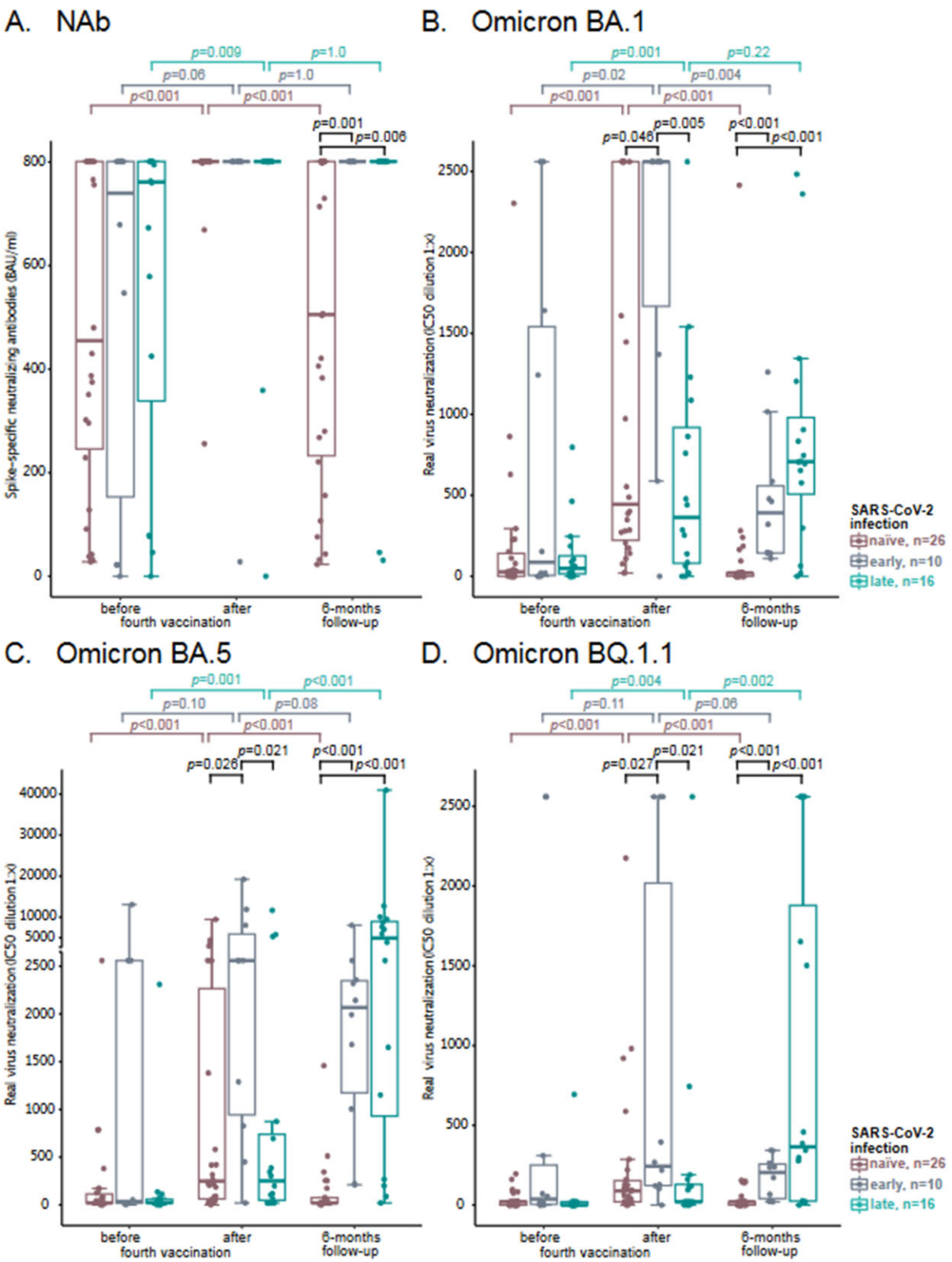


Figure 6: NAb titres before and after the fourth vaccination in infection-naïve patients and patients with SARS-CoV-2 breakthrough infections early and late after vaccination. HD patients who had experienced a breakthrough infection after the third vaccination until a median of 26 days after the fourth vaccination were grouped as early infection (early) and compared with those experiencing no infection and those experiencing an infection after the second blood examination taken a median of 26–191 days after the fourth vaccination (late). **(A)** BAU/ml according to the WHO standard using a competitive surrogate NAb assay. **(B–D)** The IC50 titres in a real-virus neutralization assay with SARS-CoV-2 Omicron VoC **(B)** BA.1, **(C)** BA.5 and **(D)** BQ.1.1. Brown, grey and green indicate neutralizing immunity of infection-naïve, early-infected and late-infected patients, respectively. Statistical analysis was performed using unpaired and paired samples Wilcoxon tests. *P*-values indicate statistical significance between groups. For unpaired analyses, only significant *P*-values are shown. For better comparability, the *y*-axis changes its linear scale at 2700 in (C).

compared with the median and IQR values of their respective groups.

Finally, some limitations must be mentioned. We focused our analyses on the most relevant VoC for Germany. Our results are not generalizable to other variants, such as the recently described Omicron XBB.1.5 VoC with emerging prevalence in the USA. This variant has been associated with immune escape and ineffectiveness of established antibody treatments [6] and even seems to have additional immune escape potential when compared with the BQ1.1 VoC [26]. However, a more detailed analysis in patient cohorts is lacking.

CONCLUSION

In conclusion, we found a significantly reduced immune response against the recent SARS-CoV-2 VoC in HD patients. Low serum neutralization capacity within 3 months after a third vaccination could not prevent Omicron breakthrough infection. In addition, we found a rapid waning of immunity within 6 months after a fourth vaccination in SARS-CoV-2-naïve patients that was not detected after an Omicron breakthrough infection. Therefore, another booster vaccination with an Omicron-adapted vaccine seems reasonable in HD patients without a SARS-CoV-2 infection. Furthermore, close monitoring of circulating SARS-CoV-2 variants will be necessary to identify those conferring an increased risk for HD patients.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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We would like to thank all the patients for their participation in this study. The study conforms to the ethical guidelines of the Helsinki Declaration and was approved by the Medical Ethics Committee of the Klinikum rechts der Isar of the Technical University of Munich (approval 163/21 S-SR, 19 March 2021) and registered at the Paul Ehrlich Institute (NIS592).

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AUTHORS' CONTRIBUTIONS

L.P., B.H., L.R., U.P. and M.C.B. wrote the first draft of the manuscript. L.P. and M.C.B. performed the statistical analysis. L.P., M.T., V.K., C.H.L., M.W., E.S., E.P., P.E., L.T., C.K. and C.S. contributed to blood sampling and data acquisition. C.C.C., C.C., C.D., R.B., O.T.K. and B.H.L. performed *in vitro* virus neutralization assays and measurements of neutralizing antibodies. L.R., U.H., U.P. and M.C.B. were responsible for project supervision. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

DATA AVAILABILITY STATEMENT

The datasets for this article are not publicly available because written informed consent did not include wording on data sharing (German data protection laws). Reasonable requests to access the datasets should be directed to the corresponding author.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. U.P. has received grants from Hoehnle AG, SCG Cell Therapy and VirBio and personal fees from Abbott, AbbVie, Arbutus, Gilead, GlaxoSmithKline, Johnson & Johnson, Roche, Sanofi, Sobi and Vaccitech and is co-founder and a shareholder of SCG Cell Therapy. O.T.K. has received grants from the Bay-VOC and FOR-COVID networks.

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