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Research Article

SARS-CoV-2 Antibodies in Patients on Hemodialysis after the BNT162b2 mRNA Vaccination

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Abstract

Background: Patients on Hemodialysis (HD) are at high risk for severe acute respiratory Syndrome Coronavirus type 2 (SARS-CoV-2) infection. To study the vaccination efficacy for such patients, we investigated SARS-CoV-2 antibodies in Japanese patients on HD.

Design/Methods: Between August 1 and December 14, 2020 and between July 1 and November 18, 2020, we analyzed serum samples of 55 patients on HD and 8,982 Japanese adults with normal renal function to evaluate SARS-CoV-2 nucleocapsid antibodies, respectively. Furthermore, we analyzed the serum samples of 42 patients (between May 1 and November 30, 2021) and 33 patients (between April 1 and May 30, 2022) on HD who received two and three doses of the BNT162b2 mRNA vaccine, respectively, to evaluate the SARS-CoV-2 spike antibodies. Additionally, we analyzed serum samples of 10 adults with normal renal function who received two doses of the vaccine, to evaluate SARS-CoV-2 spike antibodies at 4, 8, 12, 16, and 20 weeks after vaccination (between May 1 and November 30, 2021).

Results: Approximately 97.6% (41/42) of patients on HD had SARS-CoV-2 spike antibodies. The mean titers of SARS-CoV-2 spike antibodies after the second and third BNT162b2 vaccinations in all individuals were 253.5 U/mL (0.4-5,116) U/mL and 9,745.0 U/mL (2.8-12,500) U/mL, respectively. Japanese patients on HD had SARS-CoV-2 neutralizing capacities after the BNT162b2 vaccination. Most (97.6%) developed spike antibodies after the second dose. Levels of SARS-CoV-2 spike antibodies were low among older individuals. The mean titer of SARS-CoV-2 spike antibodies after the third vaccination was significantly higher than that after the second vaccination ($p<0.0001$).

Conclusion: Japanese patients on HD exhibited evidence of immunity to SARS-CoV-2 after BNT162b2 vaccination; majority of these patients developed spike antibodies after the second dose. The mean SARS-CoV-2 spike antibody titer after the third BNT162b2 vaccine dose was significantly higher than that of the second dose. Further studies on the integration of regular testing for neutralizing antibodies for patients on HD are needed.

Keywords: COVID-19; Hemodialysis; SARS-CoV-2 antibodies; Serological testing; Vaccination

Introduction

Strategies to minimize the transmission risk of Coronavirus Disease 2019 (COVID-19) in patients on Hemodialysis (HD) have been rapidly implemented worldwide [1]. However, the infection rates in the United Kingdom (UK) have remained high, with over 2,000 cases of COVID-19 confirmed in patients on HD, and a reported mortality rate of 22% in such patients. Serological testing of 356 patients on HD revealed that 129 (36.2%) were positive for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) antibodies. Of these 129 patients, 52 (40.3%) were asymptomatic [2]. In a study involving approximately 1,300 dialysis facilities across the United States of America, analysis of the plasma levels of total antibodies against the spike protein receptor-binding domain in 28,503 adult patients on dialysis revealed that the seroprevalence of SARS-CoV-2 antibodies was 8.3% [3]. SARS-CoV-2 has four major structural proteins: spike (S), membrane, envelope, and nucleocapsid proteins. The S protein comprises an S1 subunit, which mediates cell surface binding via the receptor-binding domain, and an S2 subunit, which induces viral-host cell membrane fusion. Antibodies to the highly immunogenic receptor-binding domain account for up to approximately 90% of neutralizing SARS-CoV-2-specific antibodies; there is little evidence regarding neutralizing antibodies to viral structural proteins, such as the nucleocapsid protein [4]. Speer et al. reported reduced antibody response to the first and second doses of the mRNA vaccine BNT162b2 (BioNTech) in patients on HD. Most patients on HD (82%) developed neutralizing antibodies after the second dose, but the levels were lower in the healthy controls [5]. As data on the efficacy of COVID-19 vaccination in patients on HD is limited, we investigated the levels of SARS-CoV-2 neutralizing antibodies in Japanese patients on HD.

Materials and Methods

Study Design, Population, and Data Sources

Study 1-1: We quantitatively measured the SARS-CoV-2 nucleocapsid antibodies in the serum samples of 55 patients who had undergone HD in the dialysis facilities of the Zenjinkai Group between August 1 and December 14, 2020 (Table 1).

Study 1-2: We included 42 patients on HD who had received two doses of the mRNA vaccine BNT162b2 between August 1 and November 30, 2021. We also quantitatively measured the levels of SARS-CoV-2 spike antibodies in their plasma at 4 months after the second dose of vaccine. We quantitatively measured the SARS-CoV-2 nucleocapsid antibodies.

Study 1-3: We included 33 patients on HD who had received three doses of the mRNA vaccine, BNT162b2, between April 1st and July 30th, 2022. We quantitatively measured the levels of SARS-CoV-2 spike antibodies in their plasma at 4 months after the third dose of vaccine. We also quantitatively measured the SARS-CoV-2 nucleocapsid antibodies.

Study 2-1: We tested the serum samples of 8,982 Japanese adults with normal renal function (control group) [3,716 men, mean age: 44.9 (19-77) years; 5,266 women; mean age: 43.6 (20-75 years)] for SARS-CoV-2 nucleocapsid antibodies between July 1 and November 18, 2020, at medical examination facilities of the Zenjinkai Group as the control group.

Study 2-2: We tested 10 adults with normal renal function (six men and four women), who had received two doses of the mRNA vaccine BNT162b2, for SARS-CoV-2 spike antibodies at 4, 8, 12, 16, and 20 weeks after vaccination between May 1 and November 30, 2021.

Antibody detection

We quantitatively measured the SARS-CoV-2 spike antibodies in human plasma using a fully automated Cobas® e801 analyzer (Roche Diagnostics, Santa Clara, California, USA) and Elecsys® Anti-SARS-CoV-2 S RUO electrochemiluminescence immunoassay (Roche Diagnostics), which has 100% sensitivity and 99.81% specificity to qualitatively detect SARS-CoV-2 spike antibodies in human plasma. A semiquantitative index of less than 0.8 U/mL was classified as negative, and a value of 0.8 U/mL or higher was classified as positive. The Elecsys® assay uses a modified double-antigen sandwich immunoassay with recombinant nucleocapsid protein (N), which is geared toward detecting late, mature, high-affinity antibodies independent of the subclass [6].

Statistical Analysis

Data were expressed as mean ± standard deviation or median (interquartile range) for continuous variables, and frequency (percentage) for categorical variables. The Wilcoxon signed rank test was used for proportional assessments. The correlation of SARS-CoV-2-specific neutralizing antibodies with age was examined using the Spearman correlation analysis. Statistical significance was set at $p < 0.05$, and all statistical analyses were performed using the SAS Statistics software version 9.4 (SAS Institute, Cary, North Carolina, USA).

Ethics Statement

The study was approved by the ethics committee of the Zenjinkai Group (approval number: 2021-06-03-0000178359) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients prior to the study.

Results

Study 1-1: The patient characteristics by SARS-CoV-2 antibodies status are presented in Table 1. Serological testing, revealed that two of 55 (3.64%) patients on HD were positive for SARS-CoV-2 nucleocapsid antibodies (Table 2). In total, 54 patients were asymptomatic during the study period and did not undergo

polymerase chain reaction (PCR) testing. One of the 54 (1.85%) asymptomatic patients had SARS-CoV-2 antibodies (Table 1 and 2). The seropositivity of SARS-CoV-2 nucleocapsid antibodies was negative in 42 patients on HD after receiving the second dose of the BNT162b2 mRNA COVID-19 vaccine. No patients on HD were infected with COVID-19.

	Antibody Positive (%)		Antibody Negative (%)
Variable	No PCR	Pos	No PCR
	n = 1	n = 1	n = 53
Age (years)	89	74	65.7 ± 12.6
HD duration (months)	53	62	72.7 ± 69.6
Sex Women			14
Men	1	1	39
Cause of ESKD			
DKD	1	1	16
CGN			20
Nephrosclerosis			9
ADPKD			4
Urologic			1
Unknown			3

PCR: Polymerase Chain Reaction; HD: Hemodialysis; ESKD: End-Stage Kidney Disease; DKD: Diabetic Kidney Disease; CGN: Chronic Glomerulonephritis; ADPKD: Autosomal Dominant Polycystic Kidney Disease.

Table 1: Patient characteristics by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) nucleocapsid antibodies status.

Duration	N (%)
August 1 and December 14, 2020 (before vaccination)	55
Elecsys® assay negative	53
Elecsys® assay positive	2 (3.64%)
August 1 and November 30, 2021 (after second vaccination)	
Elecsys® assay negative	42
Elecsys® assay positive	0
None of the patients on HD were infected with COVID-19.	
April 1st and July 30th, 2022, (after third vaccination)	
Elecsys® assay negative	33
Elecsys® assay positive	0
None of the patients on HD were infected with COVID-19.	

Table 2: Seropositivity of SARS-CoV-2 nucleocapsid antibodies in patients on HD.

Study 1-2: Table 3 presents the titers of spike antibodies in 42 patients on HD after receiving the second dose of the BNT162b2 mRNA COVID-19 vaccine. Out of the 42 patients on HD, 41 (97.6%) tested positive for SARS-CoV-2 spike antibodies after receiving the second dose of the vaccine. In this group, the median titer of SARS-CoV-2 spike antibodies after vaccination was 253.5 (0.4-5,116) U/mL. All the 33 patients on HD, (100%) tested positive for SARS-CoV-2 spike antibodies after receiving the third dose of the vaccine. In this group, the median titer of SARS-CoV-2 spike antibodies after vaccination was 9,745.0 (2.8-12500) U/mL. The spike antibody courses after the second and third vaccinations in patients on HD are shown in Figure 1. The mean titer of SARS-CoV-2 spike antibodies after third BNT162b2 vaccination was significantly higher than that after the second BNT162b2 vaccination (N=33: 9,745 U/mL vs, 221 U/mL; p<0.0001). Table 4 presents the spike antibodies in 42 patients on HD across different age groups. The mean SARS-CoV-2 spike antibodies titer of patients aged 56-92 years (266.7 U/mL) was lower than that of patients aged 28-53 years (1,320.4 U/mL). Figure 2 shows the age dependency of SARS-CoV-2 spike antibodies levels after vaccination with BNT162b2. After the second vaccination, the development of SARS-CoV-2 spike antibody levels correlated inversely with increasing age in patients on HD. The seropositivity of SARS-CoV-2 nucleocapsid antibodies was negative in patients on HD after receiving the BNT162b2 mRNA COVID-19 vaccine. No patients on HD were infected with COVID-19 (Table 2).

Study 2-1: Table 5 presents the positivity rates by SARS-CoV-2 nucleocapsid antibody status in 8,982 adults. Serological testing showed that 47 of 8,982 (0.52 %) Japanese adults with normal renal function tested positive for SARS-CoV-2 antibodies. The prevalence of infection was significantly higher in the Japanese population undergoing HD than in adults with normal renal function (p <0.01; Table 5).

Study 2-2: Table 6 presents the titers of spike antibodies in the healthy group after receiving the second dose of the BNT162b2 mRNA COVID-19 vaccine. The spike antibodies levels decreased gradually over time and were lower in the older group.

Humoral Responses	Patients on Dialysis
SARS-CoV-2 spike antibody response	
Participants meeting threshold	
for positive response, N (%)	
After second vaccine	41/42 (97.6%)
After third vaccine	33/33 (100%)
Anti-Spike Antibody, median (U/mL)	
After second vaccine, N=42	253.5 (0.4-5116)
After third vaccine, N=33	9745.0 (2.8-12500) ***

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2. The mean titer of SARS-CoV-2 spike antibodies after third BNT162b2 vaccination was significantly increased than that of second vaccination. ***P<0.0001.

Table 3: Severe acute respiratory syndrome coronavirus 2 spike antibody response in patients on hemodialysis after vaccination with BNT162b2.

Age (years)	N	Low	High	Mean
56-92	33	0.4	1131	266.7 (U/mL)
28-53	9	44.8	5116	1320.4 (U/mL)

Table 4: Titers of SARS-CoV-2 spike antibodies after vaccination in 42 patients on HD across different age groups.

Variable	All Participants	SARS-CoV-2 antibodies	C.O.I. (cut off index)
Antibody negative	8935 (99.48%)		
Antibody positive	47 (0.52%) [a]		
Sex			
Women		19 (40%)	31.6 (1.1-159)
Men	28 (60%)		45.0 (1.4-136)
Age (years)		44.1 (19-77)	

A semiquantitative index of less than one was classified as negative, and a value of one or higher was classified as positive; [a] $p < 0.01$

Table 5: Positivity rates by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) nucleocapsid antibody status in 8982 adult populations.

Age (years)	Weeks	Mean spike antibodies (U/mL)
55-73	03-04	1006
	8	643
	12	520
	16	464
	20	390
26-45	03-04	2685
	8	2032
	12	1731
	16	1609
	20	1527

Table 6: Titers of spike antibodies in the healthy control group after receiving the second dose of the BNT162b2 mRNA COVID-19 vaccine.

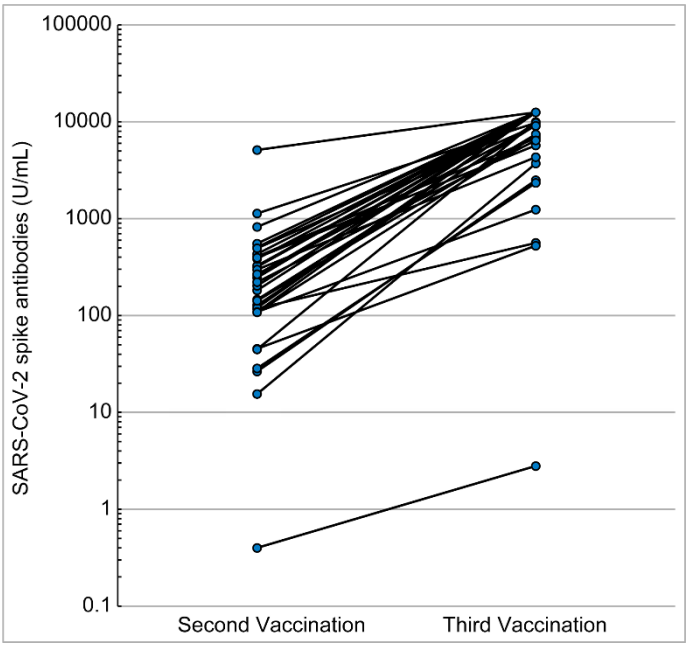

Figure 1: Spike antibody levels of patients on hemodialysis after vaccination with BNT162b2. Severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) spike antibodies represented logarithmically in patients on dialysis after the second and third Coronavirus Disease 2019 (COVID-19) vaccinations. The mean titer of SARS-CoV-2 spike antibodies after third BNT162b2 vaccination was significantly increased compared to that after second BNT162b2 vaccination ($p<0.0001$).

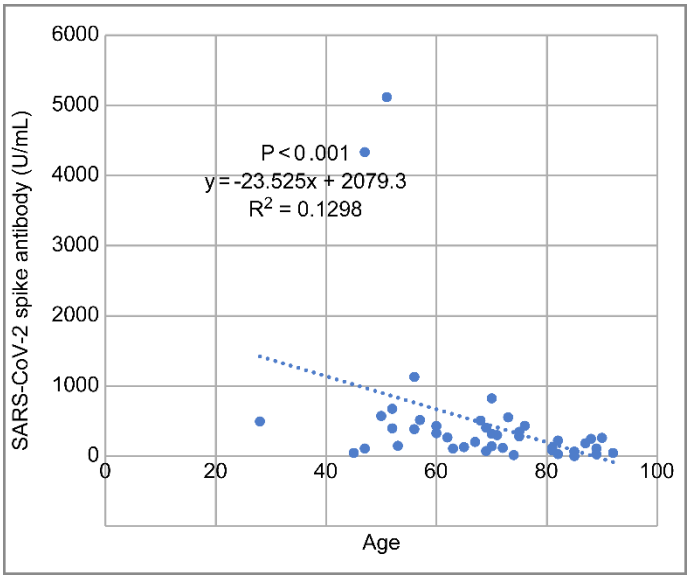

Figure 2: Age dependency of severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) spike antibodies levels after vaccination with BNT162b2. After the second vaccination, the development of SARS-CoV-2 spike antibody levels correlated inversely with increasing age in patients on Hemodialysis (HD).

Discussion

Patients undergoing HD have a higher risk of SARS-CoV-2 infection than does the general population [7]. Shaikh et al. reported a detectable amount of SARS-CoV-2 IgG antibodies against the nucleocapsid protein 2 months after SARS-CoV-2 infection in all patients [8]. Ota (2020) reported that acquired immunity against primary SARS-CoV-2 confers protection from re-infection [9]. Sethuraman et al. found that a COVID-19 infection can also be detected indirectly by measuring the host immune response. Serological diagnosis is especially important for patients with mild-to-moderate illness, who may present late in the course of their infection, particularly more than 2 weeks after the onset of illness [10]. To et al. reported that enzyme-linked immunosorbent assay-based IgM and IgG antibody tests have greater than 95% specificity for the diagnosis of SARS-CoV-2. The receptor-binding domain of S (RBD-S) is a host-attachment protein, and antibodies to RBD-S are more specific and expected to be neutralizing [11].

In study 1, more than 90% of patients on HD wore face masks, washed their hands, and maintained a social distance of 2 m within the dialysis facilities. Most patients avoided the "three Cs" (closed spaces with poor ventilation, crowded places, and close-contact settings, such as close-range conversations). Ikizler et al. found that health education regarding SARS-CoV-2 is required for both patients and healthcare workers to enable prevention and control of COVID-19 in dialysis facilities [1]. Clarke et al. reported that effective screening is likely to require a hybrid strategy comprising PCR and serological testing [2]. In this study, we found that Japanese patients on HD had a lower prevalence of SARS-CoV-2 antibodies (3.64%) than did those in the UK (36.2%; $p < 0.001$). Strengert et al. demonstrated that patients on dialysis have reduced antibody levels and neutralization following vaccination, resulting in diminished T-cell responses to SARS-CoV-2 [12]. Speer et al. reported that patients on HD (82%) developed neutralizing antibodies after the second dose, but at lower levels than did the healthy controls [5]. In a recent review, Carr et al. reported that the mRNA vaccines induced comparable neutralizing antibody titers in patients on HD and healthy controls [13]. However, some studies have reported that patients on HD have a weak immune response to two-sessional doses of the mRNA vaccine [14-16]. We previously reported that urinary Epidermal Growth Factor (EGF) levels have been associated with Acute Kidney Injury (AKI) [17]. Recently, Menez et al. reported that higher EGF levels were associated poor prognosis in patients hospitalized with COVID-19. Urinary biomarkers are associated with adverse kidney outcomes in patients hospitalized with COVID-19 and provide valuable information to monitor kidney disease progression and recovery [18]. Further studies are needed to validate urinary EGF levels associated with the levels of SARS-CoV-2 neutralizing antibodies in patients with COVID-19. Our study was limited by its design (observational cohort study), the small number of patients on HD, and the timing of serological testing. Our preliminary data requires confirmation by further testing.

Conclusions

Patients on HD in Japan had a lower prevalence of SARS-CoV-2 antibodies than did those in the UK. Serological testing can help to identify an asymptomatic patient on HD. Effective screening is likely to require a hybrid strategy involving PCR and serological testing. Following vaccination, avoiding the "three Cs" is very important in minimizing the risk of transmission of COVID-19 among patients on HD. Japanese patients on HD exhibited evidence of immunity to SARS-CoV-2 after BNT162b2 vaccination; majority of these patients developed spike antibodies after the second dose. The level of spike antibodies was lower among older patients on HD. The mean titer of SARS-CoV-2 spike antibodies after third BNT162b2 vaccination was significantly higher than that of second vaccination.

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