Observational Study

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Antibody response in patients undergoing chronic hemodialysis post-severe acute respiratory syndrome coronavirus 2 vaccination

A prospective observational study

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Abstract

Vaccination is important for patients undergoing hemodialysis (HD) to prevent coronavirus disease 2019 (COVID-19) infection since they are more vulnerable. However, they exhibit a weak response to vaccines, underscoring the importance of understanding whether antibodies are sufficiently produced and their durability post-COVID-19 vaccination. This prospective observational study assessed the antibody response of Korean patients undergoing HD for 1 year. We compared the antibody responses of patients undergoing HD to the COVID-19 vaccine with those of healthy volunteers from 2021 to 2022. The patient and control groups received 2 doses of ChAdOx1 nCoV-19 and mRNA-1273, respectively. Immunoglobulin G (IgG) and neutralizing antibody levels were measured weeks or months apart after 2 doses for 1 year using enzyme-linked immunosorbent and fluorescence-based competitive severe acute respiratory syndrome coronavirus 2 neutralizing assays, respectively. We analyzed the third dose's effect on the patient group by categorizing the group into patients who received the third dose and those who did not since it was initiated midway through the study. In the control group, we enrolled participants who had completed 3 doses of mRNA-1273 since almost all participants received the third dose. Thirty-two patients undergoing HD and 15 healthy participants who received 2 doses of ChAdOx1 nCoV-19 and 3 of mRNA-1273, respectively, were enrolled. Although antibody production was weaker in the patient group than in the control group ($P < .001$), patients showed an increase in IgG levels (0.408 ± 0.517 optical density (OD) pre-vaccination, 2.175 ± 1.241 OD in patients with 2 doses, and 2.134 ± 1.157 OD in patients with 3 doses 1 year after the second dose) and neutralizing antibodies (23 ± 8% pre-vaccination, 87 ± 23% in patients with 2 doses, and 89 ± 18% in patients with 3 doses 1 year after the second dose) post-vaccination ($P < .001$). In the patient group, 19 patients received a third dose (BNT162b2 or mRNA-1273); however, it did not increase the antibody levels ($P = 1.000$). Furthermore, the antibodies produced by the vaccination did not wane until 1 year. Two doses of vaccination resulted in a significant antibody response in patients undergoing HD, and antibody levels did not wane until 1 year.

Abbreviations: BMI = body mass index, COVID-19 = coronavirus disease 2019, ELISA = enzyme-linked immunosorbent assay, ESRD = end-stage renal disease, HD = hemodialysis, IgG = immunoglobulin G, OD = optical density, RBD = receptor-binding domain, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Keywords: antibody formation, COVID-19, COVID-19 vaccines, neutralizing antibodies, renal dialysis

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic is ongoing, with numerous infections and deaths worldwide recorded since its first emergence in 2019. The fatality of COVID-19 was prominent among specific patient cohorts, and individuals undergoing chronic hemodialysis (HD) constituted one of these groups. Reportedly, patients undergoing HD had higher

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hospitalization and mortality rates with COVID-19 infection than the general population.[1]

Vaccine development has been accelerated with the rapid spread of COVID-19. In South Korea, vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began in February 2021, and patients undergoing chronic HD were recommended to receive vaccination.

However, patients with end-stage renal disease (ESRD) are also known to have diminished immune response.[2] Several factors, including uremia, oxidative stress, erythropoietin, and vitamin D deficiency, interrupt the production of antigen-specific cells in ESRD.[3] Reduced renal clearance also increases proinflammatory cytokines, leading to chronic systemic inflammation and premature aging of the immune system.[3] Because of these immune alterations, patients with ESRD may have a weaker response to vaccination than the general population. Consequently, patients with ESRD usually take higher doses of vaccination, including Hepatitis B Virus vaccination, than the general population. Additionally, when vaccination against COVID-19 commenced, there were concerns about its effectiveness in patients with ESRD.

Studies published shortly after the vaccination commenced showed COVID-19 vaccination-induced antibody production and lowered hospitalization rate in patients undergoing HD.[4–6] Additionally, recent studies have focused on the duration of vaccination considering the prolonged COVID-19 pandemic. Many researchers have observed trends in vaccine-induced antibody levels over several months, and some have shown that antibodies wane over time in patients undergoing HD.[7]

Therefore, this study aimed to observe immunoglobulin G (IgG) levels and neutralizing antibodies in South Korean patients undergoing HD for 1 year after 2 doses of vaccination. We compared how the antibody responses of patients undergoing HD differ according to the third vaccination dose and the antibody responses of patients undergoing HD with those of the healthy population. Since COVID-19 is not yet over, we believe this study can help plan future vaccine administration strategies in patients undergoing HD.

2. Methods

2.1. Study population and design

This prospective observational study recruited adult patients undergoing chronic HD at Ajou University Hospital, a tertiary medical center in Suwon, South Korea, from February 2021 to September 2021. Patients who underwent HD at least 2 times weekly before the SARS-CoV-2 vaccination were eligible for this study. We recruited healthy adults aged > 18 years without renal disease as a control group. In both patient and control groups, only those who completed the planned 2 doses of vaccination were included in this study. Participants who were infected with COVID-19 during the study period were dropped out because the infection can change antibody levels.

Because 2 doses of vaccination were planned when the vaccination was first initiated, we set the blood sampling schedule based on the second dose. According to the vaccination schedule for each participant, blood samples were collected pre-vaccination; 2 weeks after the first dose; and at 2 and 4 weeks, 3 and 6 months, and 1 year after the second dose. IgG levels were measured in all blood samples. Furthermore, neutralizing antibody levels were estimated pre-vaccination and at 2 weeks, 3 and 6 months, and 1 year after the second dose. The process of this study is illustrated in Figure 1.

Regarding the type of vaccine, researchers or participants could not select the type of vaccine in Korea due to the unavailability of sufficient vaccines. Therefore, considering each group's homogeneity, we included the participants who received the same type of vaccine in each group.

Although 2 doses of vaccination were expected when we designed this study, a third dose was administered midway through the study as the COVID-19 pandemic progressed. We investigated whether the patients had received a third dose and classified them accordingly to analyze its effect. We compared the antibody responses between the 2 and 3 doses of vaccination in patients undergoing HD.

In the control group, because most participants but one received the third dose, those who completed 3 doses were finally enrolled in this study.

The demographic and clinical data of each patient, such as sex, age, body mass index (BMI), duration of HD, comorbidities, and administration of immunosuppressive drugs, were obtained from the health records.

2.2. IgG response to SARS-CoV-2 spike-receptor-binding domain protein

Antibodies were similarly measured as described in a previous study.[8] The antibody level was estimated using enzyme-linked immunosorbent assay (ELISA) as previously described.[9] Briefly, 100 µL of SARS-CoV-2 spike-receptor-binding domain (RBD) protein (adjusted as 0.1 µg/mL) (AIVD Biotech Inc., Shenzhen, China) was added to 96-well immune plates (Thermo Fisher Scientific, Roskilde, Denmark). The sera of patients undergoing HD, patients with COVID-19 infection, and healthy, unvaccinated individuals (each diluted 1:100 with phosphate-buffered saline) were used as test samples, positive controls, and negative controls, respectively. After final incubation, the goat anti-human whole IgG and M (1:5000 dilution) conjugated with alkaline phosphate in a substrate buffer containing 20 mg of p-nitrophenylphosphate tablet (Sigma-Aldrich, St. Louis, MO) was added. Finally, absorbance was measured at 405 nm using an ELISA reader (EPOCH2; BioTek, Santa Clara, CA).

2.3. Neutralizing ability of SARS-CoV-2 spike-RBD antibodies assessed using the neutralizing assay

The binding inhibition capacity of the patient's serum samples was detected using a fluorescence-based competitive SARS-CoV-2 neutralizing assay (GenBody FIA COVID-19 NAb; GenBody, Cheonan, South Korea), which has shown consistent results with plaque reduction neutralization tests and the SARS-CoV-2 Surrogate Virus Neutralization Test Kit (GenScript, Piscataway, NJ, FDA-approved).[10] To confirm the accuracy of the SARS-CoV-2 neutralizing assay (GenBody), we used the SARS-CoV-2 Surrogate Virus Neutralization Test Kit (GenScript) to detect neutralizing antibodies 2 weeks after the second dose. No differences were observed in the neutralizing antibodies between the 2 assays; therefore, only the neutralizing assay from GenBody was used in further experiments.

First, the recombinant human angiotensin-converting enzyme-2 (hACE-2) protein was immobilized on the test line of the device, and the recombinant spike protein of SARS-CoV-2, which could bind to hACE, was conjugated with a fluorescent dye. The mixture migrates to the membrane via capillary motion when the fluorescent conjugates react with the sample. If the neutralizing antibodies were absent, they would not interfere with the reaction of the recombinant spike-RBD protein and hACE-2; therefore, they were bound to the test line, and fluorescence was detected. In contrast, when the neutralizing antibodies were present, they reacted with the recombinant spike-RBD protein ("blocked"), and the fluorescent conjugate could not bind to the test line; therefore, the signal was reduced or undetected. The signal reduction and neutralizing ability were analyzed using a special analyzer (Confiscope

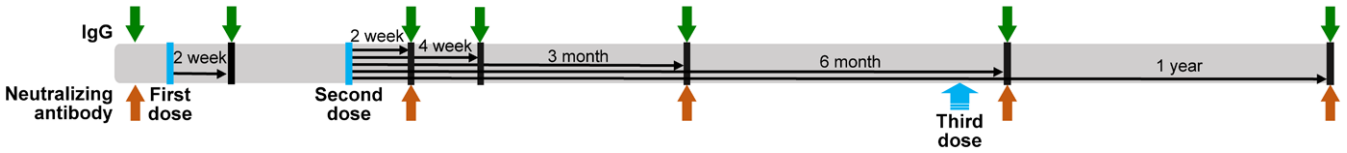

Figure 1. The study timeline. IgG = Immunoglobulin G.

F20; GenBody). The sera of patients undergoing HD examined using ELISA were applied to the GenBody FIA COVID-19 NAb assay. According to the manufacturer's instructions, neutralizing antibodies higher than 30% had protective effects against SARS-CoV-2.

2.4. Statistical analysis

We confirmed the normality test using the Shapiro–Wilk test and used the generalized estimating equation model to compare antibody responses between the control and patient groups. The *t* test was used to compare antibody levels at the 2 time points. For all results, statistical significance was considered at $P < .05$. Missing data were ignored, and statistical analyses were performed using the R software (version 4.1.2; R Development Core Team, 2021) and IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY).

2.5. Ethical statement

This study adhered to the Declaration of Helsinki, and written informed consent was obtained from all participants. The study was approved by the Institutional Review Board of Ajou University Hospital (approval No. AJIRB-BMR-SMP-21-156).

3. Results

3.1. Study population

Overall, 63 patients undergoing chronic HD at Ajou University Hospital were eligible for this study (Fig. 2). However, 7 patients refused vaccination because of concerns about adverse effects, and 9 dropped out for various reasons, including kidney transplantation, death unrelated to COVID-19, transfer, and refusal of a second dose of vaccination. Among 47 patients, 10 received different types of vaccine. Five patients were confirmed to have COVID-19 during the study period and were excluded. Finally, 32 patients undergoing chronic HD who received 2 doses of the ChAdOx1 nCoV-19 vaccine were enrolled. Overall, 13 and 19 patients were vaccinated 2 and 3 times, respectively. Furthermore, 2 and 17 patients received the mRNA-1273 and BNT162b2 vaccines, respectively, as the third dose. All patients who received 3 doses took the third dose before blood sampling 6 months after the second dose. One patient received the third dose 1 week before blood sampling 6 months after the second dose, while others received the doses > 2 weeks before blood sampling 6 months after the second dose.

In total, 34 healthy individuals participated in the control group. Among them, 5 participants dropped out for personal reasons, and 6 were excluded because they were confirmed to have COVID-19. Seven participants had different types of vaccination with the others, and one did not receive the third dose. Finally, 15 healthy participants who received 3 doses of the mRNA-1273 vaccine were included in this study. All participants received the third dose before blood sampling 6 months after the second dose. Two and one participants received the third dose 1 week and 10 days before blood sampling 6 months after the second dose, respectively. The others received the third dose > 2 weeks before blood sampling 6 months after the second dose.

Table 1 presents the baseline characteristics of the patient and control groups. The patient group's age ranged from 35 to 71 years, with a mean ± standard deviation of 57.5 ± 9.5 years, and 50% were female. In contrast, the mean age of patients in the control group was 23.9 ± 1.6 years, and 33.3% were female. No significant difference was found in sex and BMI between the patient and control group. Although patients undergoing HD had many comorbidities, such as diabetes mellitus, hypertension, coronary artery occlusive disease, cancer, and solid organ transplantation, no comorbidities were observed in the control group. Eight patients were taking immunosuppressive agents in the patient group due to solid organ transplantation. Furthermore, no significant difference was found between the 2 patient groups in age, BMI, underlying diseases, and duration of HD.

3.2. IgG response to SARS-CoV-2 spike-RBD protein

The trends of IgG levels in each group are shown in Figure 3. In the patient group, the baseline IgG level was 0.408 ± 0.517 optical density (OD) (0.521 ± 0.764 and 0.327 ± 0.208 OD in patients who received 2 and 3 doses, respectively), and it increased by 0.506 ± 0.617 OD (0.648 ± 0.929 and 0.408 ± 0.234 OD in patients who received 2 and 3 doses, respectively) after 2 weeks from the first dose. However, no significant difference was found ($P = 1.000$), suggesting that the first dose did not make a meaningful antibody response in patients undergoing HD in 2 weeks. After the second dose, the IgG level of the patient group increased up to 1.966 ± 0.959 OD (2.171 ± 1.107 and 1.827 ± 0.838 OD in patients who received 2 and 3 doses, respectively) until 3 months. Compared to pre-vaccination, the IgG level of the patient group at 2 weeks, 4 weeks, and 3 months after the second dose significantly increased ($P < .001$), indicating that 2 doses of vaccination made meaningful antibody response in 2 weeks; the effect was sustained until 3 months in the patient group.

Considering the timing of the third dose, if the third dose were to affect the IgG level, the effect should be observed 6 months and 1 year after the second dose. However, the trends of IgG levels of both groups were similar after 6 months after the second dose. Patients who received 2 doses had decreased IgG level 6 months after the second dose (1.257 ± 0.593 OD); however, it increased to 2.175 ± 1.241 OD 1 year after the second dose. Similarly, the IgG level also decreased in patients who received 3 doses 6 months after the second dose (1.449 ± 0.431 OD) but recovered to 2.134 ± 1.157 OD 1 year after the second dose. However, in both groups, the changes in IgG levels between 3 and 6 months after the second dose and 6 months and 1 year after the second dose were not significantly different ($P = 1.000$), indicating that the third dose did not make a difference in the IgG level in the patient group.

Furthermore, we compared the IgG levels of the 2 patient groups using a *t* test to observe the effect of the third dose. Between 3 and 6 months after the second dose, a significant difference was found between the 2 groups ($P = .03$). However, no significant difference was found when we compared the IgG level of 6 months and 1 year after the second dose between the 2 groups ($P = .29$). A significant difference

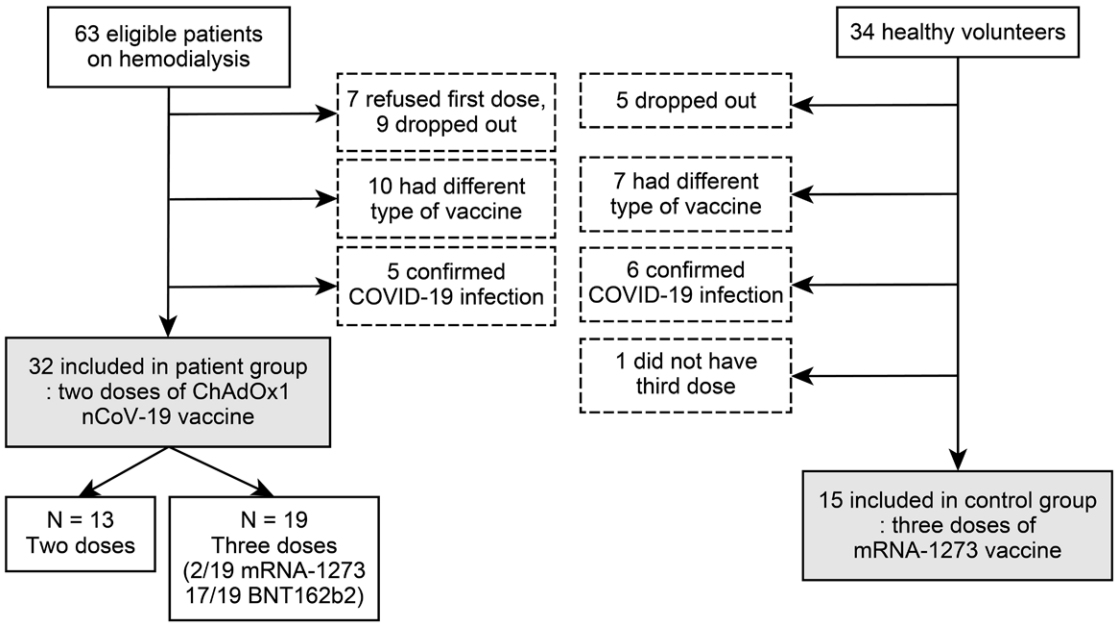

Figure 2. Selection of study participants. COVID-19 = coronavirus disease 2019.

Table 1

Baseline characteristics of the patient and control groups.

	Patient group (n = 32, %)				
	Two doses (n = 13)	Three doses (n = 19)	*P* value for the two patient groups	Control group (n = 15, %)	*P* value for the patient and control groups
Age (yr)	54.08	59.11	.15	23.93	<.001
<60	7 (53.8)	9 (47.4)		15 (100)	
≥60	6 (46.2)	10 (52.6)		0 (0)	
Sex					
Females	10 (76.9)	6 (31.6)	.03	5 (33.3)	.28
Males	3 (23.1)	13 (68.4)		10 (66.7)	
Body mass index (kg/m^2)	21.94	22.43		22.73	
<23	10 (76.9)	12 (63.2)	.73	7 (46.7)	.67
≥23	3 (23.1)	7 (36.8)		8 (53.3)	
Comorbidity					
DM	5 (38.5)	10 (52.6)	.49	0	<.001
HTN	6 (46.2)	15 (78.9)	.07	0	<.001
Solid organ transplantation	3 (23.1)	5 (26.3)	1.00	0	.04
CAOD	3 (23.1)	4 (21.1)	1.00	0	.08
Cancer	2 (15.4)	2 (10.5)	1.00	0	.29
Immunosuppressants	3 (23.1)	5 (26.3)	1.00	0	.04
HD duration (mo)	84.92	72.95	.62		

CAOD = coronary artery occlusive disease, DM = diabetes mellitus, HD = hemodialysis, HTN = hypertension.

between the 2 groups, 6 months and 1 year, should have existed if the third dose increased the IgG level; however, since no difference existed, the effectiveness of the third vaccine remains uncertain.

In both patient groups, the IgG level at 1 year after the second dose significantly differed from that pre-vaccination and 2 weeks after the first dose ($P = .004$, $P = .05$ in patients who received 2 doses, $P < .001$ in those who received 3 doses), suggesting that the IgG produced by 2 doses of vaccination did not wane until 1 year. Moreover, some patients had higher IgG levels than the positive control (SARS-CoV-2 infected serum), which shows the effectiveness of vaccination in the patient group.

The IgG level decreased 4 weeks after the second dose in the control group compared to the patient group; however, the overall trend was similar. The baseline IgG level was 0.743 ± 0.364 OD and increased to 1.910 ± 0.321 OD after 2 weeks from the first dose. Additionally, the difference between pre-vaccination and 2 weeks after the first dose was significant ($P < .001$), indicating that even a single dose made meaningful antibody production in the control group in 2 weeks. The IgG level increased 2 weeks after the second dose (2.464 ± 0.392 OD) but decreased to 1.940 ± 0.688 OD 4 weeks after the second dose, without a significant difference between these two-time points ($P = 1.000$). Furthermore, the IgG level increased to 3.069 ± 0.512 OD 3 months after the second dose, decreased to 1.919 ± 0.244 OD 6 months after the second dose, and recovered to 2.765 ± 0.854 OD 1 year after the second dose, with significant difference ($P < .001$, $P < .001$, and $P = .03$, respectively). Overall, the antibody

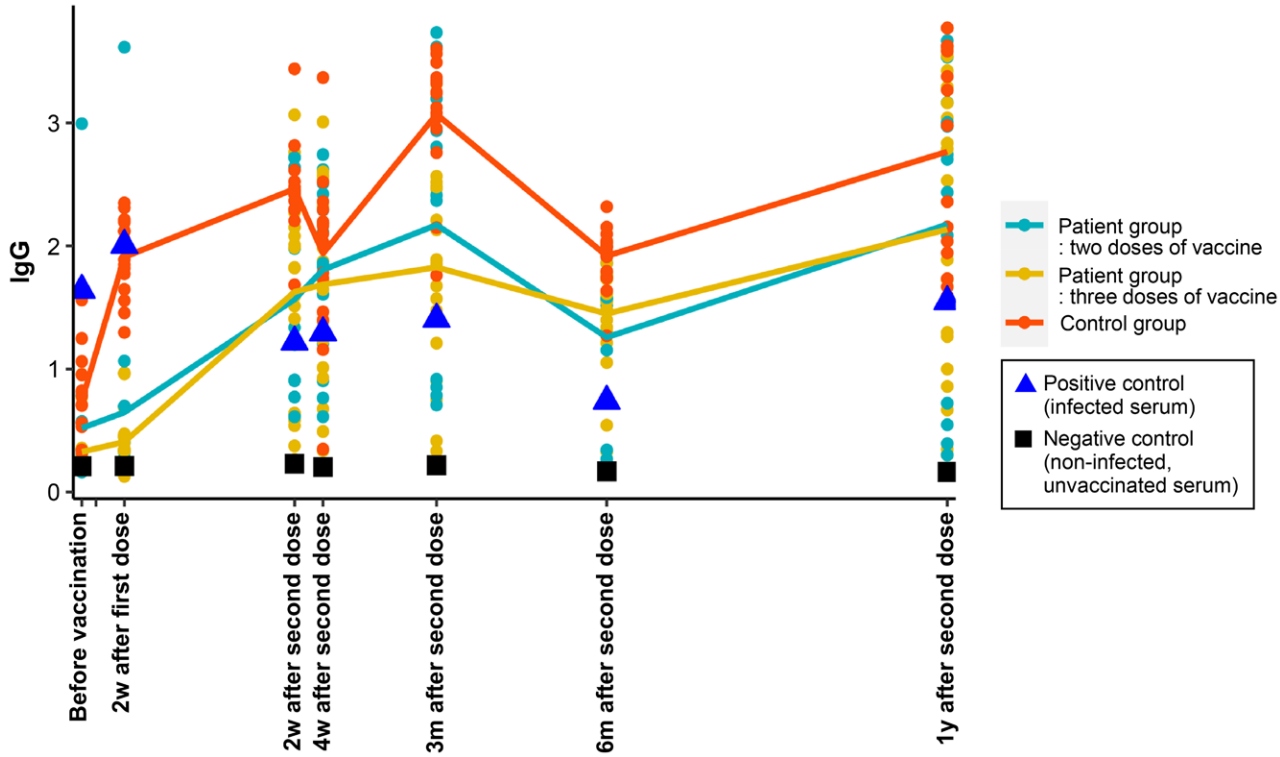

Figure 3. Changes in the IgG level post-vaccination in the patient and control groups. Patient group with 2 doses (blue); patient group with 3 doses (yellow); control group (orange); negative control (black square, unvaccinated and non-infected serum); positive control (blue arrowhead, serum of patients with COVID-19 infection). COVID-19 = coronavirus disease 2019, IgG = immunoglobulin G.

production was lower in the patient group than in the control group ($P < .001$).

3.3. Neutralizing ability of SARS-CoV-2 spike-RBD antibodies by neutralizing assay

The trends of neutralizing antibody levels in each group are shown in Figure 4. In the patient group, the baseline neutralizing antibody level was 23 ± 8% (21 ± 6% and 24 ± 9% in patients who received 2 and 3 doses, respectively), and it increased to 86 ± 24% (84 ± 22% and 87 ± 26% in patients who received 2 and 3 doses, respectively) 2 weeks after the second dose. Additionally, it decreased to 78 ± 4% (78 ± 25% and 77 ± 24% in patients who received 2 and 3 doses, respectively) 3 months after the second dose. Compared to baseline neutralizing antibody levels, antibody levels at 2 weeks and 3 months after the second dose significantly increased (P = <.001), showing the effectiveness of the 2 doses of vaccination until 3 months.

At 6 months and 1 year after the second dose, the neutralizing antibody levels of patients with 2 doses were 87 ± 20% and 87 ± 23%, respectively. However, they were 92 ± 21% and 89 ± 18% in patients with 3 doses, respectively. Changes in neutralizing antibody levels between 3 and 6 months and 6 months and 1 year after the second dose were not significantly different in both groups (P = 1.000), comparable to the IgG level. This suggests that the third dose did not affect neutralizing antibodies in the patient group.

Moreover, no significant difference was found when we compared neutralizing antibodies between 3 and 6 months and 6 months and 1 year after the second dose of the 2 groups to observe the effect of the third dose (P = .21 and P = .56), suggesting the uncertainty of the third dose's effect.

In both patient groups, the neutralizing antibody levels 6 months and 1 year after the second dose significantly differed from the baseline neutralizing antibody levels ($P < .001$), suggesting the sustained effect of the 2 doses until 1 year. Additionally, the change in the neutralizing antibody level in both patient groups was not significant after 2 weeks from the second dose (P = 1.000), suggesting that 2 doses of vaccination increased the neutralizing antibody levels rapidly in 2 weeks.

In the control group, the neutralizing antibody level was 16 ± 11% pre-vaccination, increasing to 99 ± 1% 2 weeks after the second dose. Additionally, it was 96 ± 8%, 99 ± 0%, and 99 ± 2% at 3 months, 6 months, and 1 year after the second dose, respectively. The neutralizing antibody levels were higher in the control group than in the patient group during the study period ($P < .001$).

Only 1 patient had a neutralizing antibody level < 30% during the study period. The patient received 2 doses of the vaccination, and the neutralizing antibody levels were 23%, 26%, 23%, and 33% at 2 weeks, 3 months, 6 months, and 1 year after the second dose, respectively. Additionally, the patient was taking immunosuppressive drugs (tacrolimus 8 mg and prednisolone 5 mg daily) for pancreas and kidney transplantation, and these drugs may have interrupted antibody formation post-COVID-19 vaccination. However, other patients and participants maintained neutralizing antibody levels > 30%, which was the criterion for the protective effect of neutralizing antibodies throughout the study period.

4. Discussion

This study observed trends in IgG and neutralizing antibody levels post-COVID-19 vaccination in patients undergoing HD and healthy volunteers for 1 year. Although the response to vaccination in the patient group was weaker than that in the control group, vaccination increased IgG and neutralizing antibody levels in patients undergoing HD. Moreover, all patients, except one, maintained neutralizing antibody levels of > 30%

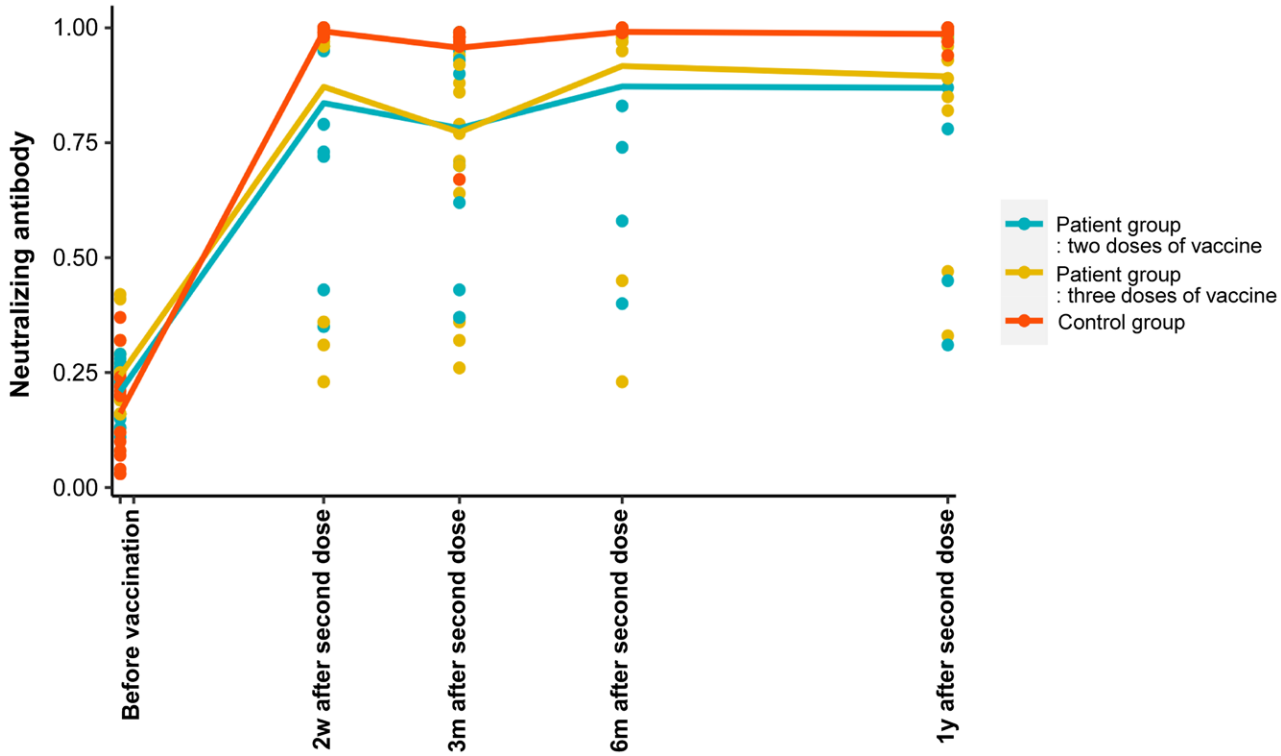

Figure 4. Changes in neutralizing antibody levels post-vaccination in the patient and control groups. Patient group with 2 doses (blue); patient group with 3 doses (yellow); control group (orange).

throughout the study period, indicating their protective effects against COVID-19. Therefore, the 2 doses of vaccination resulted in significant antibody production in patients undergoing HD.

IgG and neutralizing antibody levels were lower in the patient group than in the control group, which is consistent with the results of previous studies.[11–13] However, in this study, patients undergoing HD received 2 doses of the ChAdOx1 nCoV-19 vaccine, and healthy participants received the mRNA-1273 vaccine, which has a superior effect than other vaccines.[14,15] Moreover, participants were considerably younger in the control group than in the patient group and had no comorbidities. These differences in vaccine type, age, and comorbidities may have made the difference in antibody levels between the 2 groups even greater.

Therefore, to determine the effect of the third dose of vaccination on HD, we categorized the patient groups according to whether the patient received a third dose and compared their antibody responses. In this study, no significant differences were found in IgG and neutralizing antibody levels between the 2 groups that received 2 or 3 doses of vaccination, and the antibody levels did not significantly increase in patients who received 3 doses. However, this result differs from those of previous studies. Several studies[16–19] showed that the third dose of vaccine substantially increased antibody levels in patients receiving maintenance dialysis, and its effect was particularly noticeable in those with a lower response to the previous 2 doses of vaccine. Precisely pinpointing the reasons for the disparity between our findings and those of prior studies presents a challenge. When we separately compared the IgG response of the 2 groups at 2 weeks after the second dose, the IgG level of patients who received 2 doses showed no significant difference compared to pre-vaccination and 2 weeks after the first dose (P = .14 and P = 1.000). However, in patients who received 3 doses, the IgG level at 2 weeks after the second dose showed a meaningful increase compared to pre-vaccination and 2 weeks after the first dose (P < .001). This suggests that the patient group who received 3 doses included many patients who responded well to the previous 2 doses. Since previous studies have shown that the third dose's effect is prominent in those with lower response to the previous 2 doses,[16] this might explain why our study patients who responded well to the previous 2 doses did not show a noticeable change in the antibody level with the third dose.

In this study, the IgG and neutralizing antibody levels produced by vaccination did not wane until 1 year after the second dose. This finding differs from a previous Korean study that observed an antibody response after 2 doses of the COVID-19 vaccine in patients undergoing HD for 4 months.[20] However, patients in the study received a heterogeneous COVID-19 vaccine with ChAdOx1 and BNT162b2 as the first and second doses, respectively, and showed a decrease in the antibody after 4 months. Therefore, differences in the type of vaccine administered to patients and different observation durations could have resulted in varying results.

Since the onset of the COVID-19 pandemic started, many studies on COVID-19 have been conducted to date. In addition to causing pneumonia, COVID-19 has been associated with many diseases, including autoimmune diseases,[21] arrhythmia, and thrombosis.[22] Additionally, studies on diagnostic testing for COVID-19[23] or factors associated with the severity of its infection[24] have been conducted. Our understanding of COVID-19 has significantly expanded with these efforts, although the pandemic is not completely over. Therefore, continued vigilance towards COVID-19 remains imperative, and this study result might help plan for vaccination against the reemergence of COVID-19 or novel infectious diseases.

This study had some limitations. First, it was conducted at a single center with a small population. Therefore, further classifying the patient groups according to age, sex, history, and HD vintage was challenging because of the small population. These underlying factors may have influenced the antibody production in patients undergoing HD. Although the power was 0.89 in the neutralizing antibody analysis when we conducted post

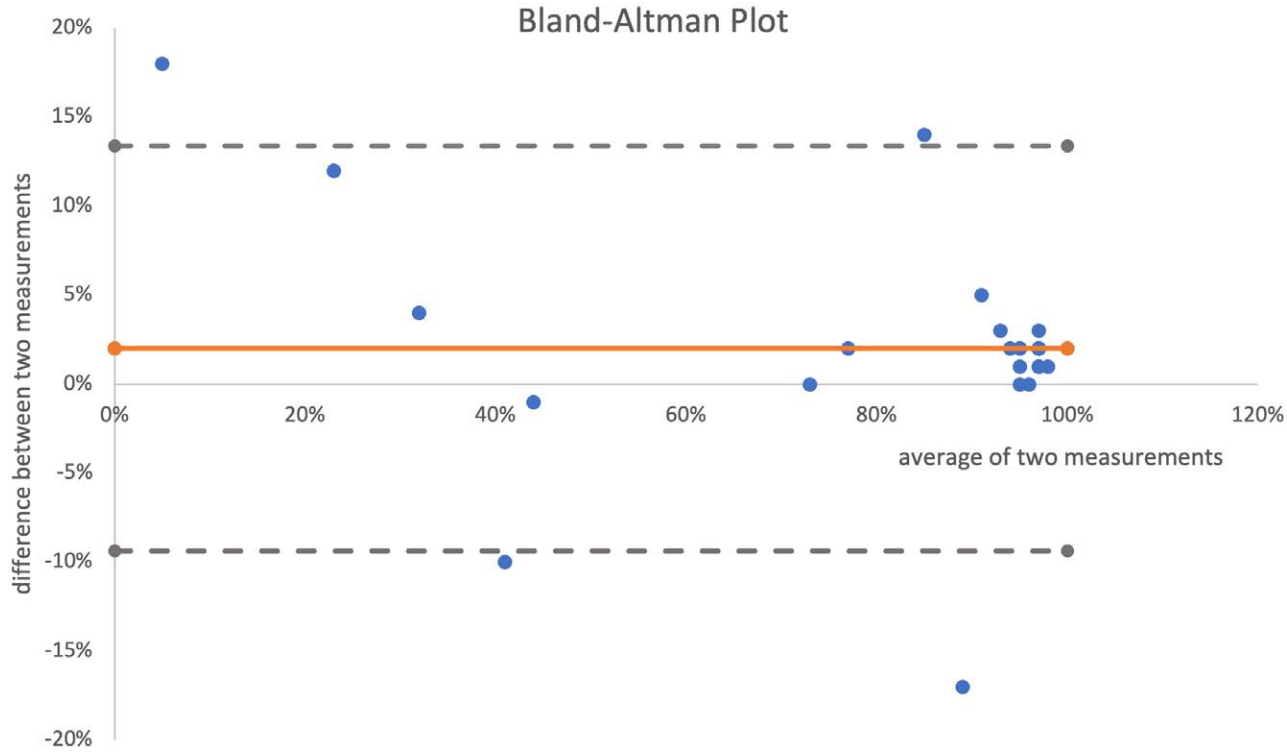

Figure 5. Bland–Altman plot of the two different measurement methods of neutralizing antibody analysis.

hoc power analyses, it was close to 0.00 in the IgG level analysis. The low power of the IgG level analysis represents a major limitation; however, the value lies in the 1-year observation of the IgG level of patients undergoing HD, coupled with the robust power achieved in the neutralizing antibody analysis. Second, the types of vaccines administered to the patient and control groups differed. Because the vaccine was insufficient when it was first developed, study participants or researchers could not adjust the type of vaccine. However, we attempted to obtain homogeneity within each group by unifying the type of vaccine in each group. Third, because the third dose was unplanned during the study design, the time interval between the third dose and blood sampling 6 months after the second dose varied among participants. Moreover, due to the introduction of an unplanned third dose, the categorization of the control group based on the third dose was not feasible compared to that of the patient group since almost all participants in the control group received the third dose. Fourth, neutralizing antibody levels were not frequently measured as the IgG levels due to high cost; therefore, we could not determine the rate of change in the neutralizing antibody levels as efficiently as IgG. Additionally, we used a fluorescence-based competitive SARS-CoV-2 neutralizing antibody assay (GenBody) to measure neutralizing antibody levels in this study. Therefore, to evaluate the accuracy of this assay, we measured the neutralizing antibody level of the patient group 2 weeks after the second dose using the fluorescence-based assay (GenBody) and SARS-CoV-2 Surrogate Virus Neutralization Kest kit (GenScript), which was approved by the Food and Drug Administration. We confirmed that the results using the 2 methods were consistent using the Bland–Altman plot (Fig. 5), which is frequently used to assess the differences between 2 different measurement methods.

In conclusion, we examined the antibody response of patients undergoing HD to COVID-19 vaccination. To the best of our knowledge, this is the first study to observe both IgG and neutralizing antibody levels produced by the COVID-19 vaccine in Korean patients undergoing HD for 1 year. Furthermore, COVID-19 vaccines significantly increased antibody levels in patients undergoing HD; 2 doses showed a similar antibody response with 3 doses, and the antibodies persisted for 1 year.

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Funding acquisition: Inwhee Park.
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