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Original Article	Humoral Response Decreases in Hemodialysis Patients 6 Months After The Third Dose of COVID-19 Vaccine	
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#### Abstract

**Background:** This study evaluated the antibody levels six months after administering the third dose of the COVID-19 vaccine in hemodialysis patients.

**Methods:** A total of 52 hemodialysis patients were enrolled in the study. Antibody levels were assessed using the Abbott SARS-CoV-2 immunoassay, designed to detect IgG antibodies targeting the receptor-binding domain of the S1 subunit of the SARS-CoV-2 spike protein.

**Results:** The incidence of COVID-19 infection within six months following the third vaccine dose was 29.6% (8 patients: 2 males, 25%; 6 females, 75%). Among patients who did not contract COVID-19 within this period, 9 were male (47.4%) and 10 were female (52.6%). There was no statistically significant association between gender and the incidence of COVID-19 within six months post-vaccination (p= 0.280). The median antibody level post-third dose was 7332.4 AU/mL (range: 10.5–40,000), which significantly decreased at the sixth month to 3238.4 AU/mL (range: 17–29,994.7) (p= 0.001). No significant difference between male and female patients was observed in the sixth-month antibody titers (p= 0.744). Furthermore, when analyzed by vaccine type, there was no statistically significant difference in the decline of SARS-CoV-2 IgG antibody levels between recipients of CoronaVac/Sinovac and BNT162b2 (Pfizer/BioNTech) [median (min-max) antibody levels: CoronaVac/Sinovac 2398.2 AU/mL (59.2–38,981.5); BNT162b2 (Pfizer/BioNTech) 11,325.7 AU/mL (17–40,000), (p= 0.181)] at the end of the sixth month.

**Conclusion:** Antibody titers in hemodialysis patients significantly decreased by the end of the sixth month following the third dose of the SARS-CoV-2 vaccine, independent of the vaccine type. This decline highlights the potential necessity for additional booster doses to enhance and maintain immune protection against SARS-CoV-2 in this vulnerable population.

Keywords: Hemodialysis, COVID-19 vaccine, SARS-CoV-2 antibody

#### **INTRODUCTION**

COVID-19, declared a pandemic by the World Health Organization (WHO) on March 11, 2020, is defined as a life-threatening viral epidemic that has significantly impacted human health (1). Since its onset in December 2019, the virus has spread globally, resulting in over 329 million confirmed cases and more than 5.5 million deaths to date (2). Hemodialysis patients represent a vulnerable population to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-associated morbidity and mortality, facing a 2- to 4-fold increased risk of death compared to the general population (3,4). While vaccination remains the most proven method to reduce the spread of the COVID-19 pandemic, maintaining long-term vaccine efficacy is crucial for combating newly emerging variants.

A recent meta-analysis reported that COVID-19 mRNA

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vaccines are highly effective, especially after second dose administration, against post-vaccination laboratoryconfirmed SARS-CoV-2 infection, symptomatic COVID-19 infection, hospitalization, and mortality (5). Hemodialysis patients have a higher risk of COVID-19 infection due to increased comorbidities, suppressed immune systems, and having to be in crowded hemodialysis rooms two/three days a week (6). It is also a known fact that 28 days after two doses of mRNA vaccine, dialysis patients and transplant recipients have lower seroconversion rates compared to controls (7-9).

Since no effective drug has been found to treat COVID-19, measures such as increasing decontamination by promoting personal hygiene and cleaning, maintaining social distancing, quarantine, and isolation, as well as increasing the number of immune people by expanding vaccination is very important to stop the spread of infection (6). Recent studies have shown that mRNA vaccines protect healthy individuals against emerging SARS-CoV-2 variants by inducing long-term immunological memory (10,11). However, especially in elderly and immunocompromised patients, antibody levels decrease rapidly within 6 months (12). These findings highlight the value of long-term monitoring of high-risk, renal disease patients to determine whether more booster vaccinations or different vaccination approaches are required.

This study examined SARS-CoV-2 IgG antibody titers against the S1 subunit of the spike protein as a marker of the humoral response to the 3rd dose BNT162b2 (Pfizer-BioNTech) or CoronaVac (Sinovac Life Sciences) vaccines in maintenance hemodialysis patients, six months after the third COVID-19 vaccination and aimed to compare the response in antibody titers and to investigate the frequency of SARS-CoV-2 infection after vaccination.

# **METHODS**

# Study Population

The study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Samsun University Clinical Research Ethics Committee, under protocol number 2022/3/8. Patients with hematological diseases, malignancies, connective tissue diseases, immunosuppressive therapy, a history of kidney transplantation, liver cirrhosis, chronic obstructive pulmonary disease, or congestive heart failure were excluded from the study.

The study included 52 adult hemodialysis patients (aged  $\geq$ 18 years) who received a third dose of the COVID-19 vaccine between March 2021 and November 2022. All participants had been enrolled in a maintenance hemodialysis program for at least six months, and their antibody titers were eligible for measurement. Of these

52 patients, only 27 had measurable antibody levels at the end of the sixth month post-vaccination and were therefore included in the analysis.

Sociodemographic data, history of SARS-CoV-2 infection, COVID-19 vaccination status (including the number, dates, and types of vaccines received), and any COVID-19-related deaths were obtained from clinical file records. The hospital's electronic medical record system was utilized to access reverse transcriptase polymerase chain reaction (rRT-PCR) results and relevant laboratory data from routine follow-ups. All participants provided written informed consent for their involvement in the study.

## Sample Collection and Analysis:

Venous blood samples were collected from participants on the 28th day following the third dose of either the CoronaVac or BNT162b2 vaccine, with a second sample collected at the end of the sixth month. Shortly after collection, the samples were centrifuged and stored at  $-20^{\circ}$ C until analysis.

The Abbott "Alinity I" platform was used in accordance with the manufacturer's instructions for the quantitative analysis of antibodies using the SARS-CoV-2 IgG II Quant assay, an automated, two-step immunoassay designed for the detection of IgG antibodies against the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein. In this assay, paramagnetic microparticles coated with SARS-CoV-2 antigen bind to IgG antibodies specific to the spike protein in serum or plasma samples, reflecting the amount of spike protein-specific IgG present. The resulting chemiluminescence, measured in relative light units (RLU), is compared to the IgG II calibrator or standard to determine antibody levels.

A result of  $\geq$ 50 AU/ml is considered positive. The analytical measurement range for this assay is 21–40,000 AU/ml, extendable to 80,000 AU/ml with a 1:2 dilution. The test has demonstrated high predictive accuracy, with a positive percent agreement of 99.4% (95% confidence interval [CI]: 96.50%–99.97%) and a negative percent agreement of 99.6% (95% CI: 99.15%–99.37%). It also showed agreement with a neutralization assay, with a positive percent agreement of 100.0% (95% CI: 95.72%–100.00%) (13).

# STATISTICAL ANALYSIS

All statistical analyses were performed using SPSS version 21.0.0.1 for Windows (IBM SPSS). Data distribution was assessed using the Kolmogorov-Smirnov test. Continuous variables were presented as mean  $\pm$  standard deviation or as median with minimum and maximum values, depending on the data distribution. Categorical variables were expressed as percentages. The Student's t-test or Mann-Whitney U test was used to compare differences in laboratory parameters between

the study

Variable	Mean ± SD (range)/ median (min/max)
Age; year	59.7±10.3
Gender (Femal/Male); n and (%)	16/11 (59.3/40.7)
Dialysis time; months	32 (18/30)
Urea; mg/dL	$123.26 \pm 36.02$
Creatinine; mg/dL	$7.4 \pm 1.9$
Albumin; g/dL	$3.58 \pm 0.32$
Alanine aminotransferase; U/L	15 (8-49)
Sodium; mmol/L	$137.5 \pm 3.45$
Potassium; mmol/L	$5.08 \pm 0.69$
Calcium; mg/dL	$8.5 \pm 0.63$
Phosphorus; mg/dL	$4.9 \pm 1.24$
Hemoglobin; g/dL	$10.6 \pm 1.16$
White blood cell; 10 <sup>6</sup> /L	$6260 \pm 1639$
Platelet; 10 <sup>6</sup> /L	$194.78 \pm 53.7$
Ferritin; ng/mL	340 (118 - 805)

 Table 1. Socio-demographic characteristics and laboratory parameters of 27 patients participating in

independent groups, based on the distribution of the data. Categorical variables were compared using the Chi-square test or Fisher's Exact test, as appropriate. Pearson correlation analysis was employed to examine correlations. The Wilcoxon test was used to assess differences between two dependent groups. A p-value of <0.05 was considered statistically significant.

## RESULTS

Of the 52 patients undergoing hemodialysis in our clinic, who received the third dose of the COVID-19 vaccine (BNT162b2 vaccine or CoronaVac), only 27 patients whose antibody levels could be measured at the end of the 6th month were included in the study [11 male 40.7%, 16 female 59.3%; mean age  $59.7\pm10.3$  years (min 37, max 80); hemodialysis duration 32 months (min18, max 30)]. Laboratory values of the patients are listed in Table 1.

Antibody titers were lower in patients who had Covid within 6 months despite vaccination  $(12112.8 \pm 6154.2)$ and in patients who did not have Covid (15172.5  $\pm$ 3851.5) (p= 0.004). In addition, antibody levels at the end of the sixth month were positively correlated with antibody levels at the end of the third dose (r= 0.58, p=0.002). Among those who did not have COVID-19 within 6 months following the 3rd dose of vaccine, 9 of them were male, 47.4%, and 10 of them were female, 52.6%. There was no statistically significant difference between gender and the rate of COVID-19 infection within 6 months following the 3rd dose of vaccine (p= 0.280). Among those who did not have COVID-19 within 6 months following the 3rd dose of vaccine, 9 of them were male, 47.4%, and 10 of them were female, 52.6%. There was no statistically significant difference between gender and the rate of contracting COVID-19 within 6 months following the 3rd dose of vaccine (p= 0.280).

The last 3rd dose of vaccine administered in 9 patients

was Biontech, and Sinovac in 18 patients. It determined that the last vaccine type of 8 patients who had COVID-19 within 6 months following the 3rd dose of vaccine was CoronaVac/Sinovac vaccine in 5 of them and BNT162b2 (Pfizer/Biontec) vacci-ne in 3. There was no statistically significant difference in the rate of contracting Covid within 6 months following the 3rd dose of vaccine, depending on the last vaccine type (p= 0.766). Excluding those who had COVID-19 in the last 6 months (n=19), while the antibody level after the 3rd dose of vaccine was 7332.4 AU/mL (median) (min/ max) (10.5-40000), a serious decrease was observed in the 6th-month antibody titer to 3238.4 AU/mL (median) (min/max) (17- 29994.7) (p= 0.001) (Table 2). When 8 patients who had Covid were excluded and the effect of gender on the 6th-month antibody titer was examined, the median 6th-month antibody titers was 3558.4 (408.8- 29994.7) in female patients (n= 10), while it was 1815.9 (17- 29262.2) in male patients (n= 9). There was no difference in 6th-month antibody levels between genders (p=0.744). When the same analysis was performed according to the last vaccine type, no statistical difference was found between the decrease in SARS-CoV-2 IgG antibody level for both CoronaVac/ Sinovac and BNT162b2 (Pfizer/Biontec) at the end of the 6th month [median (min-max) respectively; (CoronaVac/Sinovac; BNT162b2 (Pfizer/Biontec) ] [2398.2 AU/mL (59.2 – 38981.5); 11325.7 (17 – 40000),

**Table 2.** Antibody levels after the 3rd dose of vaccine and after 6 months, excluding those who had COVID-19 in the last 6 months

	Antibody Levels; N= 19, median (min-max)
After 3rd dose of vaccine antibody levels SARS-CoV-2 IgG Antibody titers (AU/mL)	7332.4 (10.5-40000)
After 6 months SARS-CoV-2 IgG Antibody titers (AU/mL)	3238.4 (17-29994.7)
P value	0.001

	BNT162b2(Pfizer/Biontec) (n=16) (min-max)	CoronaVac/Sinovac (n= 36) (min-max)	p value
End of the 6th month SARS-	11325.7	2398.2 AU/mL	
CoV-2 IgG Antibody titers (AU/	(17 - 40000)	(59.2 - 38981.5	0.181
mL) median (min-max)			

Table 3. SARS-CoV-2 IgG antibody	y level for CoronaVac/Sinovac and	BNT162b2 (Pfizer/Biontec) at the e	nd of the 6th month.

(p = 0.181)] (Table 3).

### DISCUSSION

This study demonstrated a significant decrease in anti-SARS-CoV-2 antibodies 6 months after the third dose of both CoronaVac/Sinovac and BNT162b2 (Pfizer/ Biontec mRNA vaccines) against SARS-CoV-2 in hemodialysis patients. Our findings were consistent with recently published studies describing decre-ased anti-SARS-CoV-2 antibodies over time in dialysis patients (14-16). The decrease in antibody levels was similar in both genders. Despite the third dose of vaccine, SARS-CoV-2 infection was obser-ved in approximately onethird of the patients (29.6%), but there was no deaths due to SARS-CoV-2 infection.

Patients with end-stage renal disease have been highly affected by the pandemic in terms of COVID-19 infection and complications due to having multiple comorbid conditions and a suppressed immune system, and the mortality rate is significantly high in those hospitalized (17). The frequency of SARS-CoV-2 infection in hemodialysis patients and mortality rates due to SARS-CoV-2 infection are significantly reduced in vaccinated individuals, and the administration of additional vaccine doses is important in increasing and maintaining protection against SARS-CoV-2 infection (18). In this study, even though one-third of the patients developed SARS-CoV-2 infection even after the third dose of vaccination, there was no deaths due to infection, which once again reveals the importance of vaccination.

After many vaccinations, neutralizing antibody levels decrease at a certain rate each year (19). As is known, antibody levels after naturally acquired SARS-CoV-2 infection decrease more slowly after 8 to 10 months than after vaccination (20,21). In our study, we observed a significant and rapid decrease in humoral response in hemodialysis patients in the 6th month after vaccination. This decrease was valid indiscriminately for both the CoronaVac/Sinovac vaccine and the BNT162b2 (Pfizer/Biontec) vaccine. Our findings supported other studies in the literature (12,16).

In a study conducted with healthcare workers, it was stated that the the incidence of symptomatic infec-tion with SARS-CoV-2 increased due to the rapid decline in antibody levels despite high vaccination rates, antibody levels after the second dose were higher in women than in men, antibody levels decrea-sed with age and antibody titers were lower in the group with immunosuppression (12). The fact that approximately one-third of the patients in our study were re-infected with SARS-CoV-2 within six months despite the third dose of vaccine can be explained by the fact that hemodialysis patients have a suppressed immune system compared to the healthy population, as stated in previous studies (12). Addi-tionally, the decrease in antibody levels observed over time in our study was independent of gender and age. This may be due to the small number of patients participating in the study, the high average age, and the low number of young patients.

In SARS-CoV-2 infection, neutralizing antibodies are associated with disease protection (22,23). In our study, neutralization tests could not be measured because they were complex and time-consuming, but antibody levels could be measured. The fact that the antibody titers of patients who had COVID-19 were lower than those of patients who had not COVID-19 within 6 months despite the vaccine reveals that the increase in the antibody level may protect against the disease.

Limitations of our study include limited follow-up to 6 months, single-center study, small sample size, lack of a control group, and lack of cellular immunity data. Hemodialysis patients often have comorbidi-ties and use many medications. The relationship between antibody titers and comorbidities and drug use could not be explained in the article.

## CONCLUSION

Antibody titers in hemodialysis patients decline significantly six months after receiving both the CoronaVac (Sinovac) and BNT162b2 (Pfizer/BioNTech) mRNA vaccines. While SARS-CoV-2 infections may occur following the third vaccination, none of the infected patients in this study experienced mortality. In light of the emergence of new infection waves driven by viral mutations during the pandemic, it is evident that a fourth booster dose is necessary to maintain a protective humoral response in this vulnerable population. Additionally, strategies to prolong host immunity should be explored to ensure adequate protection for this patient group against SARS-CoV-2 and its variants.

## DECLERATIONS

Ethics Committee Aproval: The study was initiated with the approval of the Samsun University Clinical

Trial Ethics Committee (Date: 2022, Decision No:3/8).

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#### REFERENCES

- Gupta D, Sahoo AK, Singh A. Ivermectin: potential candidate for the treatment of Covid 19. *Braz J Infect Dis.* 2020;24(4):369-371. doi:10.1016/j.bjid.2020.06.002
- Chavda VP, Kapadia C, Soni S, et al. A global picture: therapeutic 2 perspectives for COVID-19. Immunotherapy. 2022;14(5):351-371. doi:10.2217/imt-2021-0168
- 3. Ozturk S, Turgutalp K, Arici M, et al. Mortality analysis of COVID-19 infection in chronic kidney disease, haemodialysis and renal transplant patients compared with patients without kidney disease: a nationwide analysis from Turkey. *Nephrol Dial Transplant*. 2020;35(12):2083-2095. doi:10.1093/ndt/gfaa271 Lin YC, Lai TS, Lin SL, Chen YM, Chu TS, Tu YK. Outcomes of coronavirus 2019 infection in patients with chronic kidney
- 4. disease: a systematic review and meta-analysis. *Ther Adv Chronic Dis.* 2021;12:2040622321998860. Published 2021 Mar 19. doi:10.1177/2040622321998860
- Baradaran HR, Dehghanbanadaki H, Moradpour F, et al. The effect of COVID-19 mRNA vaccines against postvaccination laboratory-confirmed SARS-CoV-2 infection, symptomatic COVID-19 infection, 5. hospitalization, and mortality rate: a systematic review and metaanalysis. Expert Rev Vaccines. 2022;21(10):1455-1464. doi:10.1080/
- analysis. Expert Rev Vaccines. 2022;21(10):1455-1464. doi:10.1080/ 14760584.2022.2102001 Yen CC, Lin SY, Chen SC, Chiu YW, Chang JM, Hwang SJ. COVID-19 Vaccines in Patients with Maintenance Hemodialysis. J Pers Med. 2021;11(8):789. Published 2021 Aug 12. doi:10.3390/jpm11080789 Sanders JF, Bemelman FJ, Messchendorp AL, et al. The RECOVAC Immune-response Study: The Immunogenicity, Tolerability, and Safety of COVID-10 Vaccinetics in Patients With Chemic Kidney, Discost 6.
- 7. of COVID-19 Vaccination in Patients With Chronic Kidney Disease, on Dialysis, or Living With a Kidney Transplant. *Transplantation*. 2022;106(4):821-834. doi:10.1097/TP.000000000003983 Chen JJ, Lee TH, Tian YC, Lee CC, Fan PC, Chang CH. Immunogenicity Rates After SARS-CoV-2 Vaccination in People With End-stage
- 8. Kidney Disease: A Systematic Review and Meta-analysis. JAMA

Netw Open, 2021;4(10):e2131749. Published 2021 Oct 1. doi:10.1001/ jamanetworkopen.2021.31749

- Caillard S, Thaunat O. COVID-19 vaccination in kidney transplant 9 Nat Rev Nephrol. 2021;17(12):785-787. doi:10.1038/ recipients. s41581-021-00491-7
- Goel RR, Painter MM, Apostolidis SA, et al. mRNA vaccines induce durable immune memory to SARS-CoV-2 and variants of concern. *Science*. 2021;374(6572):abm0829. doi:10.1126/science. 10. abm082
- 11. GeurtsvanKessel CH, Geers D, Schmitz KS, et al. Divergent SARS-CoV-2 Omicron-reactive T and B cell responses in COVID-19 vaccine recipients. *Sci Immunol.* 2022;7(69):eabo2202. doi:10.1126/ sciimmunol.abo2202
- Levin EG, Lustig Y, Cohen C, et al. Waning Immune Humoral Response to BNT162b2 Covid-19 Vaccine over 6 Months. N Engl J 12. Med. 2021;385(24):e84. doi:10.1056/NEJMoa2114583
- SARS-CoV-2 Immunoassy. Accessed November 6, 2022. https:// www.corelaboratory.abbott/int/en/offerings/segments/infectious-13. lisease 'sars-co
- Berar-Yanay N, Freiman S, Shapira M, et al. Waning Humoral Response 14. 3 to 6 Months after Vaccination with the SARS-COV-2 BNT162b2 mRNA Vaccine in Dialysis Patients. *J Clin Med.* 2021;11(1):64. Published 2021 Dec 23. doi:10.3390/jcm11010064
- Published 2021 Dec 23. doi:10.3390/jcm11010064 Davidovic T, Schimpf J, Abbassi-Nik A, et al. Waning humoral response 6 months after SARS-CoV-2 vaccination with the mRNA-BNT162b2 vaccine in hemodialysis patients: time for a boost. *Kidney Int.* 2021;100(6):1334-1335. doi:10.1016/j.kint.2021.10.006 Beilhack G, Monteforte R, Frommlet F, Reindl-Schwaighofer R, Strassl R, Vychytil A. Humoral Response to mRNA-1273 SARS-CaV2 Vaccine Bertened Dislocit Databased L Bertenic A Series 15.
- CoV-2 Vaccine in Peritoneal Dialysis Patients: Is Boostering After Six Months Adequate?. Front Med (Lausanne). 2022;9:905798. Published 2022 Jun 24. doi:10.3389/fmed.2022.905798
- Yavuz D, Karagöz Özen DS, Demirağ MD. COVID-19: mortality rates of patients on hemodialysis and peritoneal dialysis. *Int Urol Nephrol.* 2022;54(10):2713-2718. doi:10.1007/s11255-022-03193-6 17.
- Yavuz D, Karagöz Özen DS, Başbulut E, Bilgin M, Demirag MD. Vaccination Against SARS-CoV-2 and Mortality in Hemodialysis Patients: Three is Good. *BSJ Health Sci.* 2023;6(3):398-403. doi:10.19127/bshealthscience.1274888 18.
- Seagle EE, Bednarczyk RA, Hill T, et al. Measles, mumps, and 19 the second dose of the MMR vaccine. Vaccine. 2018;36(6):818-826. doi:10.1016/j.vaccine.2017.12.075
- Dan JM, Mateus J, Kato Y, et al. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. *Science*. 2021;371(6529):eabf4063. doi:10.1126/science.abf4063
   Vanshylla K, Di Cristanziano V, Kleipass F, et al. Kinetics and correlates of the neutralizing antibody response to SARS-CoV-2 infection in humans. *Cell Host Microbe*. 2021;29(6):917-929.e4. doi:10.1016/j.chom.2021.04.015
- 22.
- doi:10.1016/j.chom.2021.04.015
  Bergwerk M, Gonen T, Lustig Y, et al. Covid-19 Breakthrough Infections in Vaccinated Health Care Workers. N Engl J Med. 2021;385(16):1474-1484. doi:10.1056/NEJMoa2109072
  Khoury DS, Cromer D, Reynaldi A, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat Med. 2021;27(7):1205 1211. doi:10.1038/ 41501-021-01277.8 23. s41591-021-01377-8