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Antibody responses to the SARS-CoV-2 vaccines in hemodialysis patients: Is inactivated vaccine effective?

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Abstract

Introduction: Vaccines generally have reduced effectiveness in hemodialysis patients and a similar condition may also apply for the SARS-CoV-2 vaccines. The aim of this study was to analyze humoral responses of hemodialysis patients to SARS-CoV-2 vaccines.

Methods: Eighty-five maintenance hemodialysis patients who received either inactivated or mRNA SARS-CoV-2 vaccines were investigated. Antibody levels were measured by a commercial antibody kit, which detected antibodies toward receptor binding domain of the SARS-CoV-2 spike protein. Comparative analyzes were carried between vaccine groups and with a control group of 103 healthy volunteers.

Results: Seropositivity rate and antibody levels were significantly lower in hemodialysis patients who received inactivated vaccine ($p = 0.000$). While mRNA vaccine had better immunogenicity, both vaccines protected from symptomatic infection when seropositivity was achieved.

Discussion/Conclusion: When used in the same dose with the general population, inactivated SARS-CoV-2 vaccines generate reduced humoral response in hemodialysis patients. mRNA vaccines have better immunogenicity in this group.

KEYWORDS
COVID-19, hemodialysis, immunization, SARS-CoV-2, vaccine

1 | INTRODUCTION

COVID-19 has been previously shown to have high mortality in hemodialysis patients that may reach up to 30%.[1,2] Therefore preventive measures to reduce the infection rates among these patients have utmost importance.[3] While immunization is the best preventive strategy, effectiveness of vaccines is a major concern in hemodialysis patients as immunological response to the vaccines are generally reduced.[4] As an example, sufficient antibody responses to hepatitis B virus (HBV) vaccine, which is more than 90% in the general population, are around 60%–70% in hemodialysis patients.[5] Disturbances of T lymphocytes and antigen presenting cells in hemodialysis patients may be responsible for low antibody response to the vaccines.[6] This may necessitate doubling the vaccine dose, administering booster doses, changing the route of administration or using alternative adjuvants.

Vaccination will be the cornerstone for ending the COVID-19 pandemic. Different vaccines currently used for COVID-19 are inactivated vaccines, protein subunit vaccines, viral vector vaccines, and mRNA vaccines.[7] Inactivated and mRNA vaccines are available in our country. Any of them can be applied according to patient preferences. Efficacy studies of these new vaccines are carried out on general population and they suggest that mRNA vaccines are slightly more effective than the inactivated vaccine.[7] However, their efficacies are not clearly defined for hemodialysis patients yet.

The aim of this study is to evaluate and compare the immunologic response toward inactivated vaccine (CoronaVac®) and mRNA vaccine (BNT162b2) in hemodialysis patients.

2 | MATERIALS AND METHODS

2.1 | Setting

The humoral responses of vaccinated hemodialysis patients who have been followed up by two tertiary healthcare centers in Istanbul were evaluated. All of the patients were maintenance hemodialysis patients over 18 years old.

2.2 | Hemodialysis sessions

Three times weekly routine hemodialysis sessions were resumed for all patients in the regular hemodialysis units. Each hemodialysis treatment was applied for 4 hours a day. Ultrafiltration was programmed according to the patient's volume status. Heparin or low-molecular-weight heparins were used as anticoagulants.

2.3 | Exclusion criteria

Patients who had previous or active infection with SARS-CoV-2, who have active malignancy or who received any kind of immunosuppressive treatments in the previous 12 months were excluded from the study.

2.4 | Vaccines

Patients received CoronaVac®, an inactivated SARS-CoV-2 vaccine, which was developed by Sinovac Life Sciences (Beijing, China) or BNT162b2, a nucleoside-modified RNA (mRNA) vaccine developed by BioNTech/Pfizer. CoronaVac® was approved for emergency use in Turkey at the end of January 2021 and BNT162b2 was introduced as another option in April 2021. CoronaVac® was administered intramuscularly in two doses of 3 μg 28 days apart and BNT162b2 was administered intramuscularly in two doses of 30-μg 28 days apart. Vaccine selection was made according to patients' preferences.

2.5 | Clinical data

Demographic data, dialysis adequacy (Kt/V urea), chronic kidney disease (CKD) related clinical data (Time on dialysis, serum albumin, CRP, parathormone and ferritin levels, complete blood count, mean arterial pressure), and antibody responses to double dose Hepatitis B vaccines (after one cycle of 40 μg HBV vaccinations on day 0 and at 1st, 2nd, and 6th months) were evaluated. Patients who were able to produce hepatitis B surface antibody (anti-HBs) titers above 10 IU/ml 2 months after completion of a cycle were considered HBV vaccine responsive. Local and systemic adverse events after SARS-CoV-2 vaccinations were questioned for 2 weeks following injections. Patients were followed up for 3 months after the second dose of the vaccines to detect any symptomatic COVID-19.

2.6 | Control group

Control group was composed of healthy healthcare workers who were vaccinated with CoronaVac® in a similar protocol with the study subjects.

2.7 | Antibody evaluation

Antibody responses in the sera of vaccinated patients and controls were analyzed 21–28 days after the second dose of the vaccines. The analysis was carried out by Abbott SARS-CoV-2 IgG II Quant (Chicago, USA) via Abbott ARCHITECT i1000 (Chicago, USA) equipment that measures IgG antibodies toward spike receptor-binding domain (RBD) of SARS-CoV-2. All sera were diluted by 1:2 (75 μl serum + 75 μl diluent) and studied in full-automated mode. According to the manufacturer's instructions, 50 AU/ml was accepted as the cut-off value for positivity. Binding Antibody Units (BAU/ml) that were recommended by WHO was calculated as 0.142*AU per manufacturer's instructions.

2.8 | Baseline control

SARS-CoV-2 antibodies were screened at baseline for all patients to exclude possible asymptomatic infections.

Presence of current SARS-CoV-2 infection was also controlled twice for all patients by polymerase chain reaction (PCR) for SARS-CoV-2 from combined oral and nasopharyngeal swabs, one before receiving the first doses and the other before receiving the second doses of the vaccines.

2.9 | Statistical analysis

Continuous parametric data were presented as average ± standard deviation and t-test was used for comparisons. Mann–Whitney U test was used for data that showed non-normal distribution. Categorical data were presented as percentages and compared by chi-square test. Correlations of continuous parameters were computed by Pearson's test. The SPSS Statistics software version 22.0 (Chicago, IL) was used to carry out statistical analysis and $p < 0.05$ was accepted as the statistical significance.

2.10 | Ethical Approval

The study was approved both by the institutional review board of the medical faculty (approval nr: 09/04/2021−A06) and by the COVID-19 research supervision committee of Ministry of Health (approval nr: 2021-03-08T10_50_25). All patients gave informed consent to be a part of the study.

3 | RESULTS

A total of 106 hemodialysis patients were screened to be involved in the study. Eleven patients had detectable SARS-CoV-2 antibodies before vaccination, two patients had positive PCR for SARS-CoV-2 before second dose of the vaccines, four patients had concomitant malignancies and four patients received immunosuppressive therapies in the previous 12 months, which necessitated exclusions from the study. Eighty-five patients met the inclusion criteria. They were 59.8 ± 14.2 years old and they were on maintenance hemodialysis for 33.2 ± 39.3 months. Fifty patients got inactivated vaccine while 35 of them received mRNA vaccine. Control group was composed of 103 healthy volunteers and all of the patients in the control group received inactivated vaccine.

When hemodialysis patients who received CoronaVac® were compared with healthy controls of similar ages, both the rate of seropositivity and antibody titers were significantly lower (Table 1).

TABLE 1 Comparison of inactivated vaccine induced antibodies in hemodialysis patients and healthy controls

	Hemodialysis (n = 50)	Controls (n = 103)	p
SARS-CoV-2 IgG antibodies (AU/ml)	408.9 ± 433.5	685.9 ± 436.9	0.000
Neutralizing antibodies (BAU/ml)	58.0 ± 61.5	97.3 ± 67.0	0.000
Seropositivity	40 (80%)	102 (99%)	0.000
Age	61.3 ± 15.1	59.4 ± 8.1	0.31

TABLE 2 Comparison of patient characteristics who received CoronaVac® or BNT162b2. (HBV: Hepatitis B virus)

	CoronaVac® (n = 50)	BNT162b2 (N = 35)	p
Age	61.3 ± 15.1	57.6 ± 12.7	0.23
Sex (M/F)	29/21	23/12	0.51
Dialysis times (months)	32.1 ± 28.2	35.0 ± 51.6	0.74
Mean arterial pressure (mmHg)	100.4 ± 10.2	101.5 ± 9.2	0.61
Kt/V urea	1.66 ± 0.31	1.67 ± 0.30	0.82
Serum albumin (g/dl)	3.9 ± 0.5	3.9 ± 0.3	0.46
CRP (mg/L)	12.9 ± 15.0	8.7 ± 9.3	0.14
WBC (*10^3/μl)	7.7 ± 2.2	7.2 ± 4.4	0.54
Lymphocytes (/μl)	1662 ± 732	1765 ± 672	0.51
Hemoglobin (g/dl)	10.6 ± 1.4	10.7 ± 1.6	0.58
Parathormone (pg/ml)	426.6 ± 441.1	413.3 ± 240.4	0.87
Ferritin (ng/ml)	852.9 ± 577.0	927.4 ± 1312.9	0.72
HBV vaccine responsiveness (n, [%])	33 (66)	28 (80)	0.17

TABLE 3 Antibody titres and seropositivity rates with different vaccines

	CoronaVac (n = 50)	BNT162b2 (N = 35)	*p*
SARS-Cov-2 IgG (AU/ml)	408 ± 433 Median: 280 Range: [1.2–1655]	525 ± 471 Median: 389.5 Range: [39–1917]	0.24
Neutralizing Antibodies (BAU/ml)	58.5 ± 61.0 Median: 39.8	74.6 ± 66.9 Median: 55.3	0.24
Seropositivity (n, [%])	40 (80%)	34 (97.1%)	0.023

TABLE 4 Comparison of responders and nonresponders to the inactivated vaccine

	Responders (n = 40)	Nonresponders (n = 10)	*p*
Diabetes (n, [%])	11 (27.5)	4 (40)	0.44
Hypertension (n, [%])	10 (25)	2 (20)	0.74
Glomerulonephritis (n, [%])	8 (20)	1 (10)	0.55
Age	59.8 ± 15.8	67.5 ± 10.2	0.15
Time on dialysis (months)	34.2 ± 30.7	23.7 ± 13.0	0.29
Kt/V (urea)	1.6 ± 0.3	1.6 ± 0.2	0.54
Mean arterial pressure (mmHg)	101.8 ± 10.1	94.9 ± 9.3	0.06
Albumin (g/dl)	3.9 ± 0.5	3.7 ± 0.6	0.44
CRP (mg/L)	14.4 ± 16.4	6.7 ± 4.8	0.15
WBC (*10^3/μl)	7.9 ± 2.2	6.6 ± 1.9	0.07
Lymphocytes (/μl)	1742 ± 767	1349 ± 493	0.13
Hemoglobin (g/dl)	10.6 ± 1.4	10.5 ± 1.4	0.9
Parathormone (pg/ml)	455.9 ± 461.9	315.1 ± 348.7	0.37
Ferritin (μg/L)	831.7 ± 549.3	935.5 ± 701.6	0.61
HBV vaccine responsiveness (n, [%])	27 (67.5)	6 (60)	0.65
SARS-CoV-2 IgG (AU/ml)	508.3 ± 430.7	11.3 ± 7.4	0.001

Clinical characteristics, dialysis times, dialysis efficacy, and HBV vaccine responsiveness were similar for patients who received different vaccines (Table 2). Seropositivity (i.e., 50 AU/ml) could be obtained in 40 (80%) of the patients who got CoronaVac® and in 34 (97%) of the patients who received BNT162b2. Seropositivity was significantly higher in BNT162b2 vaccinated patients (*p* = 0.023; Table 3).

Seropositivity could not be achieved in just one patient of the BNT162b2 group and even that patient's antibody titer was 39 AU/ml. Antibody level could be as low as 1.2 AU/ml in the inactivated vaccine group and average antibody level of 10 patients who did not yield a positive response to the inactivated vaccine was 11.3 ± 7.4 AU/ml. Among patients who received inactivated vaccine, nonresponsive patients were older than the responsive patients (67.5 ± 10.2 vs. 59.8 ± 15.8), but it did not reach statistical significance (*p* = 0.15). Etiologies of CKDs) and other clinical data were also similar for responders and nonresponders. (Table 4) Antibody titers of all patients who received inactivated or mRNA vaccines did not significantly differ.

Seventy-one percent of our patients had positive responses to the HBV vaccine. Rates of seropositivity were comparable with HBV vaccine and any of the SARS-CoV-2 vaccines (*p* = 1.0 and *p* = 0.2). However, there was a negative correlation between age and SARS-CoV-2 antibody titers (*r* = −0.42; *p* = 0.000). This negative correlation was significant for both vaccines.

Adverse reactions that developed with different vaccines can be found in Table 5. Systemic adverse effects like fever, malaise or generalized muscular pain were more often with BNT162b2 vaccine (54% vs. 24%; *p* = 0.0049). Our patients did not report any serious adverse events that needed hospitalization.

Patients were followed up for 3 months and none of the seropositive patients developed symptomatic infections, independent of the vaccine type. One 68 years old

TABLE 5 Adverse reactions to the vaccines (patients could report more than one adverse reaction)

	CoronaVac (n = 50)	BNT162b2 (n = 35)	p
Pain at injection site (n, [%])	24 (48)	20 (57)	0.41
Fever, Malaise or Generalized muscular pain (n, [%])	12 (24)	19 (54)	0.0049
None (n, [%])	14 (28)	8 (22)	0.53

female patient who was seronegative (SARS-CoV-2 IgG: 12 AU/ml) after two doses of CoronaVac®, had symptomatic COVID-19 2 months after the second dose and she could not be cured.

4 | DISCUSSION/CONCLUSION

Inactivated vaccines are thought to have limited immunogenicity. Inactivated vaccine CoronaVac® was recently shown to produce adequate humoral response in a group of healthy persons.[8] This vaccine received emergency use authorization in Turkey in early 2021 and healthcare workers were given priority to receive two doses. That is why our control group of healthcare workers without any reported illnesses received CoronaVac®. The elderly were also given priority to get vaccinated. Two months later, BNT162b2 was introduced as another option and all hemodialysis patients, independent of their ages were added to the priority list. Our patients have the chance to choose either one and they often question their doctors about the most relevant choice. With this study, it can be claimed that mRNA vaccines are more effective in the hemodialysis group.

The reason of our antibody kit selection is that it measures RBD domain and RBD specific antibodies have been shown to have the highest potential to neutralize infection.[9] Thus, the response we measured will possibly reflect the protective ability. While seropositivity rate was much higher with the mRNA vaccine, average antibody levels were not different between the groups. It is not known if higher antibody levels correlate with better protection. Cellular immune response has additional roles and these should also be studied in further studies. Prolonged longitudinal observation of vaccinated hemodialysis patients will also help us explore if they will be protected from any symptomatic COVID-19.

There have been previous reports about the use of mRNA vaccines in hemodialysis patients; some reporting reduced humoral response and others claiming high enough immunogenicity.[10–14] To our knowledge, this is one of the first reports about the use of inactivated vaccine in hemodialysis patients and we have found that mRNA vaccine is more effective than the inactivated vaccine. This should be underlined that, our patients did not

encounter any serious adverse events by any of the vaccines. On the other hand, systemic adverse events were more often in patients who received mRNA vaccine. This may be related to higher immunologic response with this vaccine.

In the general population, humoral response has been reported to be as high as 100% by two doses of mRNA vaccine[15] and 99% by two doses of inactivated vaccine.[8] Humoral response may be insufficient with any of the vaccines in the hemodialysis patients (97% for mRNA and 80% for inactivated vaccine in our cohort). A third dose for patients who are still seronegative after 1 month may be a reasonable solution. A recent strategy in our country is offering the third dose with mRNA vaccine to the hemodialysis patients who were already vaccinated with inactivated vaccine.

There was just one patient in the mRNA vaccine group who did not generate antibody response that exceeds the neutralizing threshold. Nevertheless, that one patient still had considerable amounts of antibodies (39 IU/ml), which may protect the patient to some extent. On the other hand, responses of some patients in the inactivated vaccine group stayed much lower. Among patients who received inactivated vaccine, responders and nonresponders had similar clinical characteristics. Their CKD etiologies did not differ as well. Thus, being nonresponsive to the inactivated vaccine could not be attributed to any clinical criteria other than being a dialysis patient. Higher seropositivity rates with mRNA vaccine are encouraging to prefer mRNA vaccine for hemodialysis patients.

One of the reasons of reduced immunogenicity of inactivated vaccine may be that, it is used in the same dose (3 μg) as it is used for the general population. Six micro gram dose of the inactivated vaccine was also found safe[16] and similar to the HBV vaccination strategy, the dose of inactivated SARS-CoV-2 vaccine can also be doubled for hemodialysis patients. Comparative future studies may be planned to define more effective dosing of the inactivated vaccine.

Age was negatively correlated with the antibody response for both vaccines. In settings where there are not enough resources to measure antibody responses to the vaccines, a third dose may be added to the vaccination schemes of elderly hemodialysis patients.

Immunization efficacy is overall reduced in hemodialysis patients. HBV vaccine responsiveness of our cohort was in line with previous reports in the literature and this assures the vaccine responsiveness of our patients.

This study has some limitations. First, the cellular immune response to the vaccines was not a part of our study. In addition, variation of antibody titers over time should be checked to understand the persistence of the humoral immune response with different vaccines. This may also help to detect late antibody response in some patients who are seronegative in the early phase.[11] Last, our control group was composed of subjects who received inactivated vaccine. This was because late introduction of BNT162b2 in our country.

In conclusion, when used in the same scheme and dose with the general population, inactivated SARS-CoV-2 vaccines generate reduced humoral response in hemodialysis patients. mRNA vaccines have better immunogenicity in this group.

CONFLICT OF INTEREST

Authors declare that they do not have any conflicts or interest. The results presented in this article have not been published previously in whole or part, except in abstract format.

DATA AVAILABILITY STATEMENT

The datasets of the current study are available from the corresponding author on reasonable request.

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REFERENCES

1. Hsu CM, Weiner DE, Aweh G, Miskulin DC, Manley HJ, Stewart C, et al. COVID-19 among US dialysis patients: risk factors and outcomes from a national dialysis provider. Am J Kidney Dis. 2021;77(5):748–56.
2. Valeri AM, Robbins-Juarez SY, Stevens JS, Ahn W, Rao MK, Radhkakrishnan J, et al. Presentation and outcomes of patients with ESKD and COVID-19. J Am Soc Nephrol. 2020;31(7): 1409–15.
3. COVID-19 Task Force Committee of the Japanese Association of Dialysis Physicians, Japanese Society for Dialysis Therapy, Japanese Society of Nephrology, Kikuchi K, Nangaku M, Ryuzaki M, et al. COVID-19 of dialysis patients in Japan: current status and guidance on preventive measures. Ther Apher Dial. 2020 Aug;24(4):361–5.
4. Dinits-Pensy M, Forrest GN, Cross AS, Hise MK. The use of vaccines in adult patients with renal disease. Am J Kidney Dis. 2005;46:997–1011.
5. Buti M, Viladomiu L, Jardi R, Olmos A, Rodriguez JA, Bartolome J, et al. Long term immunogenicity and efficacy of hepatitis B vaccine in hemodialysis patients. Am J Nephrol. 1992;12(3):144–7.
6. Elefthariadis T, Antoniadi G, Liakopoulos V, Kartsois C, Stefanidis I. Disturbances of acquired immunity in hemodialysis patients. Semin Dial. 2007;20:440–51.
7. Creech CB, Walker SC, Samuels RJ. SARS-CoV-2 Vaccines. JAMA. 2021;325(13):1318–20.
8. Tanriover MD, Doganay HL, Akova M, Guner HR, Azap A, Akhan S, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. Lancet. 2021 Jul 17;398(10296):213–22.
9. Fu Y, Pan Y, Li Z, Li Y. The utility of specific antibodies against SARS-CoV-2 in laboratory diagnosis. Front Microbiol. 2021 Jan;13(11):603058. https://doi.org/10.3389/fmicb.2020.603058
10. Speer C, Göth D, Benning L, Buylaert M, Schaier M, Grenz J, et al. Early humoral responses of hemodialysis patients after COVID-19 vaccination with BNT162b2. Clin J Am Soc Nephrol. 2021;16(7):1073–82.
11. Simon B, Rubey H, Treipl A, Groman M, Hemedi B, Zehetmayer S, et al. Hemodialysis patients show a highly diminished antibody response after COVID-19 mRNA vaccination compared to healthy controls. Nephrol Dial Transplant. 2021;36 (9):1709–16. https://doi.org/10.1093/ndt/gfab179
12. Yanay NB, Freiman S, Shapira M, Wishahi S, Hamze M, Elhaj M, et al. Experience with SARS-CoV-2 BNT162b2 mRNA vaccine in dialysis patients. Kidney Int. 2021;99(6):1496–8.
13. Rincon-Arevalo H, Choi M, Stefanski AL, Halleck F, Weber U, Szelinski F, et al. Impaired humoral immunity to SARS-CoV-2 BNT162b2 vaccine in kidney transplant recipients and dialysis patients. Sci Immunol. 2021;6:eabj1031.
14. Longlune N, Nogier MB, Miedouge M, Gabilan C, Cartou C, Seignuric B, et al. High Immunogenicity of a messenger RNA based vaccine against SARS-CoV-2 in chronic dialysis patients. Nephrol Dial Transplant. 2021;36:1704–9.
15. Walsh EE, Frenck RW Jr, Falsey AR, Kitchin N, Absalon J, Gurtman A, et al. Safety and immunogenicity of two RNA based COVID-19 vaccine candidates. N Engl J Med. 2020; 383(25):2439–50.
16. Wu Z, Hu Y, Xu M, Chen Z, Yang W, Jiang Z, et al. Safety, tolerability and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy adults aged 60 years and older: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis. 2021;21:803–12.