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MODESTUM

# Long-term humoral and cellular responses elicited by Gam-COVID-Vac vaccine in hemodialysis patients: A prospective cohort study

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**ABSTRACT**

**Purpose:** The aim of this study is to assess long-term immunogenicity of the recombinant adenoviruses 26 and 5 vector-based COVID-19 vaccine Gam-COVID-Vac (Sputnik V, developed by N. F. Gamaleya National Research Centre, Russia) in patients receiving maintenance hemodialysis (HD) compared to healthy subjects.

**Materials & methods:** A prospective cohort study included patients treated with maintenance HD (n=23) and healthy volunteers (n=28). The levels of anti-severe acute respiratory syndrome coronavirus-2 specific IgG as well as specific T-cell responses were quantified in all participants at two time points: one and six months after complete vaccination. All participates were adults, had been vaccinated twice with Gam-COVID-Vac and had no prior history of confirmed COVID-19.

**Results:** In both groups, IgG levels decreased from month one to six, however, antibodies did not decline more rapidly in HD group (analysis of variance p=0.7214 for the "time×group" interaction, non-adjusted model). At the end of the study, 48.0% of non-HD and 67.0% of HD participants showed T-cell positivity. T-spot counts dropped over time in non-HD controls, but not in HD subjects (p=0.0080 and p=0.1800, respectively).

**Conclusions:** Patients receiving HD maintain significant long-term humoral response after Gam-COVID-Vac vaccination, which is comparable to that in subjects with normal kidney function. Cellular response turned up to be more sustained over time in HD group.

**Keywords:** SARS-CoV-2, Gam-COVID-Vac, hemodialysis, immunity, T-cells

## INTRODUCTION

Recombinant adenovirus 26 and 5 vector-based COVID-19 vaccine Gam-COVID-Vac (Sputnik V, developed by N. F. Gamaleya National Research Center, Russia) is the most prescribed vaccine against SARS-CoV-2 in Russia. Previous studies evaluated the safety and efficacy of Gam-COVID-Vac in general population in both early and long-term period [1, 2].

Different approaches can be used to assess vaccine immunogenicity including antibody detection and quantification, pseudo-virus and live-virus antibody neutralization, flow cytometry and IFN-γ ELISPOT for measuring T-cell-mediated immunity. It has been demonstrated that antibody titers quantified via enzyme-linked immunosorbent assay (ELISA) against the spike protein correlate with virus neutralization [3].

Therefore, quantitation of anti-S antibodies may be used to monitor the humoral immune response following vaccination. IFN-γ ELISPOT assays provide reliable quantification of SARS-

CoV-2 specific T-cell immune response following both natural COVID-19 disease and vaccination [4].

Gam-COVID-Vac immunogenicity in patients receiving maintenance hemodialysis (HD), which are known to be highly vulnerable immunocompromised population, has been reported previously [5].

However, a lack of knowledge exists concerning long-term Gam-COVID-Vac efficacy in HD-dependent patients. In addition, specific antibodies kinetics in HD patients has not been compared previously with that in general population. Considering this knowledge gap, we performed a prospective cohort study aimed to compare the strength and six-months sustainability of humoral and cellular responses after two doses of Gam-COVID-Vac in patients receiving HD and individuals with normal kidney function.

We hypothesized that specific SARS-CoV-2 IgG antibodies and T-cells decline more rapidly in patients receiving HD than in healthy controls.

## MATERIALS AND METHODS

### Study Population

This investigator-driven prospective observational cohort study was carried out in a single dialysis facility from March 23, 2021, to January 30, 2022. 51 participants were enrolled, of those 23 were HD-dependent patients (test group) and 28 were healthy volunteers (control group). Healthy controls were recruited from the hospital healthcare workers of comparable age. Inclusion criteria were age of 18 years and older, previously completed Gam-COVID-Vac vaccination, and informed consent to participate in. The subjects with a history of confirmed SARS-CoV-2 infection, underlying autoimmune disease, malignancies or concomitant immunosuppressive therapy were not enrolled in the study. Exclusion criteria were revaccination or confirmed COVID-19 disease during the study.

Demographical data (age, sex, body mass index [BMI], comorbidities, chronic kidney disease etiology, and dialysis vintage) and vaccine-associated adverse events (VAAEs) were collected at baseline either from participants' medical records or self-reports. Comorbidities were assessed using a modified cumulative illness rating scale (cumulative illness rating scale-geriatric). Median interval between $1^{st}$ and $2^{nd}$ vaccine doses was 21 (range 20-23) days in HD group and 21 (range 14-33) days in the control group. All the participants were asked to report adverse events following $1^{st}$ and $2^{nd}$ vaccine administration, including general malaise, fever, myalgia, headache, allergic reactions, and injection site reactions.

### Study Procedures

Since our aim was to survey humoral and cellular responses following vaccination, we used ELISA for serological assessment, and IGRA ELISPOT method for the measurement of T-cells [6]. The levels of specific IgG as well as specific T-cells were quantified in all participants at two time points: one and six months after second vaccine shot.

IgG levels were determined in venous blood using a semi-quantitative SARS-CoV-2 S1 IgG ELISA (Euroimmun, Lübeck, Germany) according to the manufacturer's instructions [7]. This test provides a numerical value (ratio) of the luminescence intensity, which is therefore a surrogate estimation of IgG antibodies amount. To assess seropositivity rates Euroimmun's recommendation was followed, thus the ratios equal to or greater than 1.1 were interpreted as a positive test result. For the purposes of reproducibility, antibody levels were also converted to binding antibody units (BAU/ml) according to the World Health Organization International Standard [8].

Specific T-cell response was assessed using IGRA ELISPOT method [9]. TIGRA-test® reagent kit (Generium, Russia), Ficoll gradient 1.077 (Biolot, Russia), RPMI medium (Biolot, Russia) and AIM medium (Oxford Immunotec, UK) were used. The method is based on the peripheral blood mononuclear cell (PBMC) fraction samples overnight cultivation together with antigens at 37 C and 5.0% $CO_2$. In the presence of specific CD4+ and CD8+ cytotoxic lymphocytes in blood samples interferon-γ is released, which is captured by antibodies attached to the substrate and appears as cell imprints. The feature of the method is four wells used per one blood sample assessment: a negative control well (AIM medium), a positive control well (phytohemagglutinin) and two wells of the SARS-CoV-2 antigens specific sets: a well with S-protein (structural protein) and a well with the combination of N, M, ORF3a (also structural proteins of the virus), and ORF7a (non-structural protein). All procedures were performed according to the manufacturer's instructions. 340,000 PBMC were placed in each well. The cells were counted using a Sysmex 2000 automatic hematology analyzer (Sysmex, Japan). The test was considered valid if there were no more than 10 spots in the negative control well. S and N values of peptides combinations were estimated separately. A test with more than 12 spots considering the negative control was considered positive. Only spike-specific T-spots were used for the analyses.

### Statistical Analysis

Normally distributed quantitative data are presented as means ± standard deviations, whereas parameters with non-Gaussian distribution are expressed as medians and interquartile ranges ($Q_1$-$Q_3$). Absolute values and percentages are used to describe categorical data. Correlations were analyzed using Spearman's rank correlation coefficient (GraphPad Prism v.9.0.0).

Sample size was calculated using GPower v.3.1 considering assumption of "time" and "group" factors interaction significance. F=0.25 was set as effect size, corresponding to effect of average strength [10]. With number of groups=2 (ratio 1:1), and number of measures=2, it provided a study power of 0.7 with an expected significance of 0.01. Based on these parameters, a minimal sample size of 42 patients was estimated, which was increased to a total of 51 subjects considering potential drop out. Since semi-quantitative tests provided numerical values, they were analyzed quantitatively. As the observations were paired, the dynamics of IgG levels was assessed in patients at different time points using a linear mixed-effects model (analysis of variance), wherein the fixed effects were "time," "group," and the "time × group" interaction and the random effect was "id" (patient): lmer(IgG_bc~time + group + time*group + (1|id). In the age-adjusted model the "age×group" interaction was included, lmer(IgG_bc~time + group + time*group + age*group + (1|id). The analysis was performed using R Environment, version 4.1.1, and "lme4" package. We calculated the statistical significance of fixed effects using Satterthwaite approximation (lmerTest package) due to the calculation of p-values was not implemented in the lme4 software package. p-values <0.050 were considered statistically significant. Pairwise comparisons were performed using Tukey's post-hoc test. Since the assumption of homoscedasticity was not met, the Box-Cox transformation was performed (the "boxcox" function in the package "MASS"). Transformed values were used for analysis.

## RESULTS

A total of 46 patients completed the study. One patient receiving HD did not develop neither specific antibodies nor T-cells. He was vaccinated at home and a cold chain breach as a cause of low vaccine efficacy could not be ruled out; therefore, this patient was excluded from all subsequent analyses. One patient from HD group and two non-HD subjects experienced a COVID-19 episode during the study confirmed with positive real-time polymerase chain reaction (PCR) test using nasopharyngeal swabs, and one non-HD subject had been revaccinated. Their data were used for early immune responses evaluation only. Thus, 21 HD patients and 25 controls were included in the immune response dynamics analysis.

**Table 1.** Subjects' baseline characteristics & vaccine tolerability

| Characteristic | HD (n=22) | HC (n=28) | p |
|---|---|---|---|
| Female, n (%) | 13 (59.0%) | 16 (57.0%) | 0.8810 |
| Age, years | 60.4±12.0 | 52.0±12.5 | 0.0220 |
| BMI, kg/m$^2$ | 26.6±5.0 | 25.6±4.0 | 0.4450 |
| Dialysis vintage, months | 64 [33; 103] | - | - |
| Comorbidity, CIRS | 15 [13; 16] | 1 [0; 4] | <0.0001 |
| Known allergies, n (%) | 1 (5.0%) | 6 (21.0%) | 0.1175 |
| Cause of ESKD (only for HD patients) | | | |
| Glomerulonephritis (primary or secondary) | 6 (27.0%) | | |
| Hypertensive kidney disease | 4 (18.0%) | | |
| Diabetic nephropathy | 1 (5.0%) | | |
| Hereditary kidney disease | 8 (36.0%) | | |
| Other/miscellaneous | 3 (14.0%) | | |
| Vaccine-associated adverse events–after 1$^{st}$ shot, n (%) | 8 (36.0%) | 21 (75.0%) | 0.0094 |
| Weakness | 0 (0.0%) | 9 (32.0%) | 0.0030 |
| Pain at the site of injection | 4 (18.0%) | 13 (46.0%) | 0.0696 |
| Temperature | 3 (14.0%) | 3 (11.0%) | >0.9900 |
| Myalgia or joint pain | 1 (5.0%) | 8 (29.0%) | 0.0596 |
| Headache | 0 (0.0%) | 8 (29.0%) | 0.0064 |
| Vaccine-associated adverse events–after 2$^{nd}$ shot, n (%) | 8 (36.0%) | 21 (75.0%) | 0.0094 |
| Weakness | 2 (9.0%) | 9 (32.0%) | 0.0850 |
| Pain at the site of injection | 5 (23.0%) | 13 (46.0%) | 0.1373 |
| Temperature | 1 (5.0%) | 8 (29.0%) | 0.0596 |
| Myalgia or joint pain | 2 (9.0%) | 8 (29.0%) | 0.1535 |
| Headache | 0 (0.0%) | 6 (21.0%) | 0.0284 |

Note. Normally distributed data are expressed as means±standard deviations, data with a non-normal distribution are presented as medians, 1$^{st}$ & 3$^{rd}$ quartiles; Categorical values are presented as absolute numbers (percentages); CIRS: Cumulative illness rating scale; ESKD: End-stage kidney disease; & HC: Healthy controls

**Table 2.** Gam-COVID-Vac immunogenicity in patients receiving hemodialysis & non-renal controls at different time points

| Characteristic | Controls | Patients |
|---|---|---|
| IgG one month, BAU/ml | | |
| n | 28 | 22 |
| Median (Q1-Q3) | 175.7 (111.4; 230.0) | 150.2 (110.4; 193.4) |
| Mean (SD) | 170.4 (72.6) | 142.6 (69.2) |
| 95% CI | 142; 199 | 112; 173 |
| Range | 54.7-345.0 | 3.2-275.5 |
| IgG six months, BAU/ml | | |
| n | 25 | 21 |
| Median (Q1-Q3) | 60.8 (26.2; 109.1) | 35.8 (23.4; 98.2) |
| Mean (SD) | 90.3 (84.8) | 76.1 (84.7) |
| 95% CI | 55; 125 | 38; 115 |
| Range | 13.1-294.7 | 3.8-264.0 |
| Spike spots count, one month | | |
| n | 28 | 22 |
| Median (Q1-Q3) | 30.0 (15.2; 49.8) | 30.0 (12.0; 47.2) |
| Mean (SD) | 35.2 (26.7) | 32.7 (25.1) |
| 95% CI | 25; 46 | 22; 44 |
| Range | 0.0-100.0 | 0.0-100.0 |
| Spike spots count, six months | | |
| n | 25 | 21 |
| Median (Q1-Q3) | 13.0 (7.0; 32.0) | 27.0 (13.0; 33.0) |
| Mean (SD) | 22.1 (22.8) | 28.1 (26.7) |
| 95% CI | 13; 31 | 16; 40 |
| Range | 2.0-100.0 | 0.0-100.0 |

Note. Q1-Q3: Interquartile range & IgG: Immunoglobulin G

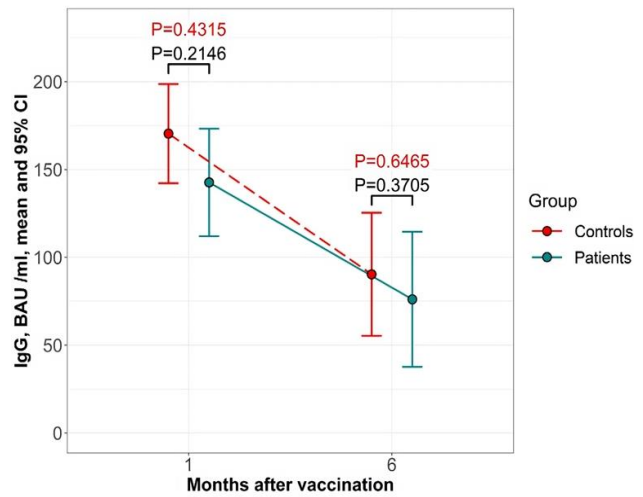Participant's characteristics and vaccine tolerability data are summarized in **Table 1**.



**Figure 1.** SARS-CoV-2 antibody levels after vaccination with Gam-COVID-Vac in patients receiving maintenance hemodialysis & non-CKD controls (p-values for post-hoc pairwise comparisons in a model that includes time, group, time×group interaction, & subject [random effect] are depicted in black; red color shows p-values for post-hoc pairwise comparisons in an age-adjusted model, including time, group, time×group interaction, age×group interaction, & subject [random effect]) (Source: Authors' own elaboration)

As expected, patients receiving HD were significantly older and had more comorbidities compared to the control group. There were no serious VAAEs observed among HD patients or in controls. Overall, HD patients experienced mild VAAEs (weakness, pain at the site of injection, elevated temperature, newly-onset or worsened myalgia or joint pain, and headache) after 1$^{st}$ and 2$^{nd}$ vaccine administrations less frequently than subjects in the control group. The majority of participants experienced more than one VAAE. The most common VAAE in both groups was pain at the site of injection.

Immunogenicity data for the groups are presented in details in **Table 2**. The seroconversion rate reached 90.9% (20 of 22) in patients receiving HD and 100% (28 of 28) in controls 4 weeks after second vaccine shot. Seropositivity rates declined over time; only 52.0% (11 of 21) in HD group and 68.0% (17 of 25) in control group remained seropositive by the end of the study. Therefore, risk of seropositivity in six months after complete vaccination with Gam-COVID-Vac did not differ between HD patients and controls: relative risk (RR)=0.77 [95% confidence interval (CI): 0.45-1.23] (reciprocal of RR=1.3 [95% CI: 0.81-2.20]), p=0.4370.

SARS-CoV-2 specific antibodies levels decreased over time in both HD patients and controls (p<0.0001 for both groups), however, dynamics did not differ between groups (analysis of variance p=0.7214 for the "time×group" interaction, non-adjusted model) (**Figure 1**).

Given the significant diversity of the groups by age and potential impact of age on the magnitude of humoral response, "age" factor was included in the second model. "Time×group" interaction effect in age-adjusted model was not statistically significant (p=0.7191). In addition, "age" factor in this model was not significantly associated with IgG levels (p=0.1588) in the presence of other factors, suggesting no effect of age on the humoral response strength.
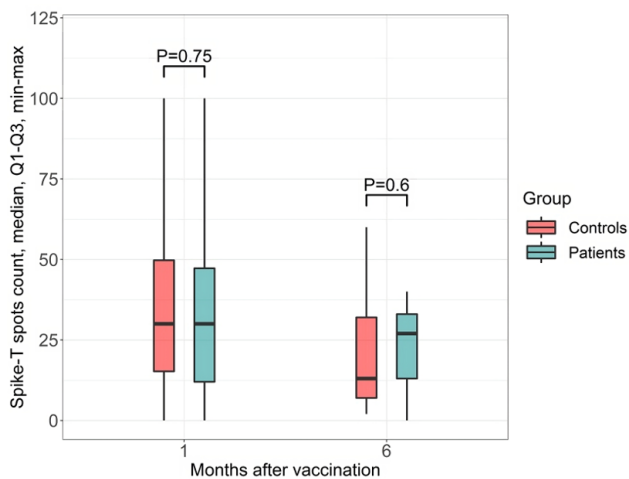
**Figure 2.** T-cell responses to SARS-CoV-2 structural peptide S after vaccination with Gam-COVID-Vac in patients receiving maintenance hemodialysis & non-CKD controls (between groups) (Source: Authors' own elaboration)
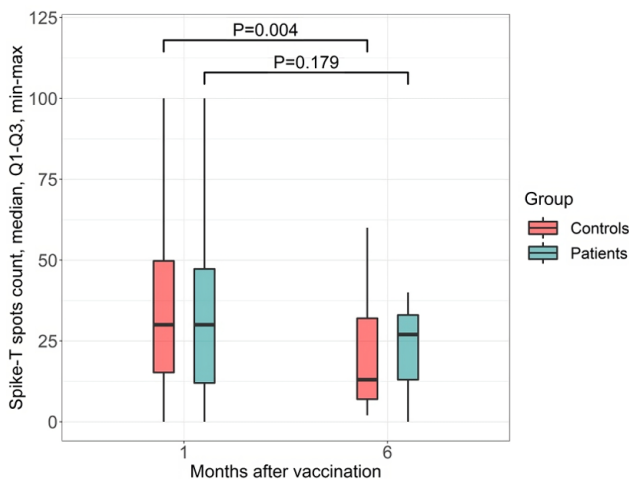


**Figure 3.** T-cell responses to SARS-CoV-2 structural peptide S after vaccination with Gam-COVID-Vac in patients receiving maintenance hemodialysis & non-CKD controls (within groups) (Source: Authors' own elaboration)

Initially, the T-test result was positive in 79.0% (22 of 28) non-CKD and 73.0% (16 of 22) HD subjects. At the end of the study, 48.0% (12 of 25) non-CKD and 67.0% (14 of 21) HD participants showed T-cell positivity. T-spot responses to SARS-CoV-2 structural peptide S did not differ in the control group and in patients receiving HD 1 month (p=0.7500) and six months (p=0.6000) after vaccination (**Figure 2**). However, T-spot counts dropped over time in non-CKD controls, but not in HD subjects (p=0.0040 and p=0.1790, respectively)–**Figure 3**. Two patients (one from each group) originally had indeterminate T-test result, the one from the control group became negative, while the one from HD group eventually showed positive T-test result by the end of the study.

There were no statistically significant correlations identified between humoral and cellular responses neither in HD group (at one month, p=0.2300; at six month, p=0.6300), nor in the control group (at one month p=0.2500; at six month, p=0.0600). There was a weak, but statistically significant negative correlation between spike-specific T-spots and age in the control group at the time point of one month (p=-0.4280

[95% CI: -0.691; -0.026], p=0.0231), meanwhile it was not found at time point of six month (p=0.9100). No statistically significant correlations were observed between cellular responses and age of HD group patients (one month, p=0.5110; six month, p=0.0950).

## DISCUSSION

To the best of our knowledge, this is the first study to compare immune responses after vaccination with two doses of Gam-COVID-Vac in HD patients and subjects with normal kidney function. The study demonstrates that noninfected HD patients are capable to develop sufficient antiviral humoral responses after Gam-COVID-Vac vaccination. Although specific IgG levels decrease over time, their kinetics in HD patients are similar with that in the general population. In addition, the intensity of cellular responses was found to be stable in HD patients for long-term period post vaccination, while it dropped in non-CKD controls. HD patients were almost twice as least likely to experience VAAEs after 1st and 2nd vaccine injections as non-CKD subjects.

HD patients are at high risk for a severe course of COVID-19 and COVID-related death because of multiple risk factors including older age, comorbidities, and frailty. Mortality rate in this specific population was reported to be 25.0-33.0% during the first wave of the pandemic, that is substantially higher as compared to the general population [11]. Little is known about COVID-related deaths among HD patients in Russia, with a reported mortality rate of 18.0% in prevalent patients [12]. Moreover, mortality among survivors is increased compared to non-infected HD patients, and they suffer more from vascular access thromboses, respiratory problems, and impaired nutritional status [13, 14]. The question about prioritizing vaccination in this highly vulnerable group was raised shortly after the onset of COVID-19 pandemic [15]. The effectiveness of different vaccines against SARS-CoV-2 in patients receiving maintenance HD have been extensively studied previously, typically including BNT162b2 (Pfizer), mRNA-1273 (Moderna), ChAdOx1 nCoV-19 (AstraZeneca), and Ad26.COV2.S (Janssen) vaccines. Initial overall immunogenicity rate in HD patients reaches 87.0-89.0%, which is slightly lower than that of the general population [16, 17]. However, vaccine-induced seroresponse seems to be waning over time across all vaccine types [18].

Data on short-term immunogenicity of the Gam-COVID-Vac vaccine in HD patients are limited, while long-term data are still lacking. The short-term antibody response after Gam-COVID-Vac immunization was investigated and a high seroconversion was found, reaching 98.0% 21 days after complete vaccination [5]. We observed a similar seroconversion rate (91.0%), which was almost halved by 6th month, indicating a strong need of boost vaccination by this time. However, subjects of the control group showed the same trend, which does not allow confirmation of the main hypothesis of our study. Based on these findings, it could be concluded that HD patients do not require any specific adjustment of boost vaccination policy, i.e., high doses or more vaccine injections, and the same recommendations could be applied to them as for the general population.

Another important finding of our study is that Gam-COVID-Vac elicits efficient long-term cellular responses in previously non-infected HD patients. As a part of adaptive immunity, T-

cell-mediated immune response plays a crucial role in severe COVID-19 defense and viral spread reduction [19]. A set of papers pointed out the importance of vaccine-produced cellular immunity evaluation, especially in those individuals with weakened immune system, and discussed personalized vaccine strategy for those with persistent poor vaccine responses [20, 21]. Many recent studies explored early cellular immunity after vaccination against SARS-CoV-2 and demonstrated a comparable T-cell responses between HD patients and the general population [22, 23]. Moreover, in one study 91.0% of HD patients maintained T-cell positivity three months after immunization with mRNA vaccines [24]. However, in another study progressive waning of cellular immunity was noted in dialysis patients six months after vaccination, resulted in reduced T-cell responses as compared to controls (T-cell positivity rates of 53.0% vs 75.0%, respectively) [25]. In contrast with the latter study, we found that Gam-COVID-Vac-elicited cellular immunity seems to be even more durable in HD patients than in non-CKD controls in terms of both detection rates and magnitude of CD4+ and CD8+ T-cell responses. Whether this finding can be extrapolated to all HD patients is uncertain and warrants further investigations to confirm in larger sample sizes. Nonetheless, functionality of T-cells in dialysis patients remains questionable as they are known to exhibit signs of T-cell exhaustion and anergia [26, 27].

In line with previous studies, no correlations were found between the magnitude of humoral and cellular responses after Gam-COVID-Vac vaccination [28, 29]. It is mainly attributed to the heterogeneity of individual immune responses, and a HD patient was observed in this study with no seroconversion, but excellent specific T-cell responses lasted over six months.

Overall, Gam-COVID-Vac-associated adverse events were common but mild, with the predominance of pain at injection site after either first or second vaccine shot. This agrees with previous study explored safety of Gam-COVID-Vac in a total of 491 HD patients [5]. Of note, no serious adverse events were encountered. Interestingly, vaccine-associated side effects occurred less frequently in HD patients compared to the control group in our study, which is consistent with previously published data [23]. It could partially be explained by suffering from physical symptoms such as pain or fatigue by HD patients so they could ignore newly-onset events. The recent study found that older age is associated with decreased risk of postvaccination adverse events in HD patients, providing another possible explanation for this phenomena [30].

The first main limitation of our study was relatively low predetermined study power. Secondly, complete demographic matching of patient and control groups could not be ensured. Next, IgG levels were not evaluated before the vaccination, thus, subjects with previous asymptomatic COVID-19 could be potentially included. Of importance, semi-quantitative IgG ELISA assay could not be acknowledged as "gold standard" of humoral immunity assessment. Moreover, although antibodies mediate long-term reinfection defense, the quantification of SARS-CoV-2 specific IgGs (both anti-S1 and neutralizing antibodies) may only serve as a surrogate marker of immune protection as the exact protective level is still not known. However, the purpose of our study was not to determine the exact IgG levels in long-term period, but to explore their dynamics in HD patients in comparison with relatively "healthy" subjects to establish the need of the vaccination boosting strategy adjustment. In this regard, we believe that IgG S1 assessment with ELISA may be representative enough. Finally, the data obtained in this study may have limited implication in the setting of SARS-CoV-2 strains shift. The strength of our study is T-cell responses quantification, which is rarely performed due to technical challenges.

## CONCLUSIONS

Patients receiving HD maintain significant long-term humoral responses after with Gam-COVID-Vac vaccination, which is comparable to that in subjects with normal kidney function. Cellular response turned up to be even more sustained over time in HD patients. Our study results shows that vaccination with Gam-COVID-Vac is safe for HD patients and no specific modification of the vaccination protocol is required for these vulnerable population. Further studies with larger sample sizes are needed in order to confirm these results and overcome the limitations previously identified.

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