ORIGINAL ARTICLE

Assessment of the humoral response to the homologous Gam-COVID-Vac (Sputnik V) or heterologous Sputnik V/mRNA-1273 (Moderna) vaccination against SARS-CoV-2 in dialysis patients

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Abstract

Background and Aim Dialysis patients are a high-risk population and have a reduced immune response to vaccination against SARS-CoV-2. The aim of this study was to assess the humoral response to homologous Gam-COVID-Vac (Sputnik V) and heterologous Sputnik V/mRNA-1273 (Moderna) vaccination in dialysis patients. The vaccination scheme depended on dose availability and the prioritization of risk populations as established by the Argentine Ministry of Health.

Methods Previous COVID-19 infection was determined in symptomatic patients. Binding IgG antibodies against the spike (S) receptor-binding domain (RBD) of SARS-CoV-2 (anti-S-RBD) concentration was assessed between 3 and 16 weeks after the boost dose. Anti-S-RBD antibodies were quantified using the Abbott Diagnostics SARS-CoV-2 IgG II Quant chemi-luminescent microparticle immunoassay (CMIA) on an Architect i2000 SR and an Alinity I analyzer (Abbott Diagnostics, Abbott Park, Illinois, USA). To standardize the results to WHO binding antibody units (BAU), a correction factor for Abbott arbitrary units (AU) was applied where 1 BAU/mL equals 0.142 AU, as previously established by Abbott with the WHO international standard NIBSC 20–136. Following the manufacturer's recommendations, samples were considered reactive for anti-S-RBD when titers were above 50 AU/mL (7.2 BAU/mL). An 80% protective effect (PROT-80) against symptomatic SARS-CoV-2 infection was assumed when anti-S-RBD titers were 506 BAU/ml or higher. Charlson Comorbidity Index

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(CCI) score was classified as mild = 1–2, moderate = 3–4, and severe ≥ 5. Side effects were evaluated until day 7 by patients´ self-reported questionnaire.

Results One hundred seven participants were enrolled [$n = 84$ homologous (SpV/SpV), nn 23 heterologous (SpV/Mod)]. Median (IQR) age was 64 (50–75) years old and 79 (73.8%) were male. Additionally, 19 (22.6%) of the SpV/SpV and 4 (17.4%) of the SpV/Mod group had a prior confirmed SARS-CoV-2 infection ($p = 0.589$). In the overall population, 103 patients reached seroconversion (96.3%). Anti-S-RBD IgG median titers (IQR) were higher in the heterologous [1222 (288–5680) BAU/mL] than in the homologous scheme [447 (100–1551) BAU/mL], $p = 0.022$. In a linear model adjusted for age, gender, days from first vaccination to boost dose and days from the boost dose to the anti-S-RBD IgG determination, previous SARS-COV-2 infection (B: 2062.2; CI95: 1231.8–2892.6; $p < 0.001$), and SpV/Mod vaccination scheme (B: 1294.6; CI95: 435.58–2147.6; $p = 0.003$) were independently associated with anti-S-RBD levels. Finally, a higher frequency of adverse effects was associated with the heterologous scheme, although they were well tolerated by all individuals.

Conclusions The present study provides evidence that the homologous SpV/SpV and heterologous SpV/Mod schemes showed good efficacy and safety in patients on chronic dialysis. These results could be useful for designing future vaccination strategies, especially aimed at this risk group.

Graphical abstract
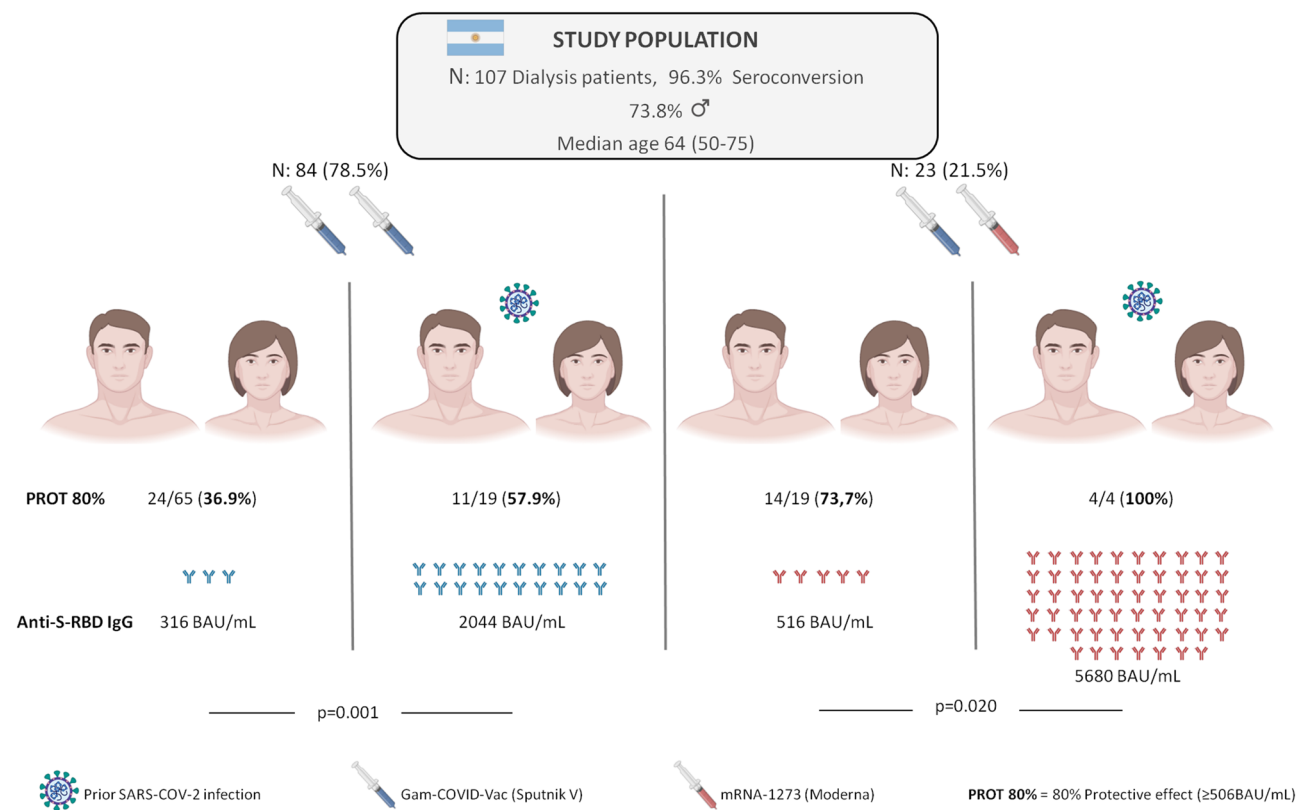
Keywords Dialysis · SARS-CoV-2 · Vaccine · Heterologous scheme · Gam-COVID-Vac · mRNA-1273

Introduction

Patients on chronic dialysis are at increased risk for severe coronavirus infectious disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) than the general population, with reported mortality rates of up to 28.3% [1, 2]. This situation is mainly related to a considerably higher mean patient age (approximately 65 years old) and the frequent presence of comorbid conditions such as obesity, diabetes, high blood pressure, socioeconomic deprivation, and frailty that are linked to a more severe COVID-19 course. Fortunately, effective vaccination schemes against SARS-CoV-2 inducing reduction of both infection and the risk
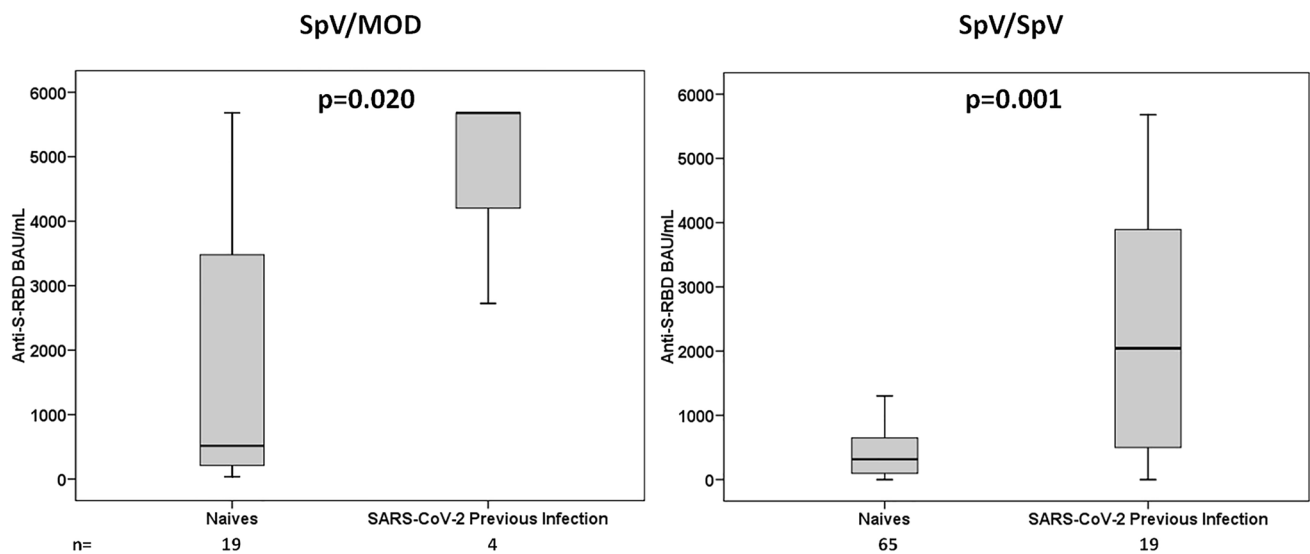
Fig. 1 Anti-S-RBD IgG levels for homologous (SpV/SpV) and heterologous (SpV/Mod) vaccination schemes in subjects who had (**A**) or did not have (**B**) a confirmed SARS-CoV-2 infection prior to immunization

Table 1 Population epidemiological characteristics ($n=107$)

Characteristic	Total, $n=107$
Age[a] (years)	64 (50–75)
Male gender, n (%)	79 (73.8)
Primary kidney diseases	
Diabetes, n (%)	15 (14)
High blood pressure, n (%)	13 (12.1)
Polycystic kidney disease, n (%)	8 (7.5)
Glomerular diseases, n (%)	10 (9.3)
Other, n (%)	23 (21.5)
Unknown, n (%)	38 (35.6)
Time on dialysis[a] (years)	4 (2–7)
Weekly total Kt/V[a]	1.5 (1.3–1.9)
Kidney transplant, n (%)	15 (14)
Immunosuppressive therapy, n (%)	6 (5.6)
Charlson Comorbidity index (%)	
Mild (1–2)	15 (14)
Moderate (3–4)	29 (27.1)
Severe (≥5)	63 (58.9)
Laboratory parameters	
Hemoglobin[a] (g/dL)	10.8 (9.7–11.6)
Albumin[a] (g/L)	4.1 (3.7–4.3)
C-reactive protein[a] (mg/dL)	4.6 (1.4–10.0)
Transferrin saturation[a] (%)	28 (23–36)
Body mass index (BMI)[a] (kg/m2)	25.3 (22.4–27.9)
Obesity (BMI > 30 kg/m2)	13 (12.1)

[*]Median (interquartile range)

of severe COVID-19 have been rapidly developed [3–6]. Moreover, when facing first dose serious adverse effects or dose supply shortages, introduced heterologous vaccination schemes have shown promising results [7–11]. Nevertheless, clinical trials do not provide information about vaccine efficacy in dialysis populations, and possible differences in immunogenicity among SARS-CoV-2 vaccination schemes are poorly understood due to their novelty. Particularly, the homologous Gam-COVID-VAC (Sputnik V) and the heterologous vaccination scheme including Sputnik V as a prime dose and mRNA-1273 (Moderna) as a booster dose have been barely studied since Sputnik V is not approved in all countries, its implementation suffers geographic limitations, and its approval by the European Medicines Agency (EMA) and the World Health Organization (WHO) is still awaited. Nonetheless, the National Administration of Medicines, Food, and Medical Technology of Argentina (ANMAT) approved Sputnik V emergency use in late December 2020. Sputnik V approval was followed by approval of the ChAdOx1 nCoV-19 vaccine (AZD1222), Sinopharm COVID-19 (BBIBP-CorV) vaccine, mRAN-1273 COVID-19 (Moderna), and BNT162b2 (Pfizer). However, due to the second dose shortage of Sputnik V, mRNA-1273 (Moderna) was frequently administered as the booster dose.

In this scenario, the present study aimed to assess the humoral response to homologous Sputnik V and heterologous Sputnik V/Moderna vaccination in dialysis patients.

Table 2 Epidemiological, clinical, and vaccination-specific determinants for binding IgG antibodies against the spike receptor-binding domain of SARS-CoV-2 (anti-S-RBD) levels assessed in univariate (uni) analyses and general linear models (GLM)

Parameter	n	Anti-S-RBD (BAU/mL)[a]	p_{uni}	B coefficient (95% CI)	p_{GLM}
Age					
30–49 years	25	605 (285–1396)		– 5.289 (– 27.995 to 17.417)	0.645
50–60 years	19	501 (88–914)			
> 60 years	63	342 (100–2873)	0.770		
Gender					
Male	79	502 (110–1740)			
Female	28	431 (105–2419)	0.859	– 275.9 (– 1077.2 to 525.4)	0.496
Time on dialysis					
≤ 3 years	42	345 (100–1551)			
≥ 4 years	65	555 (112–2634)	0.346		
Vaccination scheme					
SpV/SpV	84	447 (100–1442)			
SpV/Mod	23	1222 (288–5680)	0.022	1294.6 (435.58 to 2147.6)	0.003
Prior SARS-CoV-2 infection					
No	84	339 (99–911)			
Yes	23	2872 (508–5680)	< 0.001	2062.2 (1231.8 to 2892.6)	< 0.001
Weekly total Kt/V					
≤ 1.5	57	502 (112–1866)			
> 1.5	50	509 (98.3–2169)	0.783		
Kidney transplant					
No	92	519 (119–2055)			
Yes	15	182 (36–555)	0.097	– 544.69 (– 1544.7 to 455.35)	0.282
Immunosuppressive therapy					
No	101	508 (117–2052)			
Yes	6	295 (46–813)	0.225		
Comorbid condition[b]					
Mild-to-moderate	44	571 (218–1640)			
Severe	63	452 (90–2872)	0.326		
Diabetes					
No	92	502 (106–1787)			
Yes	15	628 (110–2873)	0.847		
Hemoglobin					
≤ 10.8 g/dL	58	519 (126–2762)			
> 10.8 g/dL	49	354 (89–1396)	0.219		
Albumin					
≤ 4.1 g/L	64	519 (100–3439)			
> 4.1 g/L	43	502 (133–732)	0.329		
C-reactive protein					
≤ 4.6 mg/dL	54	288 (94–612)			
> 4.6 mg/dL	53	518 (117–2761)	0.004	– 3.225 (– 13.557 to 7.107)	0.537
Transferrin saturation					
> 28%	50	332 (96–1904)			
≤ 28%	57	521 (219–2019)	0.178	7.888 (– 19.252 to 35.028)	0.565
Body-mass-index					
≤ 30 kg/m^2	94	502 (108–1851)			
> 30 kg/m^2	13	745 (194–3016)	0.372		
ΔP-B					
3–10 weeks	19	288 (94–612)			
11–18 weeks	88	518 (117–2761)	0.141	48.4 (– 44.244 to 141.04)	0.302

Table 2 (continued)

Parameter	*n*	Anti-S-RBD (BAU/mL)[a]	p_{uni}	*B* coefficient (95% CI)	p_{GLM}
ΔB-antiSRBD					
3–4 weeks	51	443 (114–1303)			
5–8 weeks	41	584 (105–3852)			
9–12 weeks	9	502 (126–2436)			
13–16 weeks	6	120 (53–608)	0.187	1.29 (− 104.39 to 106.97)	0.981

[a]Median (interquartile range)

[b]As determined by means of the Charlson Comorbidity Index (CCI), where mild = 1–2, moderate = 3–4 and severe ≥ 5

CI confidence interval, *SpV* Sputnik V, *Mod* Moderna, *ΔP-B* time intervals from prime to boost, *ΔB-antiSRBD* time interval from boost to anti-S-RBD IgG determination

Materials and Methods

Study Design and Population

From March to October 2021, subjects who underwent hemodialysis at the Centro de Educación Médica e Investigaciones Clínicas "Norberto Quirno" (CEMIC), Buenos Aires, Argentina, were included in this prospective cohort study. Inclusion criteria were (i) having received Sputnik V prime immunization, (ii) having received a boost dose of either Sputnik V (SpV/SpV) or Moderna (SpV/Mod) vaccines within 18 weeks post-prime dose, and (iii) having presented for monitoring of humoral immune response 3 weeks after the boost dose. Previous COVID-19 infection was determined in symptomatic patients or in persons in contact with symptomatic patients. The vaccination scheme depended on dose availability and the prioritization of risk populations as established by the Argentine Ministry of Health.

Immunogenicity

Binding IgG antibodies against the spike (S) receptor-binding domain (RBD) of SARS-CoV-2 (anti-S-RBD) concentration was assessed between 3 and 16 weeks after the boost dose. Anti-S-RBD antibodies were quantified using the Abbott Diagnostics SARS-CoV-2 IgG II Quant chemiluminescent microparticle immunoassay (CMIA) on an Architect i2000 SR and an Alinity I analyzer (Abbott Diagnostics, Abbott Park, Illinois, USA). To standardize the results to WHO binding antibody units (BAU), a correction factor for Abbott arbitrary units (AU) was applied where 1 BAU/mL equals 0.142 AU, as previously established by Abbott with the WHO international standard NIBSC 20–136 [12]. Following the manufacturer's recommendations, samples were considered reactive for anti-S-RBD when titers were above 50 AU/mL (7.2 BAU/mL). An 80% protective effect (PROT-80) against symptomatic SARS-CoV-2 infection was assumed when anti-S-RBD titers were 506 BAU/ml or higher [13]. Charlson Comorbidity Index (CCI) score was classified as mild = 1–2, moderate = 3–4, and severe ≥ 5 [14].

Side effects

All patients were invited to complete an online questionnaire to report all possible post-boost vaccination adverse events requiring medical assistance. The intensity of adverse effects was graded as mild, moderate, and severe depending on the interference with daily activities.

Statistical analysis

Descriptive statistics and univariate analyses were performed. The outcome variable was the anti-S-RBD titer at least 3 weeks after the boost dose. Differences in anti-S-RBD levels and PROT-80 according to demographic and clinical parameters were evaluated. Categorical variables were expressed as numbers (percentage) and analyzed using the Chi-square test or Fisher's exact test. Student's *t*-test and the Mann–Whitney *U* test were used to compare independent continuous variables, expressed as median (interquartile range, IQR). For related continuous variables, the Wilcoxon signed-rank test was applied. Factors associated with

anti-S-RBD levels with a $p < 0.2$ in the univariate analysis were evaluated in a general linear model adjusted for age and sex. Likewise, multivariate logistic regression models were developed to identify factors associated with PROT-80. Adjusted odds ratios (AOR) with their corresponding 95% confidence intervals (CI95) were calculated. Statistical analyses were carried out using the SPSS statistical software package release 23.0 (IBM SPSS Inc., Chicago, IL, USA).

Results

Study population

A total of 107 subjects were included in the study, 84 (78.5%) received SpV/SpV, and the remaining 23 (21.5%) the SpV/Mod scheme. Seventy-nine (73.8%) participants were male, and the median (IQR) age was 64 (50–75) years old. Overall, median time intervals were 91 (77–116) days from prime to boost dose (ΔP-B) and 32 (24–47) days from the boost dose to the anti-S-RBD IgG serological determination (ΔB-antiSRBD). Eighty-four (78.5%) individuals were *naïve* to SARS-CoV-2 infection at the time of prime vaccination, while 19 (22.6%) of those who received the SpV/SpV scheme and 4 (17.4%) who received SpV/Mod had a prior confirmed SARS-CoV-2 infection ($p = 0.589$). Seven out of 23 (30.4%) previously infected patients had SARS-CoV-2 infection between the first and second vaccine dose and two (8.7%) had SARS-CoV-2 infection between the second dose and the humoral response assessment. Table 1 shows detailed characteristics of the study population.

Immunogenicity

In the overall population, anti-S-RBD IgG was reactive in 103 (96.3%) persons, 80 (95.2%) immunized with the SpV/SpV vaccine, and 23 (100%) with SpV/Mod ($p = 0.286$). Median (IQR) anti-S-RBD titers were 42.5 (4–1297) BAU/mL after the first dose and 502 (110–1993) BAU/mL after the boost dose ($p < 0.001$). In participants with a confirmed SARS-CoV-2 infection before complete vaccination receiving the SpV/SpV scheme, the humoral response as measured by anti-S-RBD levels was 6.5-fold higher than that observed in *naïve* individuals. Similarly, people with a confirmed

SARS-CoV-2 infection before the SpV/Mod complete scheme presented 11-fold higher anti-S-RBD levels when compared to participants without prior infection (Fig. 1). Anti-S-RBD levels according to epidemiological and clinical parameters are shown in Table 2. Previous COVID-19 and an SpV/Mod vaccination scheme were independently associated with anti-S-RBD levels in a general linear model (Table 2).

A total of 53 (49.5%) individuals achieved PROT-80. Among participants without prior COVID-19 who received SpV/SpV or SpV/Mod and those with confirmed COVID-19 who received the homologous or the heterologous schemes, PROT-80 rates were 36.9%, 57.9%, 73.7%, and 100% ($p_{\text{linear association}} < 0.001$), respectively. Corresponding values according to epidemiological and clinical parameters are displayed in Table 3. In the multivariate analysis, an independent association with PROT-80 was observed for prior COVID-19, heterologous vaccination, and age in a logistic regression model (Table 3).

Side effects

The homologous and heterologous immunization schemes were well tolerated, and no medical assistance or potentially fatal events were reported. Adverse events, including local and systemic symptoms, were higher for SpV/Mod (47.6%) than for SpV/SpV (23.7%) schemes, $p = 0.031$. In general, the most frequent systemic adverse events were fatigue (9.9%), myalgia (5.9%), and fever (2.0%). No patients reported headaches, chills, nausea/vomiting, arthralgia, or diarrhea. The heterologous vaccine scheme tended to induce more systemic adverse effects than the homologous one (28.6% vs 15.0%, $p = 0.148$). Regarding local adverse events, pain at the injection site was reported by 11 patients (10.9%) and tended to be more frequent for the heterologous scheme than for the homologous one (19.0% vs 8.8%, $p = 0.178$). Prior SARS-CoV-2 infection did not significantly impact on reactogenicity. Thus, 4 (17.4%) and 14 (17.9%) patients with and without previous SARS-CoV-2 infection, respectively, showed systemic symptoms, $p = 0.959$. Reported local symptoms were 3 (13.0%) for patients with previous SARS-CoV-2 infection and 8 (10.3%) for patients without it, $p = 0.706$. Figure 2 shows the reactogenicity by adverse effects (local and systemic) according to the vaccination scheme.

Table 3 Impact of epidemiological, clinical, and vaccination-related parameters on achieving an 80% protective effect (PROT-80) following vaccination against SARS-CoV-2 in the univariate (uni) and logistic regression (LR) analyses

Parameter	n	PROT-80, n (%)	p_{uni}	Adjusted Odds Ratio (95% CI)	p_{LR}
Age[a]					
30–49 years	25	17 (68)			
50–60 years	19	7 (36.8)			
> 60 years	63	29 (46)	0.084	0.953 (0.923–0.985)	0.004
Gender					
Male	79	39 (49.4)			
Female	28	14 (50)	0.954	1.095 (0.379–3.165)	0.867
Time on dialysis					
≤ 3 years	42	18 (42.8)			
≥ 4 years	65	35 (53.8)	0.267		
Vaccination scheme					
SpV/SpV	84	38 (45.2)			
SpV/Mod	23	15 (65.2)	0.090	3.753 (1.199–11.748)	0.023
Prior SARS-CoV-2 infection					
No	84	35 (41.7)			
Yes	23	18 (78.3)	0.002	9.482 (2.697–33.338)	< 0.001
Weekly total Kt/V					
≤ 1.5	57	28 (49.1)			
> 1.5	50	25 (50)	0.928		
Kidney transplant					
No	92	48 (52.2)			
Yes	15	5 (33.3)	0.176	0.182 (0.042–0.779)	0.022
Immunosuppressive therapy					
No	101	51 (50.5)			
Yes	6	2 (33.3)	0.414		
Comorbid condition[b]					
Mild-to-moderate	44	25 (56.8)			
Severe	63	28 (44.4)	0.208		
Diabetes					
No	92	45 (48.9)			
Yes	15	8 (53.3)	0.751		
Hemoglobin					
≤ 10.8 g/dL	58	31 (53.4)			
> 10.8 g/dL	49	22 (44.9)	0.378		
Albumin					
≤ 4.1 g/L	64	33 (51.6)			
> 4.1 g/L	43	20 (46.5)	0.608		
C-reactive protein					
≤ 4.6 mg/dL	54	20 (37)			
> 4.6 mg/dL	53	33 (62.3)	0.009	1.008 (0.986–1.030)	0.493
Transferrin saturation					
> 28%	50	22 (44)			
≤ 28%	57	31 (54.4)	0.284		
Body-mass-index					
≤ 30 (kg/m^2)	94	45 (47.9)			
> 30	13	8 (61.5)	0.356		
ΔP-B					
3–10 weeks	19	7 (36.8%)			
11–18 weeks	88	46 (52.3%)	0.312		
ΔB-antiSRBD					
3–4 weeks	51	23 (45.1%)			

Table 3 (continued)

Parameter	n	PROT-80, n (%)	p_{uni}	Adjusted Odds Ratio (95% CI)	p_{LR}
5–8 weeks	41	24 (58.5%)			
9–12 weeks	9	4 (44.4%)			
13–16 weeks	6	2 (33.3%)	0.484		

[a]Entered as continuous variable in the multivariate analysis

[b]as determined by means of the Charlson Comorbidity Index), where mild=1–2, moderate=3–4 and severe≥5

CI confidence interval, *SpV* Sputnik V, *Mod* Moderna, *ΔP-B* time intervals from prime to boost, *ΔB-antiSRBD* time interval from boost to anti-S-RBD IgG determination
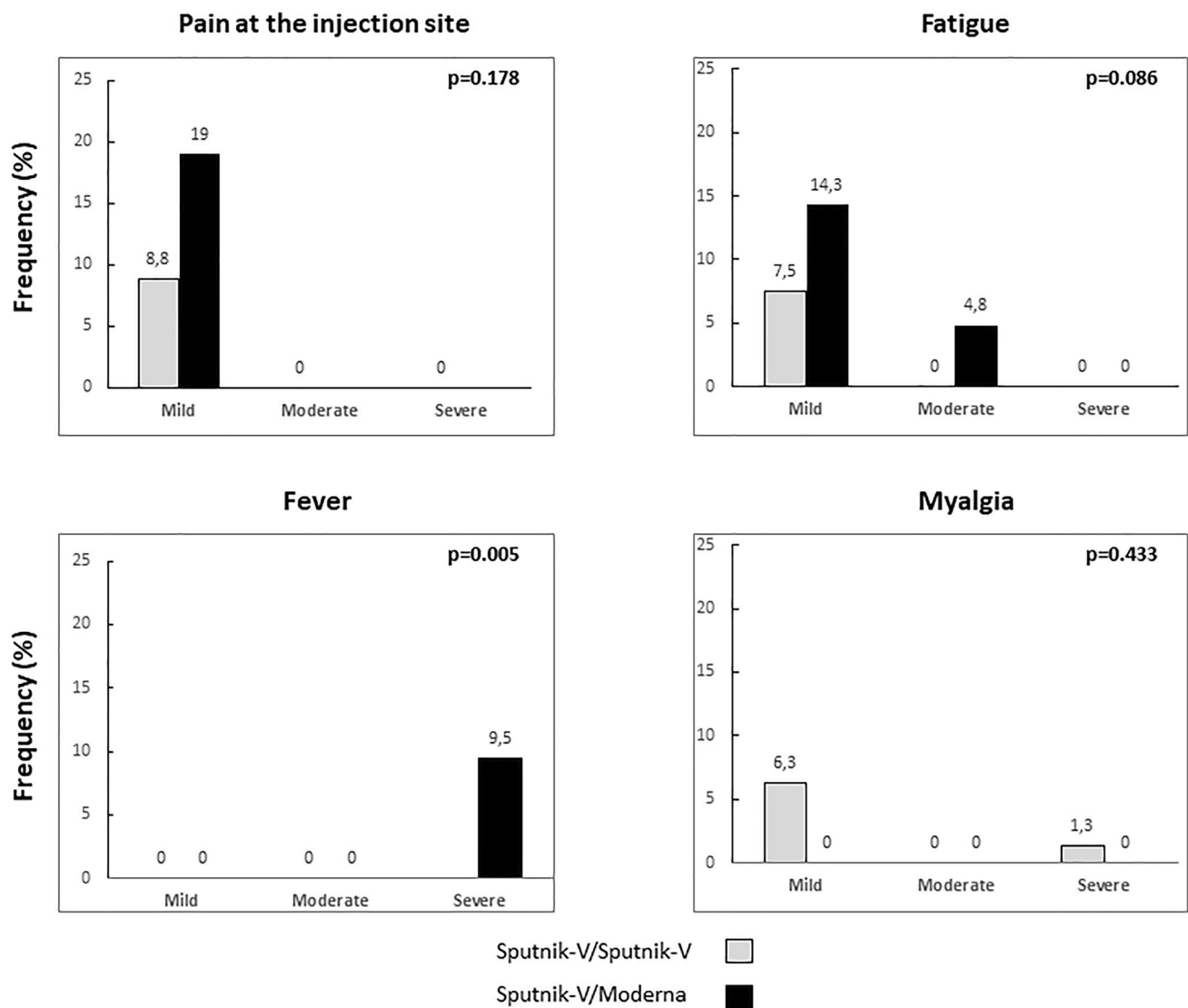
Fig. 2 Adverse events frequency of local and systemic adverse effects as reported by the participants for the homologous (SpV/SpV) and heterologous (SpV/Mod) schemes, classified by severity

Discussion

The present work shows that the implementation of SpV/SpV or SpV/Mod vaccination schemes against SARS-CoV-2 in patients under dialysis was effective, leading to a seroconversion rate of 96.3%. Overall, the heterologous scheme showed an anti-S-RBD level almost threefold higher than the homologous one. Moreover, both vaccination schemes were well tolerated, and no medical assistance was required.

To our knowledge, this is the first study on the heterologous scheme including Sputnik V and Moderna vaccines in *naïve* and previously SARS-CoV-2 infected patients under dialysis conditions. Additionally, the study allowed results comparison with the homologous SpV/SpV scheme. Findings from our study show the development of a strong humoral response in the dialysis setting in contrast to other studies reporting that patients under dialysis present lower seroconversion rates and anti-S-RBD titers than healthy controls [15]. However, the seroconversion rate of our population under dialysis was similar to that reported by previous studies showing values between 90 and 98% [16–18]. Rosa-Diez (2021) detected a 98% seroconversion rate in a study including 102 dialysis patients vaccinated with the Sputnik V scheme [17]. On the other hand, studies performed on patients under dialysis conditions immunized with Moderna vaccines have shown seroconversion rates ranging between 95 and 97.9% [16, 18, 19]. In this context, our results support the use of Sputnik V or its combination with the Moderna vaccine as an alternative for dialysis patients.

Regarding PROT-80, almost 50% of the studied population achieved this threshold. However, the response rates differed significantly when the population was categorized according to age, kidney transplant, vaccine regimen, and prior COVID history. While heterologous scheme and prior SARS-CoV-2 infection were associated with higher PROT-80 proportions, the considerably low 37% PROT-80 rate observed in patients without previous infection and immunized with the SpV/SpV scheme indicate the need for prioritization of a third dose in this particular subpopulation in order to increase and extend antibody levels, especially when further factors that may lower response such as older age or kidney transplant are present.

Concerning the individual factors associated with the humoral response, in the present study, there were no significant anti-S-RBD IgG differences between genders. These findings are consistent with several studies showing that gender does not seem to influence anti-S-RBD IgG titers achieved with both analyzed vaccine schemes [20–22]. Likewise, no difference in anti-S-RBD IgG levels according to the age of dialyzed patients was observed in our sample, while an age above 50 years was associated with lower rates

of PROT-80. Available data on the relationship between age and response to vaccines are scarce and remain controversial [11, 21, 22]. More studies on this issue are warranted as most reports analyzing the age-associated responses are conducted in healthy populations [11, 21, 22].

Regarding previous infection with SARS-CoV-2, a significant relation was found between higher anti-S-RBD IgG titers and a confirmed past infection for both the SpV/SpV and SpV/MOD schemes, with notable, 11-fold higher levels observed for the heterologous scheme. This finding is in accordance with our previously reported values for these vaccination schemes [11], for the sputnik V homologous scheme [20, 21] and for RNAm vaccines [23].

Additionally, the current study showed that body mass index, time on dialysis, weekly total Kt/V, immunosuppressive therapy, and diabetes as well as other evaluated laboratory parameters, presented no association with Anti-S-RBD levels or PROT-80 rates. Likewise, vaccine efficacy was not associated with ΔP-B, and ΔB-antiSRBD, which is in accordance with findings in the general population immunized with the SpV/SpV and SpV/MOD schemes [11]. While C-reactive protein levels showed an association with Anti-S-RBD and PROT-80 in the univariate analysis, the effect was not maintained after stratifying for other parameters. Additionally, when the Charlson Comorbidity Index was analyzed, no association was found with the vaccine response. There are previous contradictory results regarding this issue. While some authors, including ourselves, could not find an association between these variables and the anti-S-RBD IgG titers [24], other studies suggest that less comorbidity presence leads to a higher anti-S-RBD IgG titer [19, 23]. It is worthy to note that a recent study performed in hemodialysis patients also failed to detect an association between COVID-19 severity and obesity, diabetes, or comorbidity presence [3], factors that do have an impact on disease severity in the overall population. It appears that these differences are also true for vaccine response.

The better immunogenicity of heterologous schemes could be explained by recent evidence showing that mRNA vaccines have a better humoral response when compared to adenovirus-based vaccines [8, 9, 25–27]. Furthermore, the enhanced humoral activity induced by the heterologous regimen is correlated with increased frequencies of switched and activated memory B cells recognizing the SARS-CoV-2 RBD [26]. Moreover, the higher anti-S-RBD titers achieved in the SpV/Mod group of this study is in agreement with previous works performed on the general population [11, 28]. However, additional studies are necessary to assess the cellular response since the combination of vaccines appears to enhance the characteristic immune response generated by each vaccination scheme [26, 27].

There is little data on side effects of SpV/SpV or SpV/Mod in dialysis patients and this work offers a contribution to the understanding of SARS-CoV-2 vaccination in this setting. In our sample, adverse events including local and systemic symptoms were higher in dialysis patients who received the SpV/Mod scheme as we have previously described for the general population [11]. In agreement with other studies, fatigue and myalgia were the most frequent systemic complaints [11, 29]. The higher trend in the rate of adverse events in the SpV/Mod group was expected since it is well proven that stronger side effects were associated with mRNA vaccines in the general population [9, 11, 26]. It is important to note that the frequency of adverse events was lower than that observed in the general population and no patients required medical support [11]. However, the median age of the sample analyzed in the present work was higher and the effect of age on the incidence of side effects has already been described in previous studies [3, 13]. Moreover, in a study by Polewska and colleagues (2021), adverse events were less frequently observed in dialyzed patients than in the age and sex-matched control group [29].

This study has some limitations. Firstly, it should be considered that patients were not randomized to receive a particular immunization regimen. Second, patients may have had asymptomatic COVID-19 infection between the two vaccine doses or between the second dose and evaluation of the humoral response. However, it is to be expected that both analyzed groups would have been affected equally; therefore, an impact on the conclusions would unlikely be altered. Third, antibody neutralizing activity was not assessed. Nevertheless, Schmidt et al. showed a significant correlation between IgG levels and neutralizing activity [26]. Lastly, serious adverse effects have been reported with a very low frequency and the small size of the analyzed sample might have influenced this aspect.

In conclusion, both analyzed vaccine schemes were immunogenic, showed a high seroconversion rate and a significant correlation was found between higher anti-S-RBD IgG titers and a confirmed prior infection with SARS-CoV-2 for both schemes. Moreover, the heterologous scheme was also associated with a better humoral response. Finally, both schemes were safe and well-tolerated. These findings should promote patients on dialysis to receive these immunization schemes; however, those who have never been infected with SARS-CoV-2 and received a homologous vaccine scheme may be prioritized for a third dose, especially when more risk factors are present.

Declarations

Competing interests On behalf of all authors, the corresponding author states that the authors have no relevant financial or non-financial interests to disclose.

Ethical disclosures The study was designed and performed according to the Helsinki declaration and all participants gave their written informed consent (Study protocol EX-2021–06438339-UBA DME#SSA_FFYB, Ethics committee of the Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires).

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