Safety and immediate humoral response of COVID-19 vaccines in chronic kidney disease patients: the SENCOVAC study

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RUNNING HEAD: Early humoral response SARS-CoV-2 vaccines in CKD

KEY LEARNING POINTS

What is already known about the subject?

- Coronavirus-19 disease (Covid-19) has caused millions of deaths worldwide, being especially lethal in vulnerable populations, such as chronic kidney disease (CKD), dialysis and kidney transplant (KT) patients.
- Dialysis, organ transplantation and CKD patients with eGFR <30 mL/min/1.73 m^2 represent three of the four comorbidities associated with the highest mortality risk from COVID-19.
- Low seroconversion rate to mRNA vaccines has been preliminarily reported in KT patients.

What this study adds?

- SENCOVAC demonstrated the safety of SARS-CoV-2 mRNA vaccines in peritoneal dialysis, haemodialysis, KT recipients and non-dialysis CKD patients.
- Vaccination with mRNA-1273 (Moderna) resulted in better serological response than vaccination with BNT162b2 (Pfizer-BioNTech) in KT recipients and other CKD populations.
- Absence of antibody response was independently associated with KT (OR 20.56) and BNT162b2 vaccination (OR 6.03).

What impact this may have on practice or policy?

- Isolation measures should be maintained in CKD patients, especially in KT recipients, at high-risk of Covid-19.
- KT patients may benefit of a booster dose of a Covid-19 vaccine, as some authorities are now recommending.
- CKD patients at high-risk for SARS-CoV-2 infection should be monitored, even if they are asymptomatic, as 50% of them could be reinfected by SARS-CoV-2.

ABSTRACT

Background. Chronic kidney disease (CKD) patients are at high-risk for severe Covid-19. The multicentric, observational and prospective SENCOVAC study aims to describe the humoral response and safety of SARS-CoV-2 vaccines in CKD patients. Safety and immediate humoral response results are reported here.

Methods. Four cohorts of patients were included: kidney transplant (KT) recipients, haemodialysis (HD), peritoneal dialysis (PD) and non-dialysis CKD patients from 50 Spanish centres. Adverse events after vaccine doses were recorded. At baseline and on day 28 after the last vaccine dose, anti-Spike antibodies were measured and compared between cohorts. Factors associated with development of anti-Spike antibodies were analyzed.

Results. 1746 participants were recruited: 1116 HD, 171 PD, 176 non-dialysis CKD patients and 283 KT recipients. Most patients (98%) received mRNA vaccines. At least one vaccine reaction developed after the first dose in 763 (53.5%) and after the second dose in 741 (54.5%) of patients. Anti-Spike antibodies were measured in the first 301 patients. At 28 days, 95% of patients had developed antibodies: 79% of KT, 98% of HD, 99% of PD and 100% of non-dialysis CKD patients ($p<0.001$). In a multivariate adjusted analysis, absence of an antibody response was independently associated to KT (OR 20.56, $p=0.001$) and to BNT162b2 vaccine (OR 6.03, $p=0.023$).

Conclusion. The rate of anti-Spike antibody development after vaccination in KT patients was low but in other CKD patients it approached 100%; suggesting that KT patients require persistent isolation measures and booster doses of a Covid-19 vaccine. Potential differences between Covid-19 vaccines should be explored in prospective controlled studies.

Keywords: antibodies, COVID-19, humoral response, SARS-CoV-2, vaccine

INTRODUCTION

Coronavirus-19 disease (Covid-19) has caused millions of deaths worldwide, being especially lethal in vulnerable populations, such as patients with chronic kidney disease (CKD), those on dialysis and kidney transplant (KT) recipients[1]. Dialysis, organ transplantation and CKD patients with eGFR <30 mL/min/1.73 m^2 represent three of the four comorbidities associated with the highest mortality risk from Covid-19[2]. Several circumstances have exacerbated the impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on the morbidity and mortality of CKD patients. Beyond the inherent immunosuppression secondary to impaired renal function[3], haemodialysis (HD) and KT patients present specific characteristics, such as immunosuppressive therapy and comorbidities that enhance their risk for developing severe Covid-19.

The fast development and approval of SARS-CoV-2 vaccines has decreased the severity of the Covid-19 pandemic in countries with high immunization rates. However, there is concern regarding the humoral response of CKD patients to vaccination against SARS CoV-2. Data on KT patients is the most worrisome, with a seroconversion rate lower than 50% in the majority of published studies[4]. In addition, recent series have shown their limited development of anti-Spike antibodies, even after three vaccine doses[5]. In contrast, preliminary studies suggest that HD patients reach higher anti-Spike antibody levels after the administration of mRNA vaccines than KT patients, but lower than the general population[6]. Two recent reports involving peritoneal dialysis (PD) patients suggest that this population acquires similar humoral and cellular responses as HD patients, at least in the short term[7,8]. Regarding non-dialysis CKD patients, available data are limited as those patients are systematically excluded from clinical trials, and to our knowledge no specific studies have been published to date[9].

Despite the heterogeneous available data, a correct understanding of the efficiency and safety of SARS-CoV-2 vaccines in different populations of CKD patients with different immunological and comorbid background is a priority for delineating further actions according to their specific susceptibility and response to Covid-19 vaccination.

The aim of the multicentric SENCOVAC study was to evaluate the humoral response and safety of the SARS-Cov-2 vaccines in CKD patients comparing the humoral response in four different cohorts: PD, HD, KT and non-dialysis CKD patients. We now present the SENCOVAC study results in terms of adverse events and the preliminary report on the immediate humoral response as assessed by the antibody response 28 days after complete Covid-19 vaccination.

MATERIALS AND METHODS

Study design

SENCOVAC is a Spanish Society of Nephrology (S.E.N.) prospective and multicentric study including 4 cohorts of adult patients with CKD: KT recipients, HD, PD and non-dialysis CKD patients (stages 4 and 5, glomerular filtration rate [GFR] <30 ml/min/1.73m^2). All the screened participants received the complete immunization schedule with any of the available vaccines: BNT162b2 (Pfizer-BioNTech®), mRNA-1273 (Moderna®), ChAdOx1-S (AstraZeneca®) or Ad26.COV.2 (Janssen®) as per local public health authorities' prescription at their respective Autonomous Communities during routine clinical care.

Patients

Fifty centers in Spain participated in the study. Among the 1930 screened patients, 1746 were included (**figure 1**). Inclusion criteria were age older than 18 years, capability of

understanding the purpose and risks of the study, fully informed written consent, and a diagnosis of CKD as KT recipients, HD, PD or non-dialysis CKD with GFR <30 ml/min/1.73m^2. Exclusion criteria were contraindication for vaccination, solid organ transplantation different from kidney, active oncological or hematological disease, primary immunodeficiency disease, human immunodeficiency virus and immunosuppressive treatment 6 months before vaccination for non-KT recipients.

Objectives

The primary objective was to determine the rates of anti-SARS-CoV-2 Spike antibody development in CKD patients. Anti-Spike antibodies correlate with neutralizing activity[10]. Secondary objectives included safety (immediate local and systemic reactions and other adverse events [AE]), and effectivity on preventing further SARS-CoV-2 infection.

Variables and outcomes

In this interim analysis, we assessed safety and the humoral response at 28 days after completion of the vaccination schedule. Patients were studied at baseline, after the administration of the vaccine doses and at 28 days. At baseline, investigators registered epidemiological data, comorbidities (including previous Covid-19 infection [defined by the investigator with a positive antigen or polymerase chain reaction against SARS-CoV-2), long-term treatments, vital signs and laboratory values. In addition, each cohort had specific registries based on the kidney situation (Kt/Vurea, dialysis vintage, technique and vascular access for HD and PD patients; immunosuppressive therapy for KT).

Antibody testing

At baseline and at-28 days, a 2 ml serum sample was obtained and sent to a central laboratory for antibody determinations. All samples were tested by a CE-marked

commercial method, a quantitative chemiluminescence immunoassay (CLIA, Covid-19 Spike Quantitative Virclia® IgG Monotest, Vircell SL, Spain), with a sensitivity and specificity of 96% and 100% respectively that detects IgG antibodies against the SARS-CoV-2 Spike protein. This assay was calibrated against the First WHO International Standard for anti-SARS-CoV-2 human immunoglobulin (NIBSC code: 20/136) and results were expressed as IU/ml. According to the performance studies of the manufacturer, based on the analysis of prepandemic serum samples, values ≤32 IU/ml were considered as negative, between 32 and 36 IU/ml as equivocal and values >36 IU/ml as positive, reflecting the presence of anti-Spike IgG antibodies as a consequence of either previous infection or vaccination.

Adverse events and vaccine reactions

After each vaccine dose, patients were asked to complete the adverse events questionnaire.

During the study all patients were followed, and any AE was registered. Serious AE were considered if they led to death, were life-threatening, needed hospitalization or caused disability, as considered by the investigators.

Ethical concerns

The study was approved by the Ethical Committee of Fundación Instituto de Investigación Sanitaria de la Fundación Jiménez Díaz in February 2021.

Statistical methods

Data is displayed as mean (standard deviation) or median (interquartile range [IQR]) depending on the variable distribution (tested with the Shapiro-Wilk test). Categorical variables were compared using Fisher test and continuous variables with t-test or Mann-Whitney, according to the variable distribution. For comparison of continuous variables from more than 2 groups, ANOVA or Krusal-Wallis tests were used. Correlations were

calculated using the Spearman test. The statistical analysis was performed using SPSS version 26.0 (IBM Corp., Armonk, NY). Plots were drawn using GraphPad Prism version 9.02 (Graphpad Holdings, LLC).

RESULTS

Baseline characteristics

Among the 1746 participants in SENCOVAC, 1092 (62.5%) were male and the mean age was 63.67±13.28 years (**table 1**). Vaccine distribution was as follows: 1202 patients (69%) received mRNA-1273, 511 (29%) BNT162b2, 25 (1%) AstraZeneca and 8 (0.5%) Janssen vaccines. As shown in **figure 1**, 1116 (64%) patients were on HD, 283 (16%) were KT patients, 176 (10%) were non-dialysis CKD patients, and 171 (19%) were on PD. The distribution of the different types of vaccines differed between groups (**Table 1**). KT recipients, HD and PD patients were more likely to receive mRNA-1273 and non-dialysis CKD patients BNT162b2 ($p<0.001$). **Table 2** shows baseline characteristics for participants that received mRNA vaccines (BNT162b2 or mRNA-1273) in the safety and humoral response population populations. The analysis restricted to patients without anti-Spike antibodies at baseline is shown in **Table 1S.**

Local and systemic reactions after vaccination

The adverse reactions form after the first dose was completed by 1426 participants. Among them, 763 (53.5%) patients developed at least one reaction. Reactions were more frequent in KT recipients, followed by PD and HD patients ($p<0.001$) **(figure 1S)**. Vaccine reactions was more frequent in younger patients ($p<0.001$ for all groups combined, not shown). Specifically, vaccine reactions were more frequent in younger KT recipients ($p=0.016$) and in younger persons with non-dialysis CKD ($p=0.012$) than

in older participants from these groups (not shown). Previous Covid-19 infection was also associated with higher rates of reactions after the first dose (64% vs 53%) (p=0.038). The most frequent reaction was local pain (556, 73%), followed by general discomfort (163, 22%) and asthenia (160, 21%) (**table 2S**). mRNA-1273 vaccine was associated with higher rates of local pain, erythema, swelling, skin hypersensitivity, low-grade fever and fever, headache, asthenia, chills, and general discomfort. Among patients who were working, those who had received mRNA-1273 requested a work leave more frequently (p=0.015).

The adverse reactions form after the second dose was completed by 1359 patients. Among them, 741 (54.5%) developed at least one reaction. Reactions were more frequent in KT patients (p=0.006) (**figure 1S**). Vaccine reactions to the second dose were also more frequent in younger patients (p<0.001 for all groups combined, not shown). Specifically, vaccine reactions were more frequent in younger KT patients (p=0.035) and in younger non-dialysis CKD patients (p=0.003) than in older participants from these groups (not shown). Previous Covid-19 infection was also associated with higher rates of reactions after the second dose (65% vs 53%) (p<0.001). The most frequent reaction was local pain (493, 68%) followed by general discomfort (261, 36%) and asthenia (258, 36%) (**table 3S**).The second dose of mRNA-1273 produced more frequent local pain, erythema, swelling, itching, skin hypersensitivity, low-grade fever and fever, headache, asthenia, myalgia, chills, general discomfort and arthralgias than the other vaccines. Among patients who were working, those who had received mRNA-1273 asked for a work leave more frequently (p=0.002).

Anti-Spike antibodies

Development of anti-Spike antibodies 28 days after completing vaccination has been tested in 301 patients (28 non-dialysis CKD patients, 43 KT recipients, 52 PD and 172 HD patients). Baseline characteristics for these patients are presented in **table 4S**. At baseline, 69 patients (23%) presented anti-Spike antibodies, 6 (2%) had an equivocal result and 226 (75%) had no anti-Spike antibodies. Among patients with baseline anti-Spike antibodies, 35 (51%) had a known history of Covid-19.

Twenty-eight days after completing vaccination, 289 patients (95%) presented anti-Spike antibodies, 2 (1%) were equivocal and 14 (5%) had a negative result. Patients that did not develop anti-Spike antibodies post-vaccination included 9 (21%) KT recipients, 4 (2%) HD patients and 1 (1%) PD patient ($p<0.001$) (**figure 2S**).

Among the 226 patients that did not have anti-Spike antibodies at baseline, the rate of *de novo* antibody development was 94% for all groups combined. Among these patients, 170 (98%) of patients receiving mRNA-1273 developed anti-Spike antibodies as compared with 42 (81%) patients receiving BNT162b2 ($p<0.001$). Specifically, among patients without anti-Spike antibodies at baseline, 12 (5.3%) did not develop a humoral response. Patients who did not develop *de novo* antibodies included 7 (26%) of the KT recipients, 1 (2%) DP patients and 4 (3%) HD patients ($p<0.001$) (**figure 3S**).

Interestingly, in 2 patients who had positive or equivocal anti-Spike antibodies at baseline, these were not observed 28 days following vaccination. These 2 patients belonged to the KT group, displayed very low baseline anti-Spike antibody titres (34

and 42 UI/ml) and received mRNA-1273 and BNT162b2 vaccines, respectively. Among KT patients with a history of Covid-19, 100% had antibodies after vaccination.

As shown in **figure 2**, in the overall analysis, KT recipients presented lower titres of anti-Spike antibodies than HD (p=0.001), PD (p<0.001) and non-dialysis CKD (p=0.002) patients. When the analysis was restricted to patients without anti-Spike antibodies at baseline, similar results were obtained: KT was the group with lower *de novo* antibody generation (p=0.011 vs HD; p<0.001 vs DP and p=0.013 vs CKD) (**figure 4S**).

Focusing specifically on KT recipients without baseline anti-Spike antibodies, anti-Spike antibodies developed in 14 (82%) of those receiving mRNA-1273 and in 6 (60%) of those receiving BNT162b2 vaccines (p=0.365).

Factors associated to the development of anti-Spike antibodies

Among patients in whom antibodies were assessed, 53 had a history of Covid-19. Of these, 35 (66%) patients had anti-Spike antibodies at baseline (4 [80%] of KT recipients with prior Covid-19, 5 [50%] of DP, 25 [68%] of HD and 1 (100%) of non-dialysis CKD patients [p=0.249]).

Previous Covid-19 infection was associated with higher anti-Spike titres at 28 days (median 10000 [IQR 5722-10000] UI/ml vs 3529 [IQR 661-10000]; p<0.001). Within specific groups, these differences were significant in KT recipients and in HD patients (**figure 3**). Patients with baseline positive anti-Spike antibodies also presented higher

anti-Spike antibody titres at 28 days (median 10000 [IQR 2686-10000] UI/ml vs 2928 [IQR 655-10000]; p<0.001) (**figure 5S)**.

Patients receiving mRNA-1273 developed higher anti-Spike titres (median 10000 [IQR 1716-10000] UI/ml) than those receiving BNT162b2 (median 964 [IQR 109-4213] UI/ml) (p<0.0001). These differences were significant in KT, PD and HD patients (**figure 4**). Restricting the analysis to those with negative baseline anti-Spike antibodies, mRNA-1273 was superior in developing antibodies in KT, HD and CKD patients (**figure 6S**). A mild but significant indirect correlation was observed between age and anti-Spike titres in both the whole sample and in those patients without baseline anti-Spike antibodies (**figure 7S and 8S**). PD patients who had not received previously the seasonal influenza vaccine developed significantly higher anti-Spike titres at 28 days (median 4528 [IQR 1319-10000] UI/ml vs (10000 [IQR 5359-10000]; p=0.029). However, an adjusted linear regression by age and previous Covid-19 did not show any independent association between influenza vaccine and anti-Spike titres. No differences were found in anti-Spike antibodies titres between patients with or without anti-HBs antibodies.

A multivariate analysis adjusted for age, baseline anti-Spike antibodies, gender and seasonal influenza vaccine, showed that KT (OR 20.56 [95%CI (3.24-130.45)], p=0.001) and BNT162b2 vaccine (OR 6.03 [95%CI (1.28-28.23)], p=0.023) were independent predictors for the lack of development of anti-Spike antibodies (**table 3**).

Adverse events and SARS-CoV-2 infections

AE and occurrence of a SARS-CoV-2 positive antigen or PCR tests were recorded up to 52 days following completion of vaccination. During follow-up, 40 AE were registered in 31 patients (1.8%). One HD patient suffered a stroke 1 month after the second dose of mRNA-1273. One KT recipient suffered a myocardial infarction 4 days after the first dose of BNT162b2. After recovering, the patient received the second dose without any AE. Eight patients died but death was not considered a vaccine-related event. The causes of death were 2 cardiovascular events, 4 infectious diseases, 1 neoplasm and 1 dialysis withdrawal. Among patients who died, 4 (50%) had received BNT162b2 and 4 (50%) mRNA-1273.

Between the first and the second dose, 17 (1.0%) SARS-CoV-2 positive tests were recorded (4 in PD and 13 in HD patients). Two patients had received BNT162b2 and 15 mRNA-1273, representing 0.5% and 1.5% of patients having received BNT162b2 and mRNA-1273, respectively (p=0.414).

Twelve patients (1.0%) presented a SARS-CoV-2 positive test after the second dose. One was a KT recipient, one a PD patient, 9 were HD patients and one patient had non-dialysis CKD. Of them, 3 had received BNT162b2 and 9 mRNA-1273, representing 1.0% and 1.1% of patients having received BNT162b2 and mRNA-1273, respectively (p=0.982).

None of the post-vaccination SARS-CoV-2 infections were lethal.

DISCUSSION

The main findings of the interim analysis of the multicentric SENCOVAC study are the safety of current vaccination schedules for patients with advanced CKD and the poor serological response of KT in comparison to HD, PD and non-dialysis CKD patients. Due to the lack of a complete immunological response against SARS-Cov-2, KT recipients are candidates for an early third dose of the vaccine in some countries[5]. Our results demonstrated a suboptimal humoral response in KT recipients even in a very short-term assessment, only 28 days from the completion of the full vaccination schedule. In contrast to the other groups, more than 20% of KT patients did not develop anti-Spike antibodies. Moreover, loss of anti-Spike antibodies following vaccination was documented in at least one of KT recipients who had anti-Spike antibodies at baseline. Our study results agree with preliminary publications strongly suggesting that KT patients are at high risk of Covid-19 infection despite the complete two-dose vaccination schedule[11,12,13]. Our results also provide hypothesis-generating information on how to optimize seroconversion and anti-Spike antibody titres in advanced CKD patients, as the mRNA-1273 vaccine performed better from the antibody generation point of view than BNT162b2 in this population. These findings may be the basis for prospective randomized controlled studies in CKD patients, but especially, due to their enhanced risk for a suboptimal humoral response, in KT recipients. In this regard, although the study was observational, the administration of mRNA-1273 or BNT162b2 was a random choice by health authorities dependent on vaccine type availability in different Spanish regional health systems at the time that each regional system decided to vaccinate persons with CKD based on different sequential criteria (advanced age, healthcare personnel and consideration as a high-risk group). Consequently, analysis of

patient subpopulation vaccinated with one or the other vaccine did not disclose any consistent bias, and multivariate analysis identified the type of vaccine as a driver of anti-Spike antibody responses and titres, including the population most needed of an optimized antibody response, i.e. KT recipients.

An important issue not addressed is the link between immune response and efficacy. This last term refers to the possibility of preventing SARS-CoV-2 infection and, even severe disease, hospitalization and deaths after vaccination[14]. Although the relationship between neutralizing antibodies and breakthrough infections has been confirmed in healthy persons, this should be conformed in vulnerable populations[15].

Immunosuppression, age or previous Covid-19 infection influence the development of anti-SARS-CoV-2 antibodies[4,16]. Surprisingly, in our study age did not predict the strength of the humoral response. This may in part be explained by the lower age in KT recipients and in patients receiving mRNA-1273[17]. Interestingly, our data shows that the type of vaccine was an independent predictor for humoral response. Indeed, mRNA-1273 was associated to higher rates of early anti-Spike antibodies. mRNA-1273 was also associated with more frequent vaccine reactions in this population, which may be interpreted as consistent with a more vigorous immune response. In this regard, a recent network study including maintenance hemodialysis patients demonstrated higher protection from SARS-CoV-2 infections with mRNA-1273 in comparison to BNT162b2. In that study, the authors hypothesized about the difficulties in handling BNT162b2 vaccine and its impact on the thermostability, what could decrease effectivity[16]. However, one of the most feasible reason for these differences (in terms of adverse reactions and development of humoral response) might be the higher mRNA dose of mRNA-1273 (100 mcg vs 30 mcg in BNT162b2)[18]. Indeed, a higher dose of

hepatitis B virus vaccine is recommended for patients with advanced CKD in order to optimize the immunological response. As the number of breakthrough SARS-CoV-2 infections was low, we cannot yet provide information of the impact of different vaccines on the occurrence of Covid-19 in advanced CKD patients. In this regard, in some vulnerable cohorts BNT162b2 has been suggested to limit the risk of vigorous vaccine reactions.

To our knowledge, our study is the first to also analyse non-dialysis CKD patients in comparison with patients on kidney replacement therapy. Interestingly, and despite the low GFR of this subgroup, they displayed a very high rate of humoral response after completing the full vaccination schedule. Although uremia alters humoral immunity, our data suggest that, at least in the short-term, non-dialysis CKD patients have higher seroconversion rates than CKD patients on kidney replacement therapy[19]. As previously demonstrated, PD and HD patients also reached high rates of seroconversion[4]. Interestingly, the stratified analysis according to previous SARS-CoV-2 exposure shows differences in antibody production in the different subgroups. Specifically, HD patients and KT recipients without prior SARS-CoV-2 infection developed significantly lower anti-Spike antibodies responses, suggesting higher risk for post-vaccine Covid-19 infection[20]. Indeed, asymptomatic SARS-CoV-2 infections seem to be an important trigger for higher humoral response to vaccines. Thus, around 50% of participants with baseline anti-Spike antibodies lacked a history of diagnosed Covid-19. This important rate of asymptomatic Covid-19 should alert about the need for maintaining monitoring and mitigation strategies among high-risk populations with impaired immunological response to vaccines. Our results showed that PD, KT and HD patients with anti-Spike antibodies at baseline developed higher antibody titres after vaccination. In

concordance, in health care professionals, stronger vaccine responses were observed in individuals with prior Covid-19[21]. However, our study also documented that around 33% of participants with a prior diagnosis of Covid-19 had no anti-Spike antibodies at the time of vaccination. We interpret this as a warning sign of waning of the immune response against SARS-CoV-2 in advanced CKD patients over a relatively short period of time (<15 months).

Serious adverse events that investigators considered related to the Covid-19 vaccine were registered in two patients. Both were cardiovascular events, one stroke and one myocardial infarction. Although cardiovascular events have been described after SARS-CoV-2 vaccination, the potential causality is unclear, given the high risk of cardiovascular events in CKD patients[22].

Some limitations should be acknowledged. First, the small sample size of patients with measured anti-Spike antibodies, as at the planned interim analyses antibody results were available for 301 patients. This has prevented a subanalysis on the impact of factors such as dialysis efficacy. However, the information obtained is clinically relevant regarding short-term serological responses. These results are of especial interest for developing a "nephrological" common strategy in the recommendation of booster doses of vaccines, mainly to KT recipients. In this regard, the similarity of immunosuppressive regimens for KT recipients, precluded the analysis of the impact of different treatment schedules on humoral responses. Second, cellular immunity was not assessed. However, assessment of cellular immunity is unlikely to be available in routine clinical care in the near future. Thus, assessing antibody responses may provide more clinically relevant information. Third, in this first report of SENCOVAC study,

follow-up was short. This may condition the evaluation of the immediate humoral response in patients with delayed seroconversion (such as hemodialysis patients)[23]. Additionally, the dose and interval between doses of both mRNA vaccines is different, and this may impact on the dynamics of antibody development. Finally, this was an observational study. However, the choice of vaccine type was randomly dependent on availability of specific vaccine types for different regions and decided by public health officials unrelated to study participants.

In conclusion, SENCOVAC demonstrates that HD, PD and non-dialysis CKD patients develop a robust early humoral response after SARS-CoV-2 vaccine, especially if they had previous Covid-19. In contrast, KT patients present lower rates of seroconversion and anti-Spike antibody titres at 28 days suggesting that they may benefit from higher isolation measures and booster doses of vaccines. Other CKD patients may benefit from individual monitoring (including assessment of antibody titres) to assess the need for a booster dose if these are not provided to all high-risk individuals by the local health system. Safety and tolerability are acceptable in all the studied CKD cohorts. Hypothesis-generating data suggest a stronger immune response to mRNA-1273 vaccines in advanced CKD patients that should be confirmed in prospective studies and longer-term follow-up of the present cohort. This information would be especially relevant for vaccination and booster vaccines for KT recipients.

CONFLICT OF INTEREST FORM

MJ. Soler reports honorarium for conferences, consulting fees and advisory boards from Astra Zeneca, NovoNordsik, Esteve, Vifor, Bayer, Mundipharma, Ingelheim Lilly, Jansen, ICU Medical, and Boehringer. B. Quiroga has received honoraria for conferences, consulting fees and advisory boards from Vifor-Pharma, Astellas, Amgen, Bial, Ferrer, Novartis, AstraZeneca, Sandoz, Laboratorios Bial, Esteve, Sanofi-Genzyme, Otsuka. A. Ortiz has received consultancy or speaker fees or travel support from Astellas, Astrazeneca, Amicus, Amgen, Fresenius Medical Care, Bayer, Sanofi-Genzyme, Menarini, Kyowa Kirin, Alexion, Otsuka and Vifor Fresenius Medical Care Renal Pharma and is Director of the Catedra Mundipharma-UAM of diabetic kidney disease and the Catedra Astrazeneca-UAM of chronic kidney disease and electrolytes. C.J. Jarava Mantecón has received honoraria for one conference from Vifor-Pharma. P. de Sequera reports honorarium for conferences, consulting fees and advisory boards from Amgen, Astellas, Astra Zeneca, Baxter, Braun, Fresenius, Nipro, Vifor-Pharma. S. Martinez Vaquera, G. Useche, M.G. Sánchez Márquez, M. Carnerero, MT. Jaldo Rodríguez, P. Muñoz Ramos, JC. Ruiz San Millán, N. Toapanta, C. Gracia-Iguacenl, M.C. Aguilar Cervera, N. Balibrea Lara, A. Leyva, J. Rojas and RT. Gansevoort do not present conflict of interests.

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APPENDIX

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Table 1. Baseline characteristics of participants

	Total (n=1746)	KT (n=283)	PD (n=171)	HD (n=1116)	CKD (n=176)	p
Sex (male), n (%)	1092 (62)	171 (60)	100 (58)	719 (64)	102 (58)	0.170
Age (years)	64 (13)	56 (13)	60 (14)	65 (12)	64 (14)	<0.001
Diabetic kidney disease, n (%)	369 (22)	10 (4)	37 (22)	280 (25)	42 (26)	<0.001
Hemodialysis technique, n (%)		---	---		---	---
- HFHD	486 (44)			486 (44)		
- HDx	39 (3)			39 (3)		
- OL-HDF	589 (53)			589 (53)		
Vascular access, n (%)		---	---		---	---
- AVF	696 (64)			696 (64)		
- Catheter	394 (36)			394 (36)		
Immunosuppression, n (%)			---	---	---	---
- Steroids	182 (64)	182 (64)				
- Calcineurin inhibitors	216 (73)	216 (73)				
- Mycophenolate mofetil	200 (71)	200 (71)				
- mTORi	46 (16)	46 (16)				
- Azathioprine	9 (3)	9 (3)				
Anticoagulants, n (%)	270 (15)	23 (8)	28 (16)	190 (17)	29 (16)	0.003
Antiplatelet agents, n (%)	627 (36)	76 (27)	56 (31)	435 (39)	63 (36)	0.001
RAASi, n (%)	584 (33)	128 (45)	89 (52)	300 (27)	67 (38)	<0.001
ESA, n (%)	1105 (63)	42 (15)	111 (65)	853 (77)	99 (56)	<0.001
Vaccine, n (%)						<0.001
- BNT162b2	511 (29)	54 (19)	26 (15)	331 (30)	100 (57)	
- mRNA-1273	1202 (69)	225 (79)	142 (83)	766 (69)	69 (39)	
- ChAdOx1-S	25 (1)	4 (1)	3 (2)	15 (1)	3 (2)	
- Ad26.COV.2	8 (1)	0 (0)	0 (0)	4 (0)	4 (2)	
Previous Covid-19, n (5)	162 (9)	17 (6)	20 (12)	117 (10)	8 (4)	0.051
Baseline anti-Spike Ab +, n (%)	69 (23)	13 (30)	11 (21)	37 (21)	8 (29)	0.124
Hemoglobin (g/dL)	11.6 (10.7-12.6)	13.3 (11.9-14.7)	11.4 (10.6-12.4)	11.3 (10.5-12.2)	11.6 (10.7-12.4)	0.002
Leukocyte (10^3/mm^3)	6.5 (5.3- 8.0)	6.9 (5.6-8.9)	6.8 (5.5-8.0)	6.0 (4.9-7.7)	7.0 (6.1-10.7)	<0.001
Lymphocytes (10^3/mm^3)	1.3 (1.0-1.8)	1.8 (1.3-2.6)	1.4 (1.0-1.8)	1.3 (0.9-1.9)	1.6 (1.2-2.7)	<0.001
Albumin (g/dL)	3.9 (3.6-4.2)	4.2 (3.9-4.5)	3.6 (3.3-3.9)	3.9 (3.6-4.1)	4.0 (3.6-4.3)	<0.001
Prealbumin (mg/dl)	27 (22-32)	27 (21-33)	30 (26-36)	26 (22-30)	28 (22-34)	<0.001
C-reactive protein (mg/l)	0.5 (0.2-1.5)	1.1 (0.3-3.8)	1.1 (0.3-3.2)	3.9 (1.0-10.3)	1.0 (0.2-3.0)	0.006
eGFR (min/min/1.73 m^2)	36 (14-62)	49 (35-66)	---	---	13 (9-21)	<0.001*
Influenza vaccine, n (%)	1274 (73)	218 (77)	117 (68)	831 (75)	108 (61)	0.001
Anti-HBs, n (%)	710 (64)	40 (33)	83 (77)	524 (67)	63 (59)	<0.001

*Abbreviations: PD: peritoneal dialysis, KT: kidney transplant, HD: hemodialysis, CKD: chronic kidney disease, HFHD: high flux hemodialysis, HDx: expanded hemodialysis therapy, OL-HDF: online hemodiafiltration, AVF: arteriovenous fistulae, mTORi: mammalian target of rapamycin inhibitors, RAASi: renin-angiotensin-aldosterone inhibitors, Covid-19: coronavirus disease-19, eGFR: estimated glomerular filtration rate, Ab: antibodies. *eGFR difference between KT and non-dialysis CKD.*

Table 2. Baseline characteristics regarding the type of mRNA vaccine in safety and humoral response evaluation population. Safety population included patients included in the study. Humoral response evaluation population included patients with tested anti-Spike antibodies.

	SAFETY POPULATION			HUMORAL RESPONSE EVALUATION POPULATION		
	BNT162b2 (n=511)	**mRNA-1273 (n=1202)**	**P**	**BNT162b2 (n=65)**	**mRNA-1273 (n=236)**	**P**
Sex (male), n (%)	315 (62)	755 (63)	0.041	45 (69)	165 (70)	0.915
Age (years)	68 (13)	60 (13)	<0.001	65 (15)	61 (12)	0.018
Diabetic kidney disease, n (%)	113 (23)	246 (22)	0.495	12 (18)	61 (27)	0.349
Hemodialysis technique, n (%)			<0.001			0.931
- HFHD	103 (31)	375 (49)		7 (21)	34 (24)	
- HDx	15 (5)	24 (3)		1 (3)	4 (3)	
- OL-HDF	212 (64)	366 (48)		26 (76)	106 (74)	
Vascular access, n (%)			0.310			0.681
- AVF	197 (60)	487 (66)		20 (59)	78 (55)	
- Catheter	132 (40)	255 (34)		14 (41)	64 (45)	
Immunosuppression, n (%)						
- Steroids	41 (8)	217 (18)	<0.001	13 (20)	37 (16)	0.407
- Calcineurin inhibitors	42 (8)	188 (16)	<0.001	13 (20)	27 (11)	0.097
- Mycophenolate mofetil	38 (7)	173 (14)	0.001	11 (17)	29 (12)	0.311
- mTORi	9 (2)	38 (3)	0.306	1 (1)	5 (2)	1.000
- Azathioprine	2 (0)	9 (1)	0.815	1 (1)	2 (1)	0.519
Anticoagulants, n (%)	91 (18)	178 (15)	0.089	17 (26)	34 (14)	0.038
Antiplatelet agents, n (%)	188 (37)	425 (35)	0.789	26 (40)	83 (35)	0.471
RAASi, n (%)	156 (30)	416 (35)	0.109	23 (35)	109 (46)	0.158
ESA, n (%)	354 (69)	729 (61)	0.003	41 (63)	160 (68)	0.552
CKD cohort, n (%)			<0.001			0.002
- KT	54 (11)	225 (19)		12 (18)	31 (13)	
- DP	26 (5)	142 (12)		6 (9)	46 (19)	
- HD	331 (65)	766 (64)		34 (52)	144 (61)	
- CKD	100 (20)	69 (6)		13 (20)	15 (6)	
Previous Covid-19, n (5)	33 (6)	127 (11)	0.037	2 (3)	51 (22)	0.001
Baseline anti-Spike Ab +, n (%)	----	----	---	12 (18)	57 (24)	0.585
Influenza vaccine, n (%)	349 (68)	901 (75)	0.011	54 (83)	165 (70)	0.041
Anti-HBs, n (%)	229 (63)	465 (64)	0.612	36 (64)	120 (60)	0.856

Abbreviations: KT: kidney transplant, PD: peritoneal dialysis, HD: hemodialysis, CKD: chronic kidney disease, HFHD: high flux hemodialysis, HDx: expanded hemodialysis therapy, OL-HDF: online hemodiafiltration, AVF: arteriovenous fistulae, mTORi: mammalian target of rapamycin inhibitors, RAASi: renin-angiotensin-aldosterone inhibitors, Covid-19: coronavirus disease-19.

Table 3. Independent predictors for the development of humoral response.

	OR (95%CI)	P
Age (years)	1.04 (0.96-1.13)	0.318
Gender (male)	1.78 (0.38-8.32)	1.781
Baseline anti-Spike Ab +	0.47 (0.16-1.38)	0.170
Influenza vaccine	1.00 (1.00-1.00)	0.729
Type of patient (KT vs others)	20.56 (3.24-130.45)	0.001
BNT162b2 vaccine	6.03 (1.28-28.23)	0.023

Abbreviations: OR: odds ratio, Ab: antibodies, KT: kidney transplant.

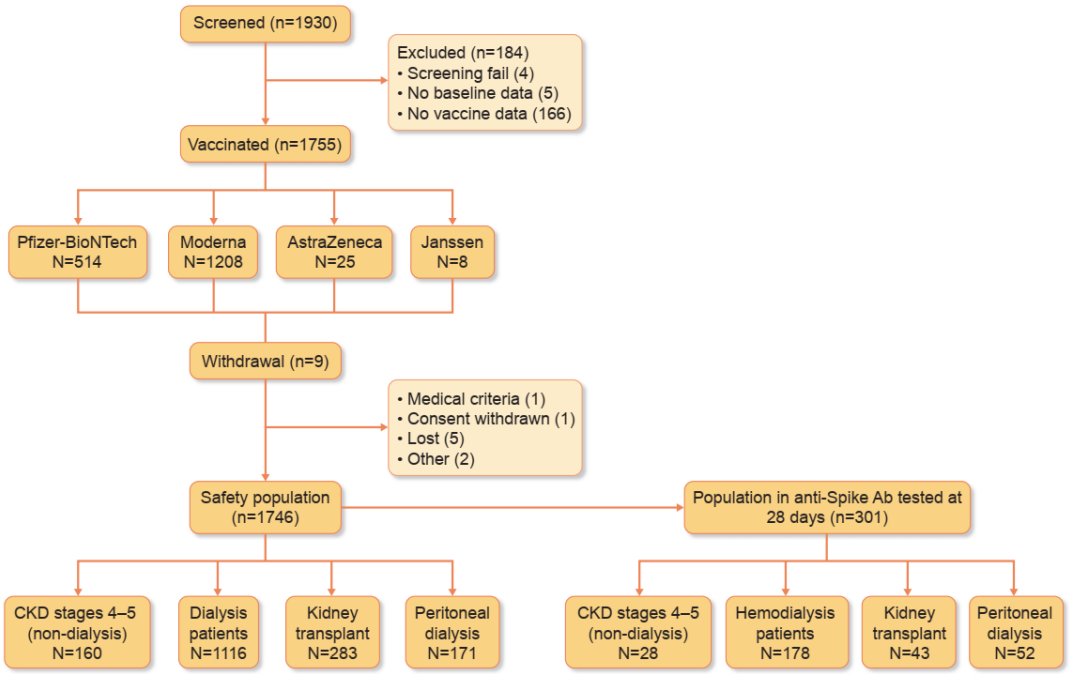

Figure 1. Participant flow chart. The humoral response evaluation population represents the first 301 patients with anti-Spike antibody results at 28 days after completing the vaccination schedule.

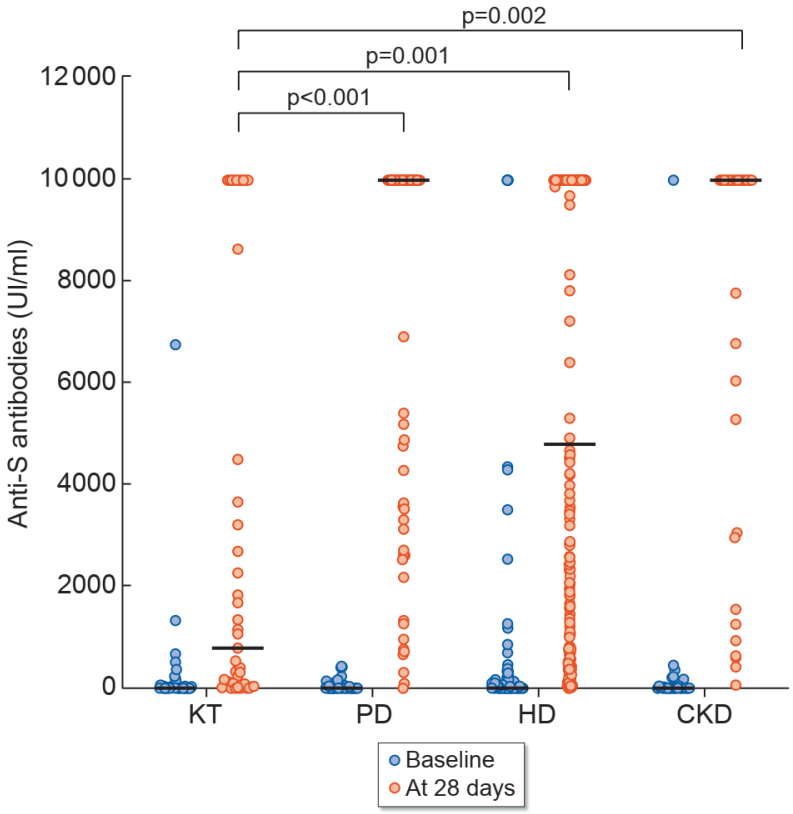

Figure 2. Titer of anti-Spike antibody titers at baseline and 28 days after completing vaccination in kidney transplant recipients (KT), persons on peritoneal dialysis (PD) or hemodialysis (HD) and persons with CKD not on dialysis (CKD). Data are for all participants, independently of a history of Covid-19 or baseline presence of anti-Spike antibodies.

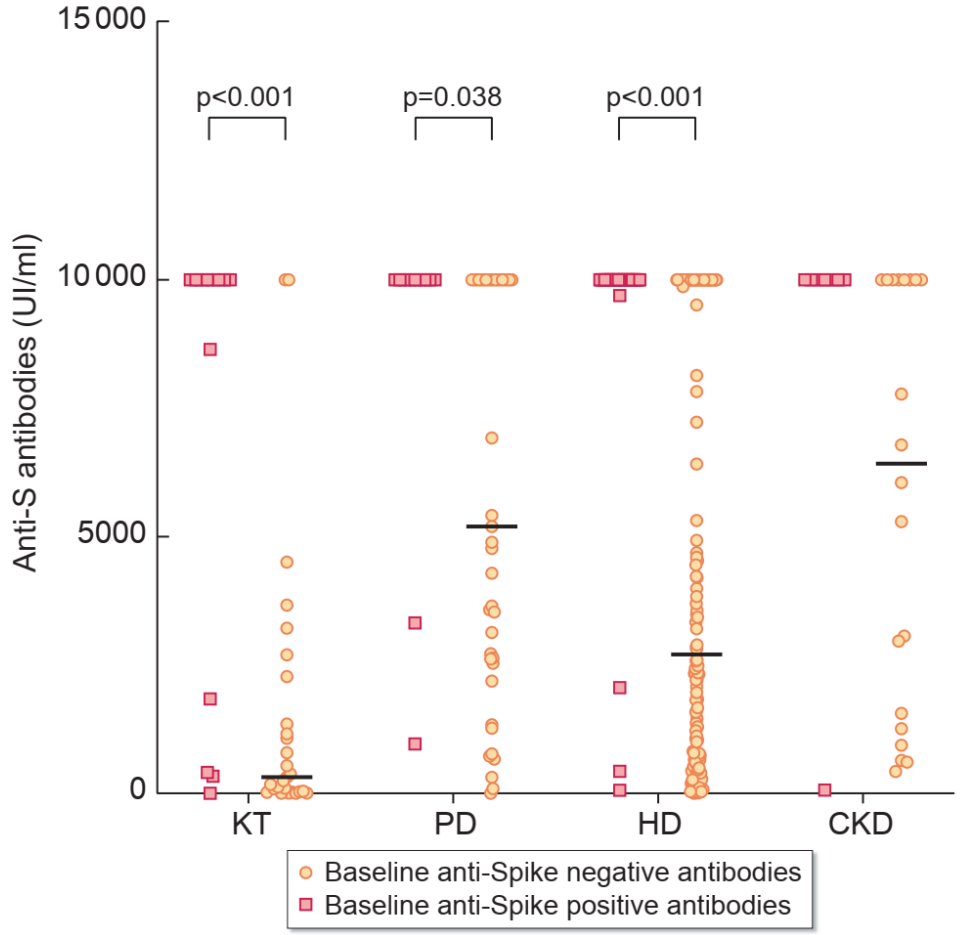

Figure 3. Anti-Spike antibodies 28 days after completing vaccination in kidney transplant recipients (KT), persons on peritoneal dialysis (PD) or hemodialysis (HD) and persons with CKD not on dialysis according prior Covid-19 history. Data are for all participants, independently of baseline presence of anti-Spike antibodies.

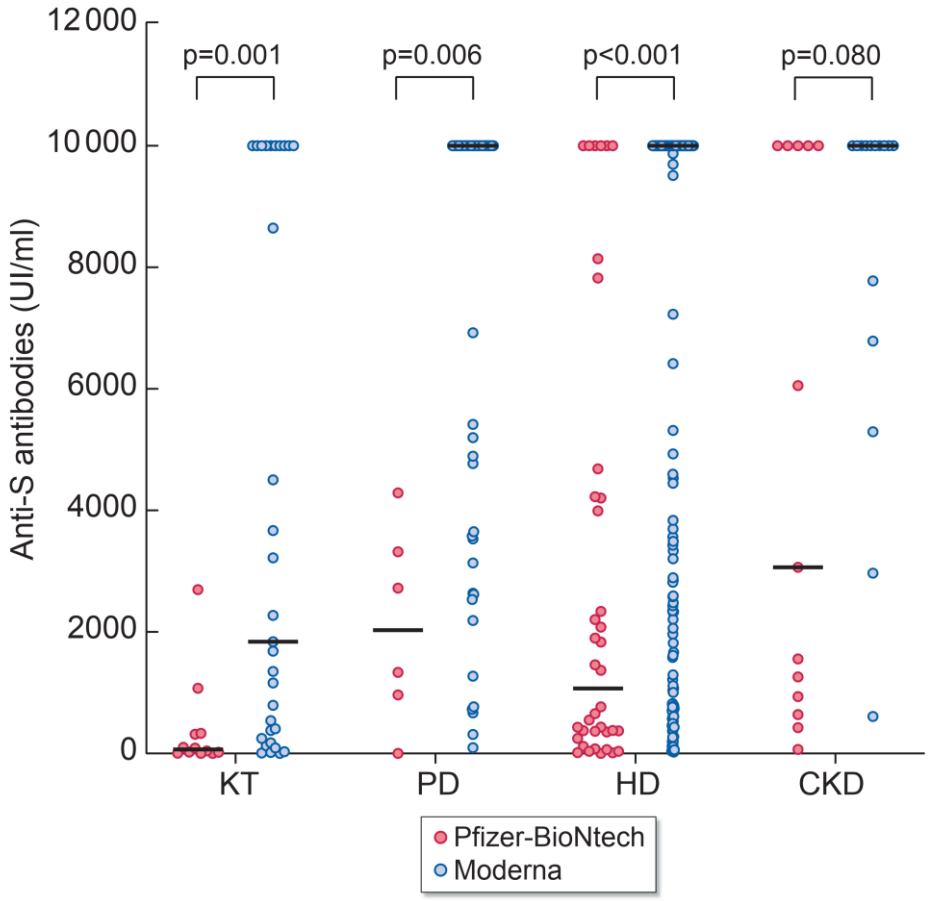

Figure 4. Anti-Spike antibodies 28 days after completing vaccination in kidney transplant recipients (KT), persons on peritoneal dialysis (PD) or hemodialysis (HD) and persons with CKD not on dialysis according the received vaccine (Pzifer [BNT162b2] or Moderna [mRNA-127]). Data are for all participants, independently of baseline presence of anti-Spike antibodies.