

Incidence of adverse events of the Covid-19 vaccine in a population of kidney transplant recipients

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ABSTRACT

Introduction: Early published series suggest that most renal transplant recipients remain at high risk of SARS-CoV-2 infection due to poor humoral response after vaccination. The aim was to study the occurrence of adverse events after two doses of mRNA-1273 vaccine in a population of renal transplant recipients.

Material and Method: Analytical, observational, and prospective study. Subjects were injected with two doses of mRNA-1273 vaccine against SARS-CoV-2 according to the schedule established by the laboratory. After injection of each dose, and up to 72 hours later, participants recorded local and/or systemic symptoms and their intensity.

Results: 187 patients were included. Eighteen percent of them became infected with SARS-CoV-2 in the pre-vaccination period or between the 1st and 2nd dose. The incidence of adverse events was 91.2%. Of these, the incidence of local (62%) was higher than that of systemic (55%). Past infection was a risk factor for the occurrence of local adverse events after vaccination (OR=2.4; p=0.045). The same association was detected for systemic adverse events, which were more frequent among those who had passed the disease (OR=3.83; p=0.003).

Conclusions: The mRNA-1273 vaccine does not appear to cause serious side effects. The incidence of local and systemic adverse events was higher in those patients with past disease.

Keywords: renal transplantation; mRNA-1273 vaccine; SARS-CoV-2 adverse reactions.

RESUMEN

Incidencia de eventos adversos de la vacuna frente a SARS CoV-2 en una población de receptores de trasplante renal

Introducción: Las primeras series publicadas sugieren que la mayoría de los receptores de trasplante renal siguen teniendo un alto riesgo de infección por SARS-CoV-2 debido a una pobre respuesta humoral tras la vacunación. El objetivo fue estudiar la presencia de eventos adversos tras 2 dosis de vacuna mRNA-1273 en una población de trasplantados renales.

Material y Método: Estudio analítico, observacional y prospectivo. A los sujetos se les inyectó dos dosis de la vacuna mRNA-1273 frente al SARS-CoV-2 según pauta establecida por el laboratorio. Tras la inyección de cada una de las dosis, y hasta las 72 horas posteriores, los participantes llevaron a

cabo un registro de síntomas locales y/o sistémicos y la intensidad de los mismos.

Resultados: Se incluyeron 187 pacientes. Un 18% de ellos se infectaron de SARS-CoV-2 en el periodo prevacunación o entre la 1ª y 2ª dosis. La incidencia de eventos adversos fue de 91,2%. De ellos, la incidencia de los locales (62%) fue mayor que la de sistémicos (55%). Haber pasado la infección fue un factor de riesgo de aparición de eventos adversos locales tras la vacunación (OR=2,4; p=0,045). La misma asociación fue detectada en el caso de eventos adversos sistémicos, que fueron más frecuentes entre los que habían pasado la enfermedad (OR=3,83; p=0,003).

Conclusiones: La vacuna de mRNA-1273 no parece provocar efectos secundarios graves. La incidencia de eventos adversos locales y sistémicos fue mayor en aquellos pacientes que habían pasado la enfermedad.

Palabras clave: trasplante renal; vacuna mRNA-1273; SARS-CoV-2 reacciones adversas.

INTRODUCTION

The SARS-CoV-2 virus emerged in the city of Wuhan, China back in December 2019 and spread creating a global health crisis with vaccination being the only hope to control the pandemic¹. Despite being an unknown virus until its appearance, vaccines with almost 100% efficacy have been developed to prevent moderate and severe disease in 90% of the overall population².

In patients with kidney disease, all-cause infection remains one of the most common causes of morbidity and mortality. Changes in the immune system explain the increased risk associated with this population³.

Solid organ transplant recipients have been excluded from vaccine clinical trials on purpose. It is likely that the immune response could be significantly compromised by their underlying primary comorbid conditions and immunosuppressive treatments received⁴. Scientific medical societies have recommended vaccination against SARS-CoV-2 for these patients, and the studies published to this date have found evidence that a significant number of kidney transplant recipients still has a high risk of SARS-CoV-2 infection and moderate-to-severe disease due to a deficient humoral response².

The safety of vaccines is well established with a solid base of scientific evidence from clinical trials conducted prior to their commercialization and quality controls^{5,6}. However, like any medication, vaccines can have unintended and harmful adverse effects that can occur coincidentally with the compatible temporal sequence following vaccine administration. Establishing causality in the occurrence of

local adverse reactions is often straightforward. However, this is not always the case with systemic reactions^{7,8}.

Therefore, a concern that has particularly worried transplant teams is the possibility that these new mRNA vaccines could alter graft functionality or cause severe side effects. Some authors have described that symptoms following vaccine administration in this population are similar to those of the overall population. Also, no safety issues contraindicating their administration have been identified⁹. However, information is still limited, and therefore, studying systemic and local reactions due to SARS-CoV-2 vaccination in transplant patients will help increase confidence in vaccination for both the healthcare personnel and patients who still remain hesitant to be vaccinated.

Therefore, the objective of this research was to study the safety of mRNA-1273 vaccine (Moderna) against SARS-CoV-2, evaluate the presence of adverse effects and the possible impact on renal function.

MATERIAL AND METHOD

Study Design and Participants

This was an analytical, observational, and prospective cohort study conducted in a tertiary hospital of the Community of Madrid, Spain.

The study was proposed to 211 patients with a functioning kidney transplant who received the SARS-CoV-2 vaccine between March 19th and April 24th, 2021. Ultimately, a total of 187 individuals who agreed to participate and undergo post-vaccination follow-up were included. Patients with active tumors and those experiencing SARS-CoV-2-like symptoms at the time of vaccination were excluded.

Study procedure

The subjects received 2 doses of the mRNA-1273 vaccine against SARS-CoV-2 following the pattern established by the laboratory that consisted of an injection on day 0 and a second dose 28 days later. The center sent a text message to all transplant recipients indicating the date and time for vaccination. Researchers, by the way, were not responsible for the selection process.

Following each dose, and up to 72 hours afterward, participants recorded symptoms, both local and systemic, on a questionnaire specifically designed for this purpose. After obtaining informed consent, the responsible nephrologist provided the patient with the registration form, and the nurse at the Renal Transplant Clinic collected the results during the patient's next visit. For each adverse event (AE), the onset time and intensity were recorded using a numerical scale from 1 to 3 being, 1 indicative of the lowest intensity and 3 the more. The local AEs recorded included pain, redness, swelling, and itching all at the injection site, axillary lymphadenopathy or swelling of neck/clavicle lymph nodes. Systemic AEs were classified as fever or low-

grade fever, headache, fatigue, digestive symptoms, myalgia, chills, general malaise, and dizziness or hypotension, as well as other unexpected symptoms.

Regarding the analysis of results, a database was created including the AEs and the following variables: comorbidities (like hypertension, diabetes), sociodemographic factors (age, sex), transplant-related factors (years since kidney transplantation, immunosuppressive treatment received, glomerular filtration rate measured by CKD-EPI prior to vaccination), and vaccination-related factors (prior SARS-CoV-2 infection before or during the vaccination process, positive humoral immune response defined as IgG titers in blood ≥ 50 AU/mL, and positive cellular response, CD4 and/or CD8).

Statistical Analysis

Quantitative variables were expressed as mean and standard deviation if they followed a normal distribution or with as median and interquartile range in cases of skewed distribution. Qualitative variables were expressed using percentages and total values. For the analysis of quantitative variables, the Student t test was used, and for the analysis of qualitative variables, the chi-square test was used. Finally, logistic regression was used for multivariate analysis to examine the relationship between each study variable and the occurrence of adverse events. The statistical analysis of results was performed using SPSS 26.0 statistical software package for Windows.

Ethical Considerations

Participation in the study was voluntary, and participants could withdraw their consent and leave the study at any time without this having any impact on their medical care relationship.

The project was conducted based on the latest version available of the Helsinki Declaration and the Good Clinical Practice Guidelines of the International Conference on Harmonization (GCP/ICH).

All personal data were identified with a code, and only the researcher could associate the data available with the patient and their medical history.

The data described in this study are part of a protocol that has been approved by Hospital Clínico San Carlos Ethics Committee.

RESULTS

The patients included had a mean age of 58.3 ± 13.4 years (61.2% were man; $n=114$).

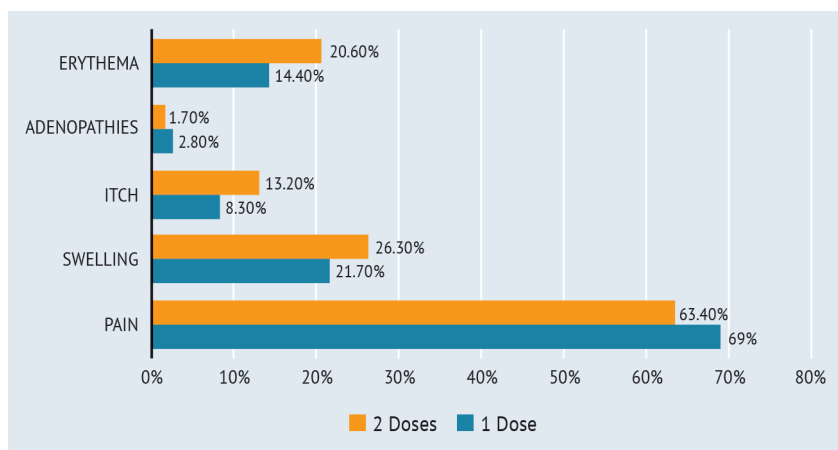


Figure 1. Rate of local adverse events.

The median time elapsed since transplantation was 9.6 years (IQR, 5.07-15). Among them, 18% ($n=34$) were infected with SARS-CoV-2 in the pre-vaccination period. A total of 92.8% ($n=178$) of the patients had hypertension, and 28.9% ($n=54$) diabetes. The mean glomerular filtration rate measured by CKD-EPI before and after vaccination was $50.78 (\pm 21.48)$ mL/min/ 1.73 m^2 and $53.33 (\pm 27.75)$ mL/min/ 1.73 m^2 , respectively ($P=0.98$).

The overall rate of adverse events was 91.2% ($n=165$) with local events ($n=151$; 80.8%) being more common compared to systemic events ($n=114$; 60.8%).

Among the reported local AEs, the most common was local pain at the injection site ($n=119$; 64%) followed by swelling ($n=49$; 26.43%) and redness in the region of interest ($n=26$; 14.44%). The frequency of pain and erythema increased from the first to the second dose as shown in figure 1 while itching, swelling, and lymphadenopathy decreased as seen in figure 1.

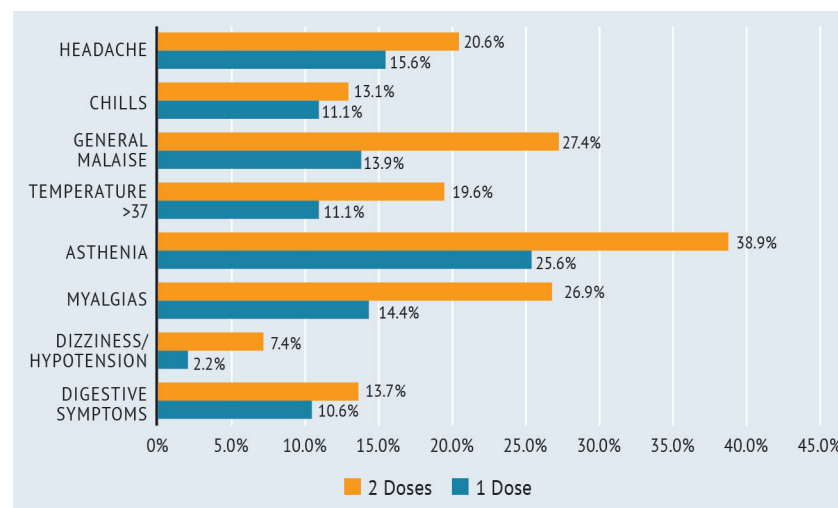


Figure 2. Rate of systemic adverse events.

Table 1. Relation of the comorbidities with the appearance of local and systemic adverse reactions.

		SYSTEMIC DRUG ADVERSE REACTIONS N (%)	P	LOCAL DRUG ADVERSE REACTIONS N (%)	P
Diabetes Mellitus	YES	26 (44.1)	0.952	45 (40.5)	0.134
	NO	49 (44.5)		31 (52.59)	
Ischemic heart disease	YES	5 (41.7)	0.800	3 (25)	0.118
	NO	70 (45.5)		75 (48.4)	
Hepatopathy	YES	1 (33.3)	0.689	3 (25)	0.105
	NO	71 (44.9)		75 (47.2)	
Stroke	YES	1 (33.3)	0.677	1 (33.3)	0.639
	NO	74 (45.9)		77 (47)	
Vasculopathy	YES	2 (28.6)	0.367	2 (28.6)	0.326
	NO	73 (45.9)		76 (47.5)	

Among the systemic AEs, the most commonly reported ones were asthenia (n=73; 39.06%) and myalgia (n=50; 27.1%). Systemic AEs were more frequent after the administration of the second dose compared to the first one as seen on **figure 2**. In the univariate analysis, a significant difference was seen based on age such that a higher number of years was associated with a lower number of systemic reactions in the population studied (P=0.022).

Also, an association was also found between the rate of AEs and prior infection with SARS-CoV-2: the percentage of local effects, in general, was higher among those who had a previous infection (n=120; 64%) compared to those who had not been infected at all (n=88; 47.5%). Therefore, prior infection was

Table 2. Association between sociodemographic and renal function variables and the appearance of systemic adverse reactions.

		SYSTEMIC DRUG ADVERSE REACTIONS N (%)	P	LOCAL DRUG ADVERSE REACTIONS N (%)	P
Age; mean ± standard deviation		60.49 (±13.2)	0.022	58.81 (±13.2)	0.533
Sex; N (%)	Men	33 (41.8)	0.410	37 (45.7)	0.084
	Women	56 (58.2)		44 (54.3)	
CKD -EPI; mean ± standard deviation		49.87 (±21.31)	0.837	49.79 (±19.67)	0.798

CKD-EPI Equation for Glomerular Filtration Rate.

a risk factor for the occurrence of local AEs after vaccination (OR, 2.4; 95%CI, 1.00-5.78; P=0.045). The same association was seen for systemic AEs, which were more common among those who had previously had the disease (OR, 3.83; 95%CI, 1.51-9.7; P=0.003).

In the multivariate analysis, prior COVID infection remained significantly associated with systemic AEs (OR, 3.42; 95%CI, 1.33-8.77; P=0.011), while age approached the significance threshold (OR, 0.97; 95%CI, 0.95-1.00; P=0.051) (**table 1** and **table 2**).

Following the administration of both doses, local AEs were more common compared to the systemic ones as shown on **figure 4**.

Finally, the relationship between local and systemic AEs with the development of humoral and cellular immunity post-vaccination was studied. However, no statistically significant differences were found as shown in **figure 5** and **figure 6**.

DISCUSSION

The unique circumstances surrounding the renal transplant process like associated comorbidities and immunosuppression put transplant recipients at a higher risk for developing severe disease from SARS-CoV-2¹⁰. Therefore, effective and safe vaccination is considered crucial in this population.

Back in 2021, Spanish health authorities recommended a three-dose regimen of mRNA vaccines against SARS-CoV-2 for immunocompromised individuals assuming a lower immunogenicity to these vaccines in solid organ transplant recipients compared to the overall population¹².

Regarding the sociodemographic variables of the study sample, they are consistent with those of former studies conducted on renal transplant recipients in the Spanish population¹³. This suggests that the findings associated with adverse reactions to the vaccine in this study could be extrapolated to the renal transplant population.

The data from this research show an association between age and the number of systemic adverse reactions reported. This finding is consistent with the data reported for the overall population in the pharmacovigilance report issued by the Spanish Agency of Medicines and

Medical Devices (AEMPS)¹⁴ regarding COVID-19 vaccines. It indicates that overall adverse reactions were reportedly 10 times more common in individuals under 65 years of age and 3 times more common in women. These differences may be attributed to immune, genetic, and hormonal factors¹⁵, although no gender differences were found in our study.

Regarding immunosuppressive treatment of transplant recipients included in the study, the data are very much consistent with those reported in the study conducted by López-Oliva et al¹⁶. The approaches followed for cases of SARS-CoV-2 infection were similar among the different Spanish hospitals involved since with mild symptoms treatment was not warranted. However, as the infection grew adjustments were made based on the patient's needs.

During the vaccination process against SARS-CoV-2, it has been reported that mRNA vaccines can cause mild to moderate side effects with local adverse events (AE) being predominant. The most common local AE reported is pain at the injection site, which is consistent with the findings of this research¹³.

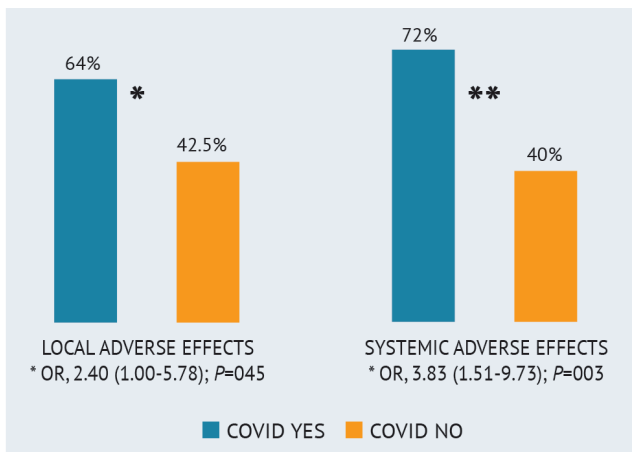


Figure 3. Relation between local and systemic adverse events and prior COVID-19 infection.

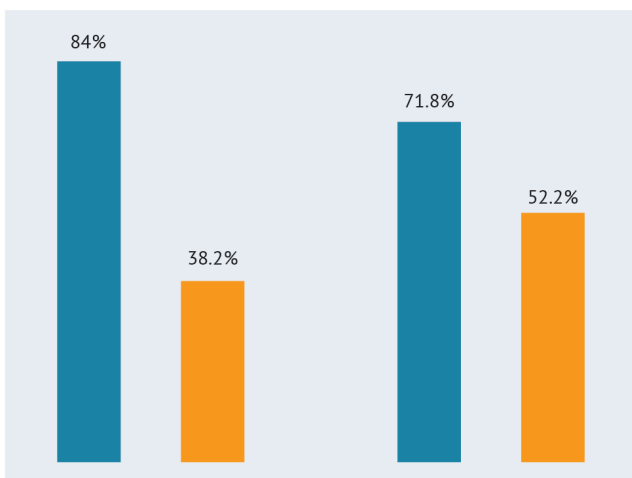


Figure 4. Percentage of local and systemic events after each dose.

The rate of AEs in the study population increased from the first to the second dose as observed in the investigation conducted by Massa et al¹³. However, other studies have reported that reactogenicity with booster doses was higher especially regarding systemic adverse effects¹⁷. This is consistent with the results found in our study as shown in **figure 2**.

The findings of our study are similar to those reported in clinical trials of the BNT1162b and mRNA-1273 vaccines being pain at the injection site and asthenia two of the most commonly reported symptoms in healthy adults just like in our study population¹⁸.

Overall, the adverse reactions reported by the patients in this study are similar to those reported in the general population by the AEMPS¹⁴. However, there is a discrepancy in the percentages of symptom presentation being systemic AEs (headache [21%], fever [33%], and myalgia [15%]) more prevalent in the overall population and local AEs (pain at the injection site reported by 13% of the sample) more prevalent in renal transplant recipients. The reason for this difference may be attributed to the method of information collection, as our study methodology relied on a questionnaire while the data reported by the AEMPS come from pharmacovigilance changes that may not be as comprehensive.

In this study, no significant safety issues like myocarditis or neurological symptoms were observed, which is somehow similar to what has been reported in clinical trials and vaccine registries of mRNA-based COVID-19 vaccines^{19,20}.

In the study conducted by Connolly et al²¹, patients on immunosuppressive therapies for rheumatic and musculoskeletal diseases who received the BNT162b2 or mRNA-1273 vaccine reported that 69% of participants experienced, at least, one systemic side effect being fatigue the most commonly reported symptom, and 86% reporting local symptoms being pain at the injection site the most prevalent of all. These results are consistent in terms of percentages (62% for local AEs and 55% for systemic AEs) and symptomatology with those found in our study. This coincidence may be due to both studies being conducted in immunocompromised patients. However, these data were only collected after the first vaccine dose and were obtained through a questionnaire from those who voluntarily decided to participate, which could introduce information bias.

In the study conducted by Fernández Prada M.²² that focused on the safety and efficacy profile of other vaccines administered to immunocompromised patients, the rate of AEs was higher with inactivated virus vaccines at around 88.7%. Regarding the percentage of adverse event reports, 35.8% were local, 49.1% systemic, and 15.1% both types. The difference with the results found in our study could be attributed to the type of vaccine and the specific dosing regimen administered to the patients. However, the symptoms reported by the patients were similar being pain and fever the most commonly described symptoms of all²².

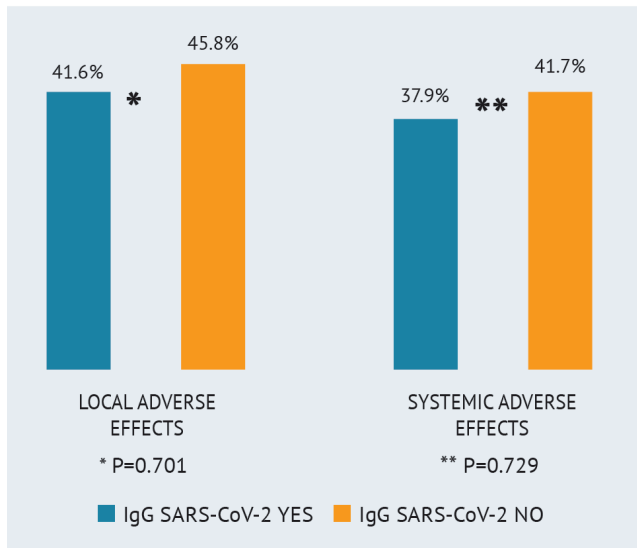


Figure 5. Relation between local and systemic adverse events and development of humoral immunity post-vaccination.

The main strengths of our study include a representative sample of the renal transplant population as participation was offered to all vaccinated patients. Also, the rate of refusal was low. The information was collected thoroughly using a specifically designed questionnaire. However, a major limitation is that it is a single-center study.

CONCLUSIONS

The conclusions drawn from the results obtained in this study are of great relevance to the medical community, as they provide crucial data on the frequency of adverse events caused by the SARS-CoV-2 vaccine in kidney transplant patients. Systemic and local adverse events were found to be significantly more frequent in subjects who had previously been infected with SARS-CoV-2. Additionally, the rate of systemic adverse events was higher in younger patients, showing a significant association. In our sample, vaccination mostly resulted in local adverse events, which is consistent with the overall population.

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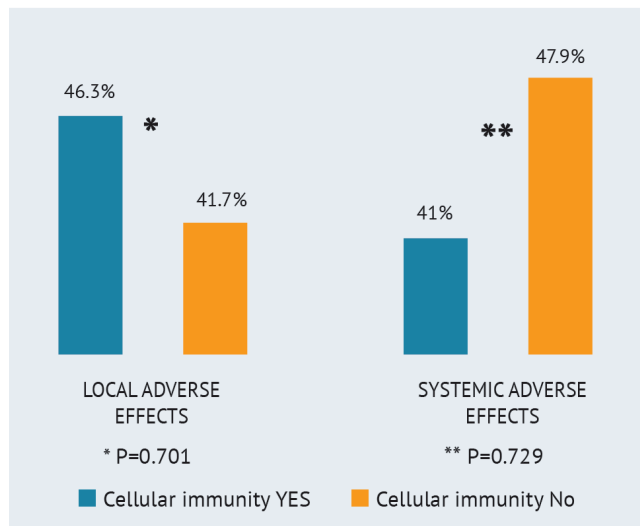


Figure 5. Relation between local and systemic adverse events and development of humoral immunity post-vaccination.

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