Haemodialysis patients show a highly diminished antibody response after COVID-19 mRNA vaccination compared to healthy controls

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ABSTRACT

Background. Haemodialysis (HD) patients are exposed to a high risk due to the SARS-CoV-2 pandemic. They are prone to acquiring the infection and are threatened by high mortality rates in case of infection. However, HD patients were not included in the efficacy trials of the SARS-CoV-2 vaccines. Such efficacy data would have been critical because HD patients show decreased responses against various other vaccines and this could translate to the SARS-CoV-2 vaccines as well.

Methods. We conducted a prospective cohort study that contained a group of 81 HD patients and 80 healthy controls. All of them had been vaccinated with the BioNTech/Pfizer mRNA vaccine (two doses, as per the manufacturer's recommendation). The anti-SARS-CoV-2 S antibody response was measured for all participants 21 days after the second dose. The groups were compared using univariate quantile regressions and a multivariate analysis. The adverse events (AEs) of the vaccination were assessed via a questionnaire. Finally, a correlation between the HBs-Antibody response and the SARS-CoV-2 antibody response in the HD patients was established.

Results. The HD patients had significantly lower Anti-SARS-CoV-2 S antibody titres than the control patients 21 days after vaccination (median was 171 U/ml for dialysis patients and 2,500 U/ml for the controls). Further, the HD group presented less AEs than the control group. No correlation was found between the antibody response to previous Hepatitis B vaccination and that of the SARS-CoV-2 vaccine.

Conclusions. HD patients present highly diminished SARS-CoV-2 S antibody titres compared to a cohort of controls. Therefore, they could be much less protected by SARS-CoV-2 mRNA vaccinations than expected. Further studies to test alternative vaccination schemes should be considered.

Keywords: antibodies, dialysis, SARS-CoV-2, vaccination

KEY LEARNING POINTS

What is already known about this subject?

Haemodialysis (HD) patients are vulnerable to SARS-CoV-2 (prone to infection, present high probability of severe disease and show high mortality rates) and are therefore prioritised in vaccination programs. However, no HD patients were included in the efficacy trials of the SARS-CoV-2 vaccines.

What this study adds?

In our study, HD patients showed significantly lower titres than the control group three weeks after the second BNT162b2 dose, which entailed a weaker response to the vaccine. Certain patients also showed a delayed response. We found that HD patients reported fewer adverse events after vaccination than the control group.

What impact this may have on practice or policy?

For HD patients, alternative vaccination schemes must be considered and preventive measures must be maintained after vaccination. Testing for vaccine response should be implemented.

INTRODUCTION

The SARS-CoV-2 pandemic has had, and continues to have, a profound impact on our daily lives and all aspects of medicine[1–3]. Patients who undergo dialysis on a regular basis are especially prone to being infected by the virus due to unavoidable exposure (frequent travel to and from dialysis centres and the procedures performed there[4,5]) and to a severe course of the disease, with a 28-day mortality of up to 16–35%[5–7]. Consequentially, in most countries, dialysis patients are prioritised for receiving vaccines against COVID-19.

One of the first vaccines approved worldwide, BNT162b2 (Comirnaty, Pfizer/BioNTech), was shown to elicit a measurable antibody response in study participants, which correlated with protection from severe disease[8]. A two-dose vaccination regimen was found to reduce the occurrence of severe disease by over 90%[8]. However, no end-stage renal disease patients were included in the associated study, and the efficacy and safety data of this patient group are therefore lacking. These data would have been critical, as dialysis patients showed a decreased response against various other vaccines (e.g., Hepatitis B[9], Pneumococcus[10] or Influenza vaccines[11]). Decisions associated with various factors, such as vaccine schedule and dosing, depend on such data. Therefore, the aim of this study is to measure the antibody response in dialysis patients and compare it to that of a control group of healthy volunteers (healthcare workers). In addition, we will compare the adverse events reported in both cohorts and analyse whether there exists a correlation between the humoral response to the Hepatitis B vaccine and that to BNT62b2.

MATERIALS AND METHODS

We used a prospective cohort study design to elucidate the antibody response upon being vaccinated with BNT162b2 for dialysis patients vs healthy controls.

Study population

Haemodialysis patients were considered eligible if they had been on dialysis for at least three months and had been vaccinated with the mRNA vaccine BNT162b2 (BioNTech/Pfizer Comirnaty™, two doses administered with an interval of 21 days according to the national vaccination schedule). The participants of the healthy control group consisted of volunteer healthcare workers who had been vaccinated using the same regimen. The participants of both groups needed to be 18–99 years old. Pregnant women and individuals who were known to have had the COVID19 infection in the past (diagnosed via patient history and a serological test for nucleocapsid (N) antibodies, see Serological assessment) were excluded from the study. The study protocol was approved by the local ethics committee, and all participants were enrolled after written informed consent had been obtained.

Initially, 92 dialysis patients were recruited for the study. Of these, three patients were excluded after testing positive for antibodies against the SARS-CoV-2 N protein, 5 five were excluded because the conditions had not allowed for them to get vaccinated within the required 21-day period, two were excluded because they passed away, and one was excluded due to undergoing a transplantation. Finally, 81 dialysis patients were included in the study: 23 women and 58 men. The mean age of the participants was 67 years (median 70 years, age range 34–86 years).

In total, 22 patients were classified as low- or non-responders to BNT162b2 because they did not achieve protective antibody titres (> 29 U/ml) three weeks after their second vaccine dose. Of these patients, 21 were resampled (one passed away) 10 weeks after the second vaccine dose and analysed for S antibody titres to check for a possible delayed response. The later

samples of this subgroup were also analysed for N antibodies to exclude possible COVID infections (see Serological assessment).

Further, 81 volunteer healthcare workers were initially recruited for the study, but one person was excluded due to presenting a positive N antibody test. Finally, 80 healthy controls were included in the study: 50 women and 30 men. The mean age of the controls was 49 years (median 52 years, age range 29–65 years). All demographic data are summarised in Table 1.

The medical histories of the dialysis patients were obtained from their medical records, while those of the control group were assessed using a standardised questionnaire.

Processing of blood samples

Blood draws were performed three weeks after the second dose of BNT62b2. Additional blood draws were performed for the low- or non-responder subgroup 10 weeks after the second dose. The samples were centrifuged using a Hettich Rotanta 460r centrifuge at 3,000 rpm for 10 minutes, aliquoted and anonymised. They were then stored at -70° C and thawed prior to testing.

Serological assessment

All the samples were analysed with an Elecsys® Anti-SARS-CoV-2 test, which measured the nucleocapsid (N) antibodies in the blood. A positive result in this test led to an exclusion of the participant from the study due to a high probability of a clinical or subclinical COVID19 infection in the past[12].

The antibody response elicited by BNT62b2 was measured using an Elecsys ® Anti-SARS-CoV-2 S on a Cobas e 801 platform according to specifications[13]. The recorded results ranged from 0 (≤ 0.40 U/ml, lower limit of detection (LOD)) to 2500 (≥ 2500 U/ml, upper LOD) and were assigned to anonymised patient data.

For the correlation between the Hepatitis B vaccination responders and the SARS-CoV-2 vaccination responders, we defined the following cut-offs: the Hepatitis B vaccine responders

were defined as Hepatitis B antibody titre > 20 IU/ml after at least one completed Hepatitis-B vaccination cycle (three doses of Engerix B 40 µg). The samples collected for the antibody titres were also used for this analysis. They were measured using the Elecsys Anti-HBs II Kit on a Cobas e 801 platform.

Adverse events

AEs associated with the vaccination were assessed separately for both vaccine doses and both groups using a standardised questionnaire.

AEs were divided into two categories: local AEs (pain, redness and/or swelling and induration at the injection site) and systemic AEs (fatigue, headache, muscle and/or joint pain, fever, gastrointestinal symptoms (diarrhoea, nausea, vomiting) or other AEs).

The patients were asked to grade their AEs after both vaccine doses in terms of subjective severity. The grading was performed using a scale of 1–4. A Grade-1 AE represented mild symptoms (does not interfere with activity), Grade 2 entailed moderate symptoms (interferes with activity), Grade 3 entailed severe symptoms (prevents daily activity) and Grade 4 involved an emergency department visit or hospitalisation). The Grades were established according to the FDA toxicity grading scale[14].

Statistics

The differences between the two groups with regard to demographic characteristics and medical history were assessed using the t-test (age), chi-square test (gender and hypertension risk factor) and Fisher's exact test (all risk factors except hypertension). To analyse the influence of the group (dialysis patients vs controls), sex and age on the titres, univariate quantile (median) regressions were performed. Because of the imbalances in the sex and age parameters between the two groups, a multivariate analysis was computed for all the variables that were significant in the univariate analysis. The quantile regression was chosen due to the skewed distribution of the titres (many patients presented a maximum titre observation of

2,500). The bootstrap method was applied to derive the standard errors and perform statistical tests for each independent factor (5,000 replications), and the median and interquartile range (IQR) were provided to compare the groups descriptively.

A further quantile regression was performed for the variable hepatitis, which was only available for the dialysis group. In case a significant result was obtained, the age and sex of the participant were also considered. The significance level was set to 0.05. The analyses were performed using R 4.0.2 and the quantreg package[15].

The boxplots were generated using Prism (GraphPad, 2021 version), whereas the AE bar graphs were created in Excel 2019 (Microsoft, included in Office 365).

RESULTS

In total, 81 dialysis patients and 80 control group patients were tested with respect to their antibody response after they had received two doses of BNT162b2 (BioNTech/Pfizer, Comirnaty™). Their characteristics, risk factors and other data are shown in Table 1.

The anti-SARS-CoV2 antibody titres were measured three weeks after the second vaccine dose was administered in both groups. The univariate analysis shows that dialysis patients have a highly significant lower titre count than the control group (median was 171 U/ml for the dialysis patients, with an IQR of 477.7, and 2,500 U/ml for the controls, with an IQR of 943.5). Gender and age also have a significant influence on titre (see Table 2). Note that the variables group and gender are confounded: in the control group, 62.5% are women, whereas, in the dialysis group, only 28.4% are female. In our study cohort, men were found to have a lower median titre (median for men was 367.5 U/ml, IQR = 1650, and was 1542 U/ml for women, IQR = 1,790) than women. Age has a negative influence on titre count; with an increasing in age, the titre decreases, on average. The Spearman correlation coefficient for the two variables is -0.62.

The multivariate analysis indicate a highly significant influence of group type – the dialysis patients have significantly lower titres than the controls – and a small amount of influence of age on titre (Table 2). The sex of the participant has no significant influence in the multivariate analysis anymore.

It was found that 22 of the 81 dialysis patients (27%) did not develop a protective antibody titre (i.e., their titre was < 29 U/ml). To assess a possible delayed response to the vaccine, we took another blood sample at 10 weeks after the second vaccine dose from those 21 patients (one participant passed away during this time) and measured the antibody titres. Of the 21 analysed low- or non-responders, five (24%) had developed a protective antibody titre (> 29 U/ml) after 10 weeks of the second vaccine dose, indicating a delayed vaccine response.

The AE reports for the two groups were analysed and compared. No Grade-4 AEs (emergency department visit or hospitalisation) were reported in either group. The control group reported significantly more local AEs (first dose: $p = 0.006$; second dose: $p < 0.0001$) and more systemic AEs after both vaccine doses (first dose: $p = 0.0005$; second dose: $p < 0.0001$) compared to the dialysis group. See Figure 2 and Figure 3 for a graphical representation.

In the dialysis group, patients with an antibody response of more than 20 IU/ml to the Hepatitis B vaccine ('responders') presented a higher SARS-CoV-2 antibody titre (responders: median = 223.5, IQR = 587; non-responders: median = 159, IQR = 450). However, this difference is not significant in the quantile regression (value: -50, t-value: -0.37, $p = 0.71$). Note that the sample size for this analysis is only 81 patients.

DISCUSSION

The antibody titres after diverse vaccinations tend to be considerably lower in dialysis patients, with a greater percentage of said patients failing to present measurable titres using a conventional vaccination scheme compared to healthy patients, e.g. Hepatitis B vaccine[9,16], Pneumococcus[10] or Influenza vaccines[11]. Therefore, it is unclear whether vaccinating against SARS-CoV-2 in this patient group will result in an adequate immune response and, thereby, protection against infection.

In the control group, three weeks after two doses of BNT162b2, the antibody titres were found to be significantly higher than in the dialysis group ($p < 0.0001$). All the individuals in the control group had a titre greater than 200 U/ml, entailing a robust antibody response. On the other hand, in the dialysis group, 43 patients (53%) had an antibody titre lower than 200 U/ml (signifying neutralisation below maximum), 22 (27%) had a titre lower than 29 U/ml (likely no neutralisation) and seven (9%) had no detectable antibodies at all. These results are comparable to the numbers obtained by Yanay et al. [17], who also demonstrate that antibody titres are lower in HD patients as compared to healthy controls. This implies a weaker antibody response in dialysis patients overall, making them less likely to be able to neutralise the SARS-

CoV-2 virus even after two doses of the vaccine. Since these patients are more exposed to infection[4,5] and prone to a severe course of disease, this could pose a grievous problem in this vulnerable community.

Longitudinal follow-up studies are warranted, especially since it was proven that the antibody levels after natural COVID-19 infection seem to decline over time in haemodialysis patients[18], and the same could happen after vaccination. The studies would also be useful for detecting delayed antibody responses to the vaccine, which could occur due to the immunosuppression of HD patients. Forbes et al. [19] reported that the seroconversion rates in COVID-infected HD patients increased with time, indicating that, in the case of natural infection, a delayed response is possible. Thus, to quantify the delayed antibody response after vaccination, longitudinal follow-up studies are needed. To assess a delayed response in the HD patients, we re-sampled 21 of the low- or non-responders 10 weeks after their second dose and measured their antibody titres again. It was found that five of them (24%) had developed a protective antibody titre (> 29 U/ml) 10 weeks after the vaccine's second dose, indicating a delayed vaccine response. We excluded antibody production that occurred due to an asymptomatic infection using the N antibody assay, so the detected rise in titres appears to be a consequence of vaccination. The remaining 16 patients had still not developed an adequate humoral immune response. No method for predicting a delayed response in such cases has been found to date.

The gold standard for measuring the neutralising capacity of patient serum antibodies is the plaque reduction neutralisation test[20], where cells are incubated with the virus and the dilution in which the virus growth is inhibited is measured. A plaque assay was also used in the efficacy studies for the BNT162b2 (Pfizer/BioNTech) COVID-19 vaccine as a surrogate marker for protection from severe disease[8].

The test used in our study, the Elecsys ® Anti-SARS-CoV-2 S, is not a neutralisation assay by nature. It uses a recombinant protein representing the receptor-binding domain (RBD) of the

SARS-CoV-2 S (spike) protein as an antigen and quantitatively measures the antibodies directed against this protein. Nonetheless, recent data indicate a good correlation between a direct virus neutralisation test and a surrogate neutralisation assay (GenScript® cPass™ SARS-CoV-2 Neutralisation Antibody Detection Kit)[21].

Briefly, the serum of all the patients who achieved an antibody titre of 29 U/ml or higher in the Elecsys test system correlated with a 1:5 titre in the neutralisation assays and, therefore, possessed some measure of neutralising capacity. The sera with an Elecsys antibody result of equal to or greater than 200 U/ml correlated with the maximal neutralising capacity in the neutralisation assays[22].

The Elecsys test was also used to quantify the samples from the WHO International Standard and Reference Panel for the anti-SARS-CoV-2 antibody[23], and it showed a good correlation[22].

Therefore, we feel comfortable using this test as a robust and accepted surrogate marker for an immune response achieved by vaccination.

We chose to perform the tests three weeks after the second dose because the system used in this study measures both IgM and IgG. With reference to a natural infection, after three weeks, the initial IgM boost response should subside in most patients, while the IgG response is at its peak[24]. Thus, in theory, this is the optimal point of time to measure protective, durable IgG responses.

AEs were reported significantly more frequently and were of higher grades for the control group than the dialysis group. It is not known whether the immunosuppression in HD patients also has an influence on the manifestation of AEs. Whether they are correlated to the amount of immunosuppression and can be used as an indirect predictor of vaccine response are fascinating aspects for research. Further studies would be needed to uncover a potential causal relationship between the occurrence of AEs and the immune response of dialysis patients.

No statistically significant correlation was found between the responders to the Hepatitis B vaccination (defined by an HBs-Antibody Titre of less than 20 IU/ml after at least one completed vaccination cycle) and the response to BNT162b2. This could reflect different immune mechanisms and levels of reactogenicity in response to the two vaccines. The basis for the non-response to the Hepatitis B vaccine has not yet been elucidated; probably multifactorial in origin, at least some part can safely be attributed to the immune suppression of dialysis patients (a low antibody response seems to correlate with the degree of renal failure[25]). Possible explanations for this include immune cell disturbances[26–28]. Further, gene variations in the vaccine response genes (e.g., Interferon-λ4 polymorphisms) were shown to influence the Hepatitis B vaccine response in dialysis patients[29].

Age and gender were distributed unequally between the control and dialysis group: while the majority of the patients were female in the control group, the dialysis group was predominated by males. Furthermore, the patients in the control group were, on average, younger than those in the dialysis group. To account for these confounding factors, we performed a multivariate analysis. We found that the dialysis vs control group showed the highest impact on the antibody titre, while the age parameter influenced the antibody titres to a much lesser extent. Moreover, gender was not a significant factor in the multivariate analysis, indicating that its significance in the univariate analysis was a consequence of group composition.

One limitation of our study is that the clinical significance of even a plaque-based neutralisation assay has not been widely tested. It is probable, but not yet proven, that high antibody titres in our test system and, by correlation, in neutralisation assays protect patients from severe infection courses. Further studies are needed to validate the impact of protective antibody titres in clinical settings.

Another limitation in this regard is that our test system only tested humoral (antibodies) and not the cellular (T-cell) immune response. Since the correlates of protection in a SARS-CoV-2 infection remain unknown as of today, the cellular component of the adaptive immune system

probably plays a role in the protection from COVID-19[30], which is not reflected in our investigation. Recent data from Clark et al. [31] show that, in convalescent HD patients, the T-cell responses are robust. Anft et al. [32] demonstrate for a small patient cohort that the cytokine levels from T-cell activation are equal to those of the controls who did not receive haemodialysis. Taken together, these findings indicate that the T-cell response in HD patients correlates with the healthy controls in convalescence, but no data is available for vaccinated HD patients.

In summary, our data show that the haemodialysis patients in our study, who are at an extremely high risk for getting infected with COVID-19 and experiencing severe course of disease and mortality[5–7, 33], developed an antibody response that is significantly lower than that found in our control group. This finding has implications for the preventative measures beyond vaccination (masks, social distancing and hand hygiene, testing strategies, patient isolation, etc.) that need to be maintained for protection. The integration of regular testing for neutralising antibodies after vaccination for haemodialysis patients should be evaluated. Further studies on alternative vaccination strategies (dosing and schedule) are urgently needed.

CONFLICT OF INTEREST STATEMENT

The kits and reagents used for the SARS-CoV-2 antibody tests were supplied by Roche Diagnostics.

AUTHORS' CONTRIBUTIONS

B.S. carried out the coordination between the healthy control group, data processing, literature research and writing.

H.R. oversaw the sample analysis, test performance and provided technical supervision.

B.H., A.T. and M. G. performed patient recruitment and blood and data collection.

S.Z. performed statistical analyses.

B.K. handled the coordination between the dialysis group, data processing, literature research and writing.

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Tables

	Dialysis patients (n = 81)	Control group (n = 80)	p Value
Age (y, mean, range)	67 (34–86)	49 (29–65)	< 0.0001
Men	71 (55%)	30 (24%)	< 0.0001
Risk factors			
Diabetes	31	2	< 0.0001
COPD	23	0	< 0.0001
Hypertension	68	21	< 0.0001
Primary Kidney Disease			
Diabetes	25	n.a.	-
Vascular disease	27	n.a.	-
Glomerulonephritis	10	n.a.	-
Unknown	1	n.a.	-
Other	18	n.a.	-
Medication			
RAAS-Inhibitors usage	35	0	-
Immunosuppressants usage (Steroids, CNI, MMF)	9	2	-
Vitamin D supplements usage	61	0	-
EPO usage	74	0	-

Table 1. Demographics of the studied population. The differences between the groups were analysed using the t-test (age), chi-square test (gender and hypertension risk factor) and Fisher's exact test (all risk factors except hypertension). The p values less than 0.05 were considered significant. COPD: chronic obstructive pulmonary disease; RAAS: Renin-Angiotensin-Aldosteron system; CNI: calcineurin inhibitors; MMF: Mycophenolat-Mofetil; EPO: erythropoetin.

Variable	Value	t value	p value
Dialysis group	-2329.0	-14.27	< 0.0001
Age	-53.7	-15.94	< 0.0001
Female	1126.0	3.52	0.0006

Table 2. Univariate analysis of the variables' influence on antibody titre, calculated using univariate quantile regressions. The p values of less than 0.05 were considered significant.

Variable	Value	t value	p value
Dialysis group	-1998.1	-10.27	< 0.0001
Age	-9.4	-2.57	0.011
Female	17.4	0.17	0.86

Table 3. Multivariate analysis of the variables' influence on antibody titre, calculated using univariate quantile regressions. The p values of less than 0.05 were considered significant.

Figure Legends

Figure 1: Boxplot of SARS-CoV-2-specific antibody titres (controls vs dialysis patients) 21 days after the second vaccine dose. Note that the maximum titre in the test system used is 2,500 U/ml (cut-off). The control group titres are significantly higher than the dialysis group titres ($p < 0.0001$).

Figure 2: Local AEs after vaccination with BNT162b2. All numbers represent the percentages of the dialysis (n = 81) and control (n = 80) patients. The AEs were recorded using a standardised questionnaire and graded by the patients (Grade 1: mild, does not interfere with activity; Grade 2: moderate, interferes with activity; Grade 3: severe, prevents daily activity. No Grade-4 events (emergency department visits or hospitalisation) were reported). #, $p < 0.05$; *, $p < 0.0001$

Figure 3: Systemic AEs after vaccination with BNT162b2. All numbers represent the percentages of the dialysis (n = 81) and control (n = 80) patients. The AEs were recorded using a standardised questionnaire and graded by the patients (Grade 1: mild, does not interfere with activity; Grade 2: moderate, interferes with activity; Grade 3: severe, prevents daily activity. No Grade-4 events (emergency department visits or hospitalisation) were reported). GI: gastrointestinal AEs (diarrhoea, nausea and vomiting). #, $p < 0.05$; *, $p < 0.0001$

Figures

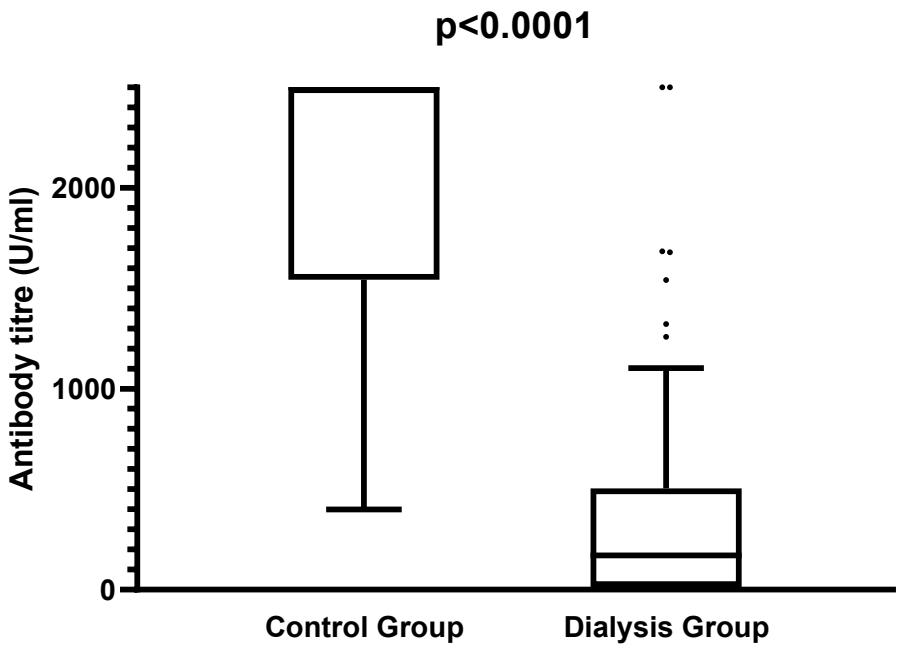

Figure 1

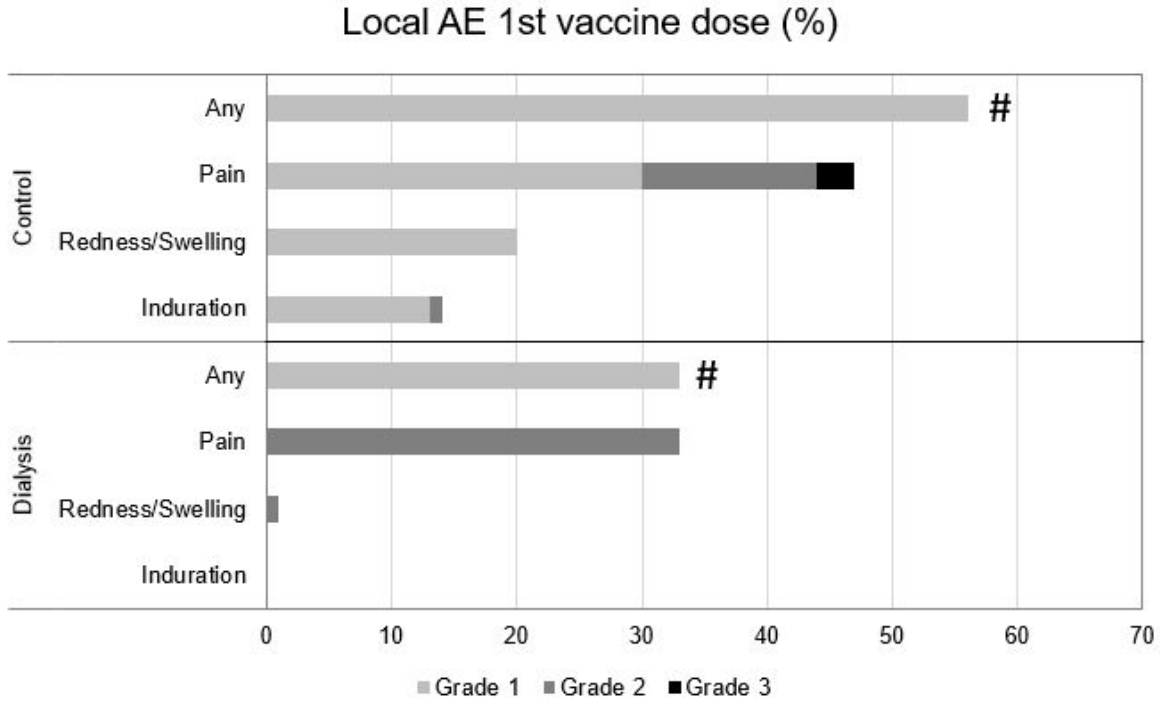

Figure 2a

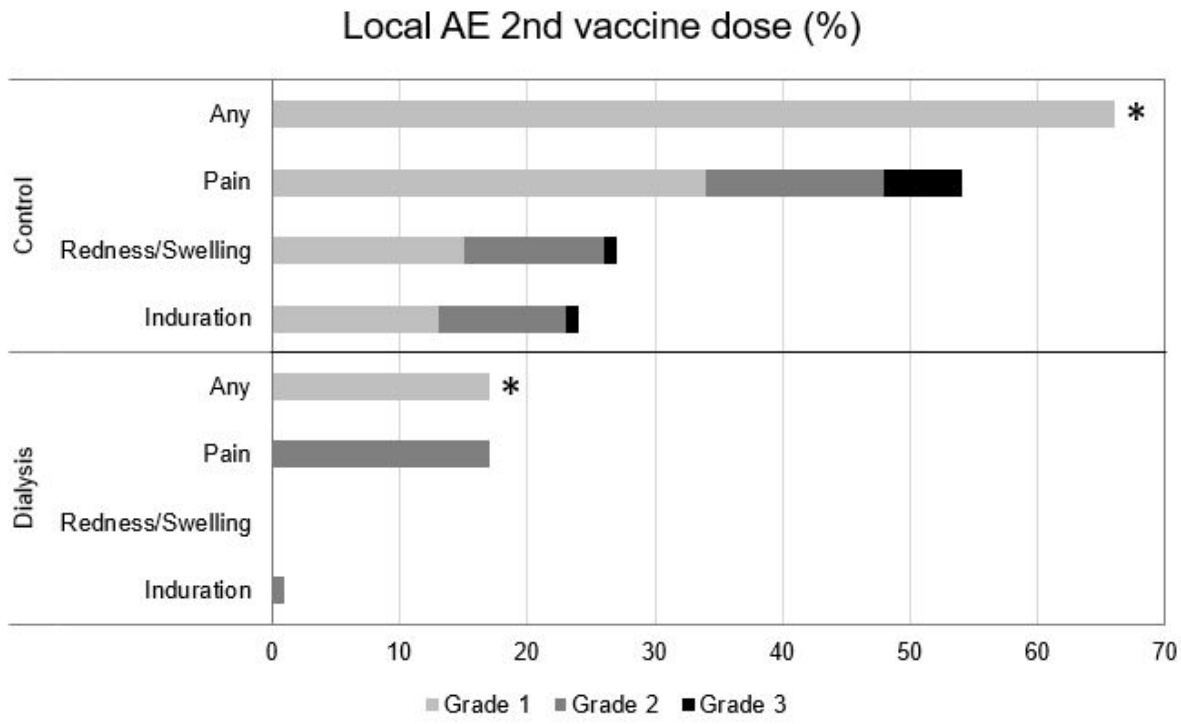

Figure 2b

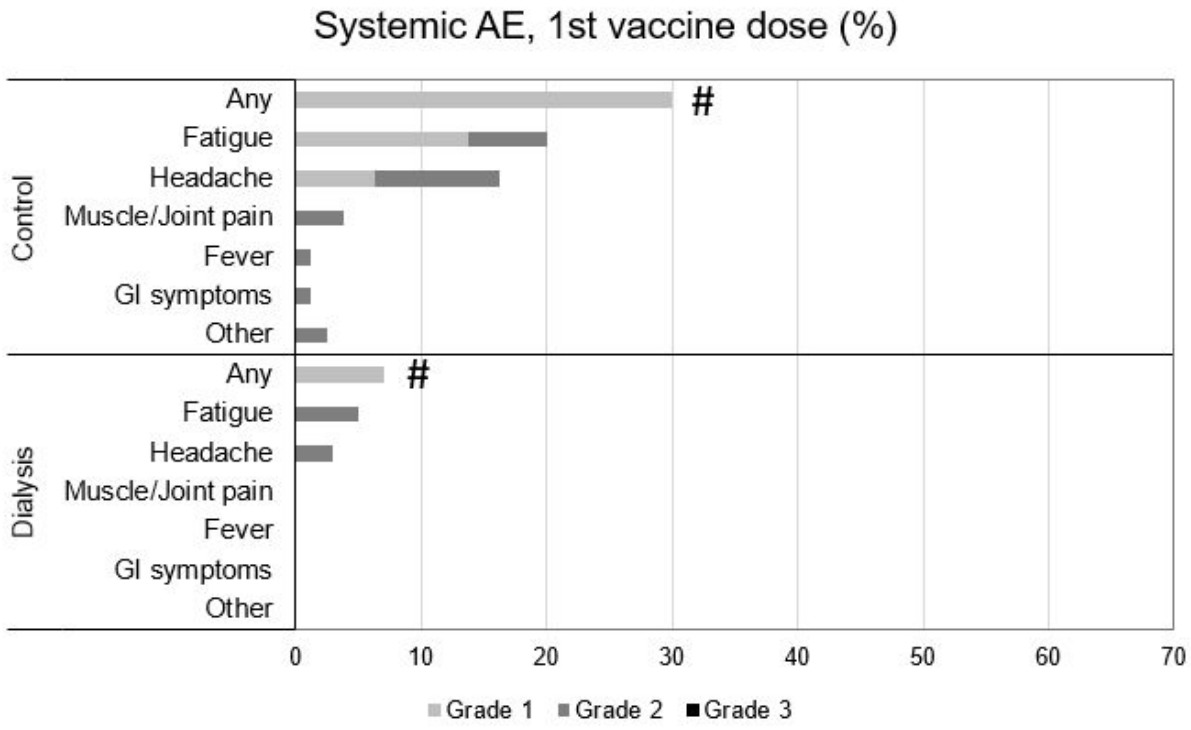

Figure 3a

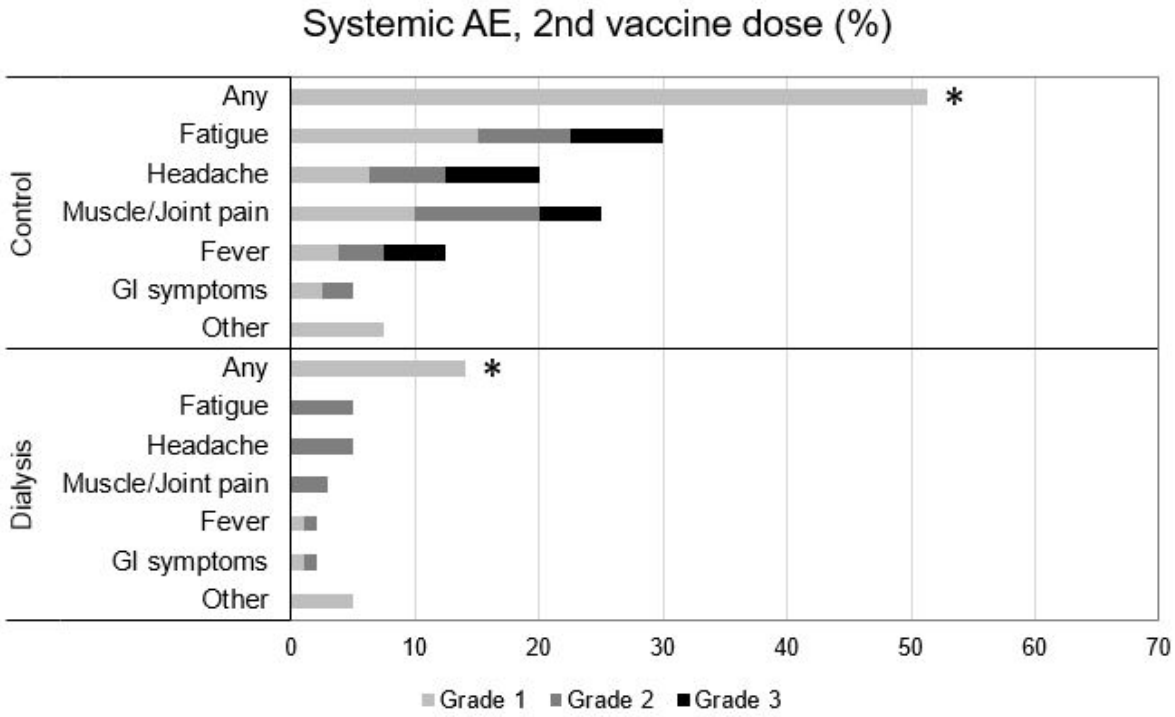

Figure 3b