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Humoral Response after SARS-Cov-2 mRNA Vaccine in a Cohort of Hemodialysis Patients and Kidney Transplant Recipients

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Abstract: Background Kidney transplant recipients and patients receiving hemodialysis are immunocompromised populations that are prioritized for COVID-19 vaccination but were excluded from clinical trials of SARS-CoV-2 mRNA vaccines. Antibody titers and rates of seroconversion following vaccination are lower among patients with chronic kidney disease and those taking immunosuppressants compared with controls. Data are lacking regarding their humoral response to vaccination to prevent COVID-19.
Methods This investigation of early serological response after COVID-19 vaccination with the Pfizer/BioNTech (BNT162b2) mRNA vaccine included 78 patients undergoing hemodialysis, 74 kidney transplant recipients, and 7 healthy controls. We recorded data from the medical file for various clinical parameters, including response to hepatitis B vaccination, and measured antibody titers against SARS-CoV-2 at 0, 14, 28, 36 and 58 days after the first injection.
Results In controls, we detected antibodies at a positive level (>13 arbitrary units per milliliter [AU/ml]) at day 14 postinjection, which increased progressively to peak at day 36 (1082 AU/ml; interquartile range [IQR], 735.0â€“1662.0]). Patients undergoing hemodialysis had lower titers that peaked at day 58 (276 AU/ml [IQR, 83.4â€“526.0]. We detected a positive antibody level in only three transplant recipients at day 36. In hemodialysis patients, those younger than 75 years had a higher antibody response versus those older than 75 years and serum albumin and Kt/V were positively correlated with serological response (P< 0.043 and P<0.019, respectively); nonresponders to HBV vaccine had the lowest antiâ€“SARS-CoV-2 antibody titers.

Conclusions Our results suggest that the postvaccination humoral response is strongly inhibited by immunosuppressant therapy in kidney transplant recipients and is reduced by the uremic condition in patients undergoing hemodialysis.

Significance Statement

Data are lacking regarding the humoral response to COVID-19 vaccination in kidney transplant recipients and patients on hemodialysis. This study of humoral response to an mRNA vaccine in 78 patients undergoing hemodialysis, 74 kidney transplant recipients, and 7 healthy controls found that anti–SARS-CoV-2 antibodies peaked at day 36 post-vaccination among controls, whereas hemodialysis patients had lower titers that peaked at day 58, and only 3 kidney transplant patients exhibited detectable antibody levels. Among hemodialysis patients, age <75 years, serum albumin, and Kt/V were positively correlated with serological response; those who were nonresponders to HBV vaccine had the lowest anti–SARS-CoV-2 antibody titers. These findings suggest that postvaccination humoral response is strongly inhibited by immunosuppressant therapy in kidney transplant recipients and is reduced by the uremic condition in hemodialysis patients.

Humoral Response after SARS-CoV-2 mRNA Vaccination in a Cohort of Hemodialysis Patients and Kidney Transplant Recipients

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Short Title: Humoral Response to COVID-19 Vaccine in Kidney Patients

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Abstract

Background Kidney transplant recipients and patients receiving hemodialysis are immunocompromised populations that are prioritized for COVID-19 vaccination but were excluded from clinical trials of SARS-CoV-2 mRNA vaccines. Antibody titers and rates of seroconversion following vaccination are lower among patients with chronic kidney disease and those taking immunosuppressants compared with controls. Data are lacking regarding their humoral response to vaccination to prevent COVID-19.

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Conclusions Our results suggest that the postvaccination humoral response is strongly inhibited by immunosuppressant therapy in kidney transplant recipients and is reduced by the uremic condition in patients undergoing hemodialysis.

INTRODUCTION

Kidney transplant recipients and patients on hemodialysis are immunocompromised populations that are prioritized for COVID 19 vaccination [1]. Both these groups were excluded from studies of SARS-CoV-2 messenger RNA (mRNA) vaccines [2, 3, 4]. It is well established that patients with chronic kidney disease and those taking immunosuppressants have lower antibody titers and lower rates of seroconversion following vaccination compared to healthy controls [5, 6]. Indeed, this lower post-vaccine response led to the adaptation of hepatitis B and influenza immunization schedules [5, 7, 8].

For the COVID 19 vaccine, data are scarce regarding the post-vaccine response in immunocompromised patients. In the present study, we analyzed the kinetics of serological response after anti-COVID 19 vaccination with the Pfizer/BioNTech (BNT162b2) mRNA vaccine (Comirnaty®) in patients of our nephrology unit.

PATIENTS AND METHODS:

Patients

Patients were recruited from among patients undergoing hemodialysis in our Nephrology unit, and from kidney transplant recipients who were followed in our center. The control group was constituted by members of the medical staff, vaccinated between February and March 2021 and included in the institutional post-vaccine follow-up program.

Patients and healthy subjects included in the study received two doses (30 µg each) of the Pfizer/BioNTech (BNT162b2) Comirnaty® vaccine, 28 days apart, according to the recommendations of French National Health Authority (Haute Autorité de Santé, HAS) [9], between February 2, 2021, and March 15, 2021. None of the subjects included had a prior polymerase chain reaction (PCR)–confirmed diagnosis of COVID-19. For each patient, the following clinical parameters were recorded from the medical file: age, sex, body mass index (BMI), primary renal disease, cardiovascular comorbidities, response to hepatitis B

vaccination, renal function, lymphocyte count, gammaglobulin level, antibody titer level against SARS-CoV-2 at days 0, 14, 28, 36 and 58 after the first injection. Specific data regarding transplantation or hemodialysis were also collected for each subgroup of patients, namely: date of transplantation, induction therapy, immunosuppressant treatment, Kt/V, type of dialysis, duration of dialysis. The study was authorized by the French commission for data privacy (CNIL) under the number 2210609609/(V0).

Anti-SARS-CoV-2 antibody response

All patients were tested for anti-N antibodies (Abbott Alinity SARS-CoV-2 IgG, Chicago, IL, USA) on the day of the first injection, and at each time-point during follow-up, to eliminate past SARS-CoV-2 infection or infection occurring during the vaccination program.

The anti-SARS-CoV-2 antibody response against the spike protein was assessed at 14, 28, 36 and 58 days post-injection using the LIAISON SARS-CoV-2 TrimericS IgG (DiaSorin, Saluggia, Italy), with titers >13 arbitrary units per mL (AU/mL) being considered as positive (detection range: 1.85–800 AU/mL; positive agreement: 98.7% ; negative agreement: 99.5%). Values over 800 were diluted to 1:20 to obtain the exact value. Antibodies detected over the threshold of 13 AU/mL are considered as neutralizing antibodies according to the manufacturer's data. Both tests are based on chemiluminescence microparticle immunoassay and were performed according to the manufacturer's instructions. We performed additional analyses to focus on the antibody response at day 36 (D36), reported in the literature to be the time point associated with the highest antibody level in the general population [3,4].

Statistical analysis

Qualitative variables are described as number and percentage. Quantitative variables are described as median and interquartiles, or means and standard deviation. For comparisons, the Chi square, Fisher's exact, Mann-Whitney or Wilcoxon tests were used according to their conditions of application. Correlations were investigated using Pearson's

correlation coefficient between the main outcome (antibody titers >13 AU/mL) and each of the following quantitative variables: age, BMI, Kt/V, albuminemia, anti HBs antibodies, lymphocyte count, total IgG. Finally, because reduced post-vaccine humoral response is a common feature of patients with end stage renal disease, we analyzed for each patient, the link between previous humoral response to Hepatitis B Virus (HBV) vaccine and response to the Pfizer-BNT162b2 anti-COVID vaccine. To this end, patients undergoing hemodialysis were categorized into 3 groups, depending on the titers of anti-HB surface antibodies (Anti-HBs): patients with no detection of anti-HBs antibodies were considered non-responders to HBV vaccine; patients with a titer of antibodies between 10 and 200 mUI/ml were considered mild responders (intermediate), and patients with Anti-HBs > 200 mUI/ml were considered as high responders. Humoral response to anti-COVID vaccination was compared across HBV responder groups. Statistical analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and Graphpad PRISM® version 9.1.

RESULTS

Description of the study population

The baseline characteristics of the population are detailed in **Table 1**. In the kidney transplant recipient group, average age was 64.8±11.5 years, 38.9% were women, and mean time since transplantation was 6.42±7.8 years. The maintenance immunosuppressant regimen included calcineurin inhibitors (87%), corticosteroids (45.4%), antimetabolites (82.4%), m-Tor inhibitors (10.4%), and belatacept (2.6%). The antimetabolites used were: mycophenolate mofetil (85.2%), mycophenolic acid (11.5%) and azathioprine (3.3%). Mean glomerular filtration rate (GFR) was 44.5±18.5 mL/min, as estimated by the CKD Epi equation. All patients in the hemodialysis group were undergoing hemodialysis in the University Hospital of Limoges; mean age was 73.5±12.8 years, 40.2% were women, and the mean duration of dialysis was 5.1±6.3 years. Subjects in the control group were aged 51.6 ± 6.8 years, and 42% were women (**Table 1**).

Kinetics of humoral response

The anti-SARS-CoV-2 antibody response against the spike protein was analyzed at 14, 28, 36 and 58 days post-injection, in each group. In the control group, antibodies were detected at a positive level (>13 AU/ml) starting at day 14 post-injection, and increased progressively to peak at day 36. The median antibody titer in the control group was: 59 AU/mL [IQR: 26.5-216.5] at day 14, 1082 AU/mL [IQR 735.0-1662] at day 36, and 925 AU/mL [IQR 637-3624.5] at day 58 (**Figure 1**).

Patients undergoing hemodialysis had a similar pattern of response, but at a lower magnitude, with greater heterogeneity and a longer time to maximal response, which was reached at day 58. In this group, median antibody titer was 4.0 AU/mL [IQR: 1.85-12.2] at day 14; 6.6 AU/mL [IQR 2.1-19.0] at day 36; and 276 AU/mL [IQR 83.4-526.0] at day 58.

A positive antibody level was detected in only 3 kidney transplant recipients at day 36. These three patients had immunosuppressant regimens comprising cyclosporine monotherapy.

Intensity of humoral response

We then focused on the antibody response at day 36 (D36), reported to be the time point associated with the highest antibody level in the general population (**Table 2**). At D36, 100% of the control group had responded to the vaccine, with an antibody titer higher than the threshold of 13 AU/ml. In the groups of patients, 81% of patients on hemodialysis were responders, but only 4.1% of kidney transplant recipients had developed antibody titers above the positivity threshold. The proportion of responders (as defined by the threshold of 13 AU/ml) in the hemodialysis group was not statistically different from that of the control group (81 vs 100%, *p=0.38*). However, the median antibody level in the control group was

significantly higher than in the hemodialysis group: 1082 AU/ml [IQR: 293 – 5500] for controls *vs* 114 AU/ml [IQR: 15 – 1482] for hemodialysis patients, p< 0.0001.

Factors associated with humoral response in patients on hemodialysis

We investigated the factors associated with the antibody titer in the hemodialysis group. We did not find any significant relation between diabetes, gender or BMI and antibody production. However, we observed higher antibody production in patients aged <75 years compared to those aged >75, suggesting that antibody response was associated with age: 115 AU/ml [IQR: 1.85 -1482] *vs* 60 AU/ml [IQR: 1.85 – 526], p<0.031. In addition, serum albumin and Kt/V were also positively correlated with serological response: p<0.043 and p<0.019, respectively.

Association between humoral response to Hepatitis B virus vaccine and humoral response to SARS-Cov-2 vaccine

Comparison of the humoral response to anti-COVID vaccination according to prior response to HBV vaccination showed that the median titer of anti SARS-Cov-2 antibodies differed between these 3 groups of patients (**Table 3)**. Indeed, non-responders to HBV vaccine had the lowest SARS-Cov-2 antibody titers (36 AU/ml [IQR:1.85 – 526]), whereas patients with intermediate and high levels of anti HBs antibodies had significantly higher SARS-Cov-2 antibody titers: 113 AU/ml [IQR: 1.85-1482] for the intermediate group (p=0.016) and 209 AU/ml [IQR: 9.06 – 565] (p=0.03) for the high HBV response group (**Table 3)**.

DISCUSSION

In the present study, we describe the kinetics of humoral response after Pfizer BNT162b2, Comirnaty ® vaccination in kidney transplant recipients, patients undergoing hemodialysis and healthy controls. To the best of our knowledge, this is the first study to compare post-vaccine humoral response of subgroups of patients with chronic kidney

disease. Our results confirm previous reports of lower antibody responses among transplanted patients and also highlight novel findings as regards the pattern of response in patients on hemodialysis, since we found that non-responders to HBV vaccine were less likely to develop humoral response after the Covid vaccine. This finding is of particular interest not only for clinical care, but also as an avenue for future research focusing on common pathophysiological mechanisms linking HBV and SARS-Cov-2 humoral response.

Kidney transplant recipients in our study were younger, and had a satisfactory renal function (44.5 ± 18.5 ml/min), but we found a significantly lower humoral response in this group, with only 4.3% of them found to be responders at 36 days after the first injection. Patients in the hemodialysis group were older, and had lower residual renal function compared to the kidney transplant recipients. However, despite these differences, 85.5% were found to be responders in the hemodialysis group. This suggests that, rather than age or chronic kidney disease condition, the immunosuppressant therapy may be a critical factor implicated in this lack of humoral response.

Our study is in line with recent published reports describing lower humoral response in kidney transplant recipients. For example, Boyarsky and colleagues reported an immunization rate of 54% in a population of solid organ transplant recipients, while publications from Benotman et al and Grupper et al respectively observed that 48% and 37.5% of kidney transplant recipients mounted a humoral response after two doses of mRNA vaccine [10, 11, 12]. Hence, our results are markedly different, with a lower immunization rate. We hypothesize that the presence of several factors associated with poor humoral response could account for this discrepancy. First, our transplant recipients were older than previous published cohorts, by at least 5 years on average [10-12]. Second, the impact of mycophenolate mofetil (MMF)-based immunossupressant regimens has been reported [10-12], and most of our patients were treated with a combination of anti-rejection drugs including MMF. Lastly, our vaccination protocol was homogeneous, with the use of only one mRNA vaccine, i.e. Pfizer

BNT162B2, but recent reports suggest that the Moderna vaccine leads to higher immunization rates [10, 13].

Taken together, our data and recent reports in the literature argue for a revision of the vaccination protocol in kidney transplant recipients, the type of vaccine, number of injections, and doses should be redefined in light of these recent findings.

In the present report, we describe for the first time the profile of humoral response to the Pfizer BNT162B2 Comirnaty ® vaccine in patients undergoing hemodialysis. We found that antibody production in this population had a pattern similar to that of healthy subjects, with a similar rate of responders at day 36. However, humoral response in patients on hemodialysis was delayed, heterogeneous, and of lower intensity, as assessed by the antibody level. Lower humoral response in hemodialysis patients has recently been reported [14] , and our results are in agreement. In addition, we found that the humoral response of the hemodialysis population was correlated with age, serum albumin and Kt/V. These factors are well established as being associated with immune status and therefore, able to influence humoral response in the general population, particularly in uremic subjects [6, 7].

A finding of interest in our study is the link between the humoral response to the Pfizer BNT162B2 Comirnaty ® vaccine, and previous response to Hepatitis B vaccination. Patients who were non-responders to HBV vaccine were those who also displayed the lowest level of anti SARS-CoV-2 antibodies, suggesting that similar mechanisms are involved in the failure to mount an immune response to these two vaccines [15-17]. Taken together, these findings suggest that the humoral response to the Pfizer BNT162B2 Comirnaty ® vaccine in patients undergoing hemodialysis is guided by factors related to the uremic condition, leading to delayed humoral response of lower magnitude.

Furthermore, our results suggest that response to the vaccine could be predicted for each patient by analyzing the level of anti-HBs, reflecting the magnitude of the humoral response to HBV vaccine. This could help us to personalize the anti-COVID vaccination protocol.

Our study has several limitations, including its single-centre and retrospective design. However, the strengths of our study include the comparison of 2 populations with chronic kidney disease, and the precise and dynamic analysis of humoral response.

Our results suggest that i) immunosuppressant therapy in kidney transplant recipients is a key factor inhibiting their humoral response to the Pfizer BNT162B2 vaccine; ii) humoral response in patients undergoing hemodialysis is regulated by factors related to the uremic condition, leading to a significant number of responders but with a delayed response, of lower magnitude. Interestingly, the levels of antibodies detected with the LIAISON SARS-CoV-2 TrimericS IgG Elisa assay were shown to be correlated with SARS-CoV2 neutralizing antibodies [18, 19], suggesting that low titer of anti-SARS-Cov2 may still be efficient in neutralizing the virus. Further studies are warranted to determine whether the humoral response obtained in the hemodialysis group is sufficient to confer efficient protection against Covid 19 disease.

CONTRIBUTIONS: CD, JPR, SH, FB, SA and FT designed the study. CD, SH, SP, AD, collected the data. CD, JPR, SH, FB, AD, BB, MD, ZEO, SA and FT, analyzed the data. FT, CD, SH, SA wrote the manuscript. All the authors approved the manuscript.

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TABLE 1: Baseline characteristics

	Transplant recipients (n=74)	Hemodialysis patients (n=78)	Control Group (n=7)
Age (years)	64.8 ± 11.5	73.5 ± 12.8	51.6 ± 6.8
Females (n, %)	30 (38.9)	32 (41)	3 (42)
BMI, kg/m²	26.7 ± 5.8	26.8 ± 5	24.1 ± 1.2
First transplantation (n, %)	66 (85.7)		
Mean time since transplantation (years)	6.42 ± 7.8	----	
Mean duration of dialysis (years)	----	5.1 ± 6.3	
Primary renal disease			
Glomerular (n,%)	24 (32.4)	5 (6)	
Vascular (n,%)	8 (10.8)	21 (26.9)	
Interstitial (n,%)	5 (6.7)	6 (7,6)	
Polycystic kidney disease (n,%)	13 (17.5)	8 (10)	
Diabetes (n,%)	6 (8.1)	20 (26.9)	
Other (n,%)	18 (24.3)	18 (24.3)	
Comorbidities			
Diabetes (n)	27	42	
HIV (n)	1	2	
Ischemic heart disease (n)	14	11	
Cirrhosis (n)	2	6	
History of cancer (n)	2	5	
Anti HBS-Ab			
Negative <10	25	40	
Intermediate: 10-200	26	26	
High: >200	23	12	
Albumin level (g/dl)	4.07 +/- 0.37	3.54 +/- 0.47	
Lymphocyte count (x10³/mm3)	1.630 +/-1250	1.200 +/- 600	
Total Ig level (g/l)	7.58+/- 4.7	8.1 +/- 3,8	
Immunosupressant Regimen			
Induction therapy (n,%) Antithymocyte serum/ Basiliximab (n,%)	77 (100) 27 (35.1) / 49 (64.9)		
Calcineurin inhibitors (n,%)	68 (91.8)	1 (0.01)	
Belatacept (n,%)	2 (2.6)		
Everolimus (n,%)	8 (10.8)		
Anti-metabolite (n,%) Mycophenolate mofetil Mycophenolic acid Azathioprine	61 (82.4) 52 (85.2) 7 (11.5) 2 (3.3)		
Steroids (n,%)	34 (45.9)	3 (3.7)	
Rituximab	---	2 (2.5)	
Type of dialysis HD/HDF (n/n)	---	66/12	
Mean Kt/V	**---**	1.3 +/- 0.2	

BMI = Body Mass Index; HIV; human immunodeficiency virus; HBS-Ab, hepatitis B surface antibodies; HD = Hemodialysis; HDF = Hemodiafiltration.

TABLE 2: Post-vaccine serological response at 36 days after the first injection

	Kidney Transplant Recipients (n=72)	**Hemodialysis patients (n=75)**	**Healthy controls (n=7)**	***p***
% of total study population	46.8%	48.7.8%	4.5%	
Responders (n, % of the group)	3 4.1%	59 85.5%	7 100%	p<0.001 (KTR vs HD) p<0.001 (KTR vs Control) p-0.38, (HD vs Control)
Sars-Cov 2 Antibody level, AU/ml (Median (Q1-Q4))	NA	114 (15 – 1488)	1082 (293 – 5500)	p< 0.0001

KTR = Kidney Transplant recipients **HD** = Hemodialysis **Contr.** = Controls

NA = Not Applicable (low number of responders)

TABLE 3: Post-COVID-vaccine serological response according to titers of anti HBs antibody in patienst undergoing hemodialysis

	Anti HBs-Ab Negative <10 mIU/ml (n=40)	**Anti HBs-Ab Intermediate: 10-200 mIU/ml (n=26)**	**Anti HBs-Ab High: >200 mIU/ml (n=12)**
Titer of anti-SARS-CoV-2 antibody (AU/ml)	36 [1.85 – 526]	113.5 [1.85-1482]	209 [9.06-565]
p	p= 0.016 Negative vs Intermediate	p= 0.295, Intermediate vs High	
	p = 0.03 Negative vs High		

FIGURE LEGEND

Figure 1: Kinetics of humoral response to anti-COVID vaccination in kidney transplant recipients, patients undergoing hemodialysis, and healthy controls.

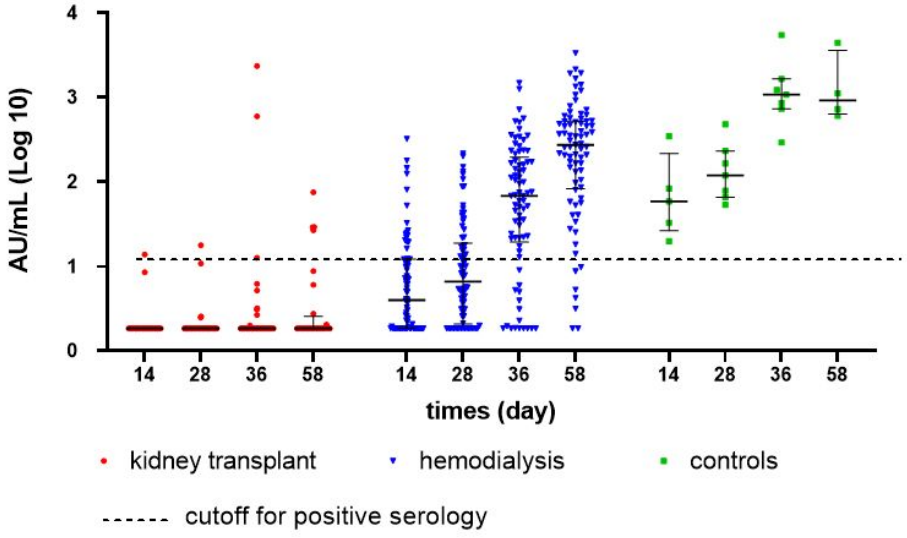
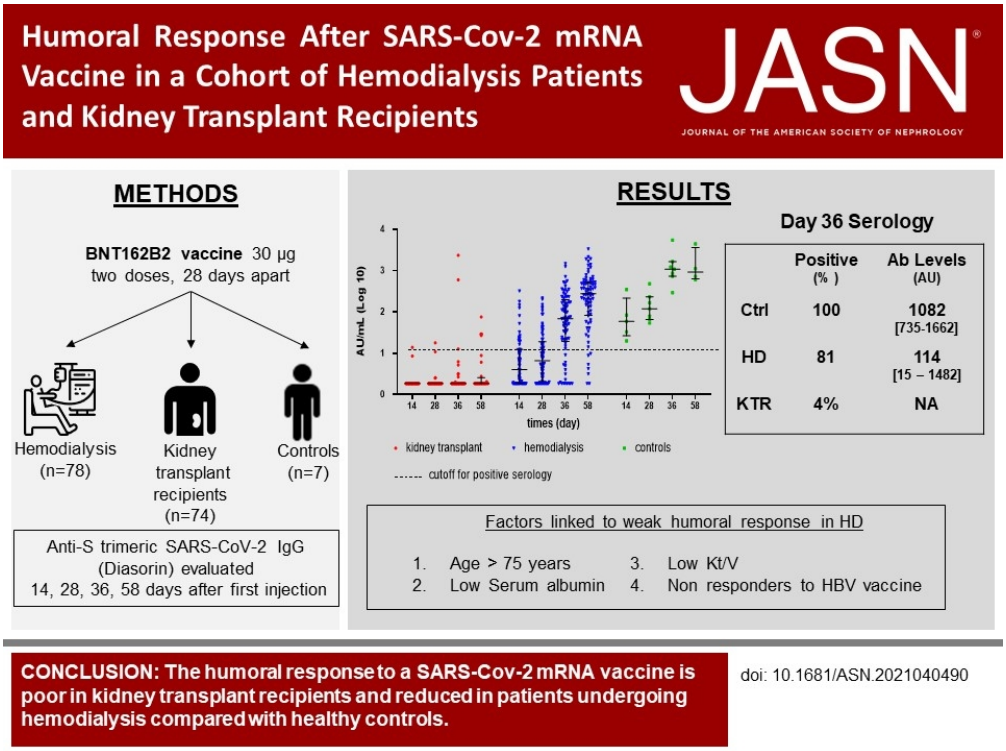


Figure : Evolution of SARS-CoV-2 IgG anti Spike antibody titer for each patient at 14,28,36 and 58 days after the first injection of vaccine (mediane and Interquartile range), number of patients. Cutoff for detection IgG was define for a titer > 1.85 arbitray units per mL (AU/mL), Cutoff for positive serology was defined according to the manufacturer for a titer >13 AU/mL.

Course of SARS-CoV-2 IgG anti spike antibody titers for each patient at 14, 28, 36 and 58 days after the first injection of vaccine (median and interquartile range). Cut-off for detection was a titer >1.85 arbitrary units per mL (AU/mL), and the cut-off for positive serology was defined according to the manufacturer's instructions as a titer >13 AU/mL.



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