

Journal Pre-proof

Low performance of Sinovac vaccine and effect of Belatacept therapy in a study with different types of COVID-19 vaccines in transplanted patients.



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PII: S0041-1345(23)00069-6
DOI: <https://doi.org/10.1016/j.transproceed.2023.02.034>
Reference: TPS 31342

To appear in: *Transplantation Proceedings*

Please cite this article as: Yazmin Rocio Arias-Murillo , María Angèlica Salinas-N , Tatiana Caicedo , Marisol Galindo -Borda , Ximena Meneses-Gil , Camilo Montero , Fernando Giron , Nestor Pedraza , Gustavo Aroca , Martha Lucia Ospina-Martinez , Marcela Mercado-Reyes , Low performance of Sinovac vaccine and effect of Belatacept therapy in a study with different types of COVID-19 vaccines in transplanted patients., *Transplantation Proceedings* (2023), doi: <https://doi.org/10.1016/j.transproceed.2023.02.034>

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HIGHLIGHTS

- The COVID-19 vaccination plan of Colombia included several types of these vaccines offering an opportunity for assessing simultaneously differences in humoral response to them among transplant recipients.
- We found a differential response among vaccines including an absence of humoral response in transplant recipients who received CoronaVac *and were been treated with Belatacept*.
- Patients with hybrid immunity have a greater response, confirming that, despite immunosuppression, kidney transplant recipients are capable of developing a measurable humoral immune response and could achieve greater efficacy in response to vaccination.

Low performance of Sinovac vaccine particularly with Belatacept therapy in a study with different types of COVID-19 vaccines in transplanted patients.

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in a study with different types of COVID-19 vaccines in transplanted
patients.

ABSTRACT

The huge impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections on organ transplant recipients makes it necessary to optimise vaccine efficacy in this population. To effectively implement multiple strategies, it is crucial to understand the performance of each type of available vaccine. In our study the antibody titre was measured, and the presence of antibodies against SARS-CoV-2 was evaluated after 90 days of

immunisation, furthermore, the differences between hybrid immunity, immunity by vaccination and immunosuppressant type were identified. As a result, of the patients included in this study (n=160), 53% showed antibodies against SARS-CoV-2 at 90 days after the first dose in patients who had completed the vaccination schedule. Antibody titres were higher in patients with hybrid immunity, and the proportion of non-responsive patients was higher among those who received the immunosuppressant Belatacept in their post-transplant regimen ($p = 0.01$). Only 15% of patients treated with this medicine seroconverted, and patients vaccinated with CoronaVac and treated with Belatacept showed no response. In conclusion, a reduced response to vaccines against SARS-CoV-2 was identified in the transplant population, and this response varied with the type of vaccine administered and the immunosuppressive treatment.

KEYWORDS

COVID-19, SARS-CoV-2, immunosuppression, kidney transplant, vaccines

ABBREVIATIONS:

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus type 2

INTRODUCTION

Organ transplant recipients represent a special population that is vulnerable to serious infections due to the conditions of prolonged immunosuppression after transplantation. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in patients with transplants may pose a higher risk of mortality (15%–30%)^{1,2}. In the Colombian population, patients with solid organ transplants had three times the mortality rate as the general population³. Therefore, to mitigate the associated clinical outcomes for this group of immunocompromised patients, vaccination against coronavirus disease 2019 (COVID-19) is thought to be of utmost importance⁴. A limitation of developing vaccines against COVID-19 in phase-3 clinical trials is that immunocompromised populations, such as patients with solid organ transplants, are considered only to a small extent⁵. This led to an initial uncertainty in the immune response of this at-risk population.

The Dutch Renal Patients COVID-19 Vaccination (RECOVAC5) multi-center immune response study, which evaluated the immunogenicity, tolerability, and safety of the mRNA-1273 COVID-19 vaccine (Moderna), reported that seroconversion was significantly lower in 288 patients with a kidney transplant than in controls and patients with chronic kidney disease (CKD) (56% vs. 99.4%–100%). Furthermore, patients with kidney transplants who had mycophenolate acid, a low lymphocyte concentration, a lower glomerular filtration rate, a shorter kidney transplantation time, and an older age during the immunosuppressive regimen had a non-immunological response to the vaccine⁵. Similarly, various studies have demonstrated that patients with transplants who received the BNT162b2 COVID-19 mRNA (Pfizer) and Moderna vaccines had low levels of anti-S antibodies against COVID-19 after receiving the first dose on day 28 of administration (10.18%–17%)^{6,7}, and the second dose (36.4%–63%) between days 28, and 31 after the completion of the vaccination schedule⁷⁻¹⁰. Recent studies have attempted to determine whether seronegative kidney transplant recipients exhibit some degree of cellular response that provides immunization against COVID-19 after vaccination, despite the low seroconversion rates in these recipients. Cellular and humoral response of 65% was reported in a study that included 148 kidneys (n = 133) and dual pancreas (n = 15) transplant

recipients¹¹. In a study that was published in Chile¹², only 20.6% of solid organ transplant patients developed neutralizing antibodies and seropositivity after two doses of the CoronaVac vaccine. To the best of our knowledge, this is the only published study on the immune response in patients with solid organ transplants in Latin America.

No published studies on the transplant population have examined the immunological response to the COVID-19 vaccine in Columbia. Characterizing and establishing the immune response in kidney transplant recipients following COVID-19 vaccination at the local level is crucial and necessary. Therefore, the present study aimed to determine the presence of antibody titers against SARS-CoV-2 in a cohort of patients with transplants after 90 days of immunization using different types of SARS-CoV-2 vaccines.

MATERIALS AND METHODS

Type of Study

This was a longitudinal study conducted on patients with transplants who received immunization as per the vaccination schedule with any of the following vaccines against SARS-CoV-2: CoronaVac (SinoVac), AZD1222 (AstraZeneca), Ad26.COV2.S (Janssen), ARNm-1273 (Moderna), or BNT162b2 (Pfizer-BioNTech).

Study population

The study population included 160 functional organ transplant recipients who were recruited from four health entities and vaccinated with one of the following vaccines: CoronaVac (SinoVac), Ad26.COV2.S (Janssen), AZD1222 (AstraZeneca), mRNA-1273 (Moderna), or BNT162b2 (Pfizer-BioNTech). The included participants were those who voluntarily decided to participate in the investigation after signing the informed consent form, and they had undergone a follow-up examination on day 90 post-immunization. Blood transfusion recipients and/or individuals who had recently experienced organ rejection within the previous 3 months were excluded from the study. Samples for analysis were collected at three follow-ups. The first follow-up was conducted 30 days after the administration of the first dose or 21 and 28 days, depending on the type of vaccine; this

follow-up period coincided with the second vaccination dose for two-dose vaccines. The second follow-up was conducted 60 days after the administration of the first dose. The third follow-up was conducted 90 days after the administration of the first dose with patients who had completed the vaccination schedule.

Data collection and sampling

Patient information was collected in a pre-coded format specifically designed for data collection, with the following components: individual, clinical conditions, and vaccines. A venous blood sample was collected in a dry tube with a gel to determine antibodies against SARS-CoV-2 at each of the three follow-up visits.

Laboratory tests for detecting antibodies against severe acute respiratory syndrome coronavirus 2

Two commercial kits manufactured by Siemens were used to detect total SARS-CoV-2, total (COV2T), and SARS-CoV-2 IgG (COV2G) antibodies to detect the presence of antibodies against the S and N proteins of the virus. They enabled the detection of antibodies against the S antigen of the virus (angiotensin receptor binding domain).

Additionally, to detect targeted antibodies against the nucleocapsid of SARS-CoV-2, ID. Vet (SARS-CoV-2-N IgG Indirect), an analysis based on the enzyme-linked immunosorbent assay was performed on the samples of participants who had received BNT162b2, AZD1222, and Ad26.COV2.S. Because the S antigen has greater immunogenicity against the virus, monitoring IgG antibodies against this protein allows for monitoring of post-vaccination antibodies, whereas monitoring antibodies against the N antigen provides an idea of previous infections by the virus.

The results of the antibody titers were reported in terms of binding antibody units (BAU)/ml, with a measurement range between 21.8 and >2,180 BAU/ml.

Analysis plan

For qualitative variables, a descriptive analysis was performed with absolute and relative frequency measurements. Measures of central tendency (means or medians) were used as quantitative variables.

The population was characterized using the variables of age group, sex, socioeconomic status, place of residence, education level, creatinine levels, years of transplantation, reactivity, non-reactivity and hybrid immunity, and other co-morbidity-related variables.

Absolute and relative frequencies were estimated for the categorical variables presented in the frequency tables. Measures of central tendency and dispersion were calculated for the numerical variables using the medians and interquartile ranges (difference in the 75th and 25th percentiles). The presence of antibody titers against SARS-CoV-2 post-immunization with a type of immunosuppressant was analyzed. The chi-square and Fisher's tests were used to verify the statistical significance and the strength of the bivariate association.

After the bivariate analysis with immunosuppressive drugs, a multivariate analysis using a logistic model was performed. The response variable was coded as being reactive or not. The type of immunosuppressive drug, age, and sex was also included. The final model selected will be the one where the p-value to obtain the OR is less than 0.05. Box-and-whisker plots were made to analyze the BAU/ml values at each follow-up by comparing the hybrid categories and types of vaccine.

Statistical analyses were performed with a Type I error rate of 10% (90% confidence) using the IBM SPSS 25 software.

Ethical considerations

This research was conducted following aspects mentioned in the Declaration of Helsinki on Research Ethics (World Medical Association, 2013) and the Resolution 8430 of 1993 of the Ministry of Health, which sets the academic, technical, and administrative standards for health research. Title II, Chapter I, Article 11 on the ethical aspects of research involving human beings classifies this research as having minimal risk. Each participant signed an informed consent form that was approved by the National Institute of Health Research Ethics and Methodologies Committee (CEMIN).

RESULTS

General characteristics of the study population

Antibody titers against SARS-CoV-2 were analyzed in 160 kidney transplant recipients. Of these, 55.6% were men, and the median age was 50 years (range, 19–74 years), 56.9% were >48 years old, 31% had a basic secondary school degree, and 75.6% resided in the city of Bogota (Table 1). The median creatinine level was 1.3 mg/dL; the median number of years from the transplant to the start of the vaccination schedule was 7 years (range, 1 month–23 years). A total of 55.6% had high blood pressure, 18.1% had diabetes, 2.5% had chronic obstructive pulmonary disease, 11.3% had hypothyroidism and 5.6% had heart disease.

Reactivity and antibody titers in binding antibody unit/ml values according to follow-up and type of immunity

In total, 19 patients were included in the first follow-up. Of these, 42% were non-reactive and 58% were reactive (including 42% with hybrid immunity and 16% with vaccine immunity). In the second follow-up, 56 patients were included; of these, 36% were non-reactive and 64% were reactive (including 32% with hybrid immunity and 32% with vaccine immunity). At the third follow-up, 160 patients were included. Of these, 47% were non-reactive, and 53% were reactive (including 23% with hybrid immunity and 30% with vaccine immunity) (Figure 1).

Patients from the first and second follow-ups were included in the total number of patients analyzed in the third follow-up. Because not all participants were enrolled at the first follow-up, the number of participants in each follow-up varied.

Of the 160 patients who were enrolled in the study with a follow-up cut-off of the third visit or 90 days after vaccination, 59% (94) received the Pfizer vaccine, 23% (36) received Sinovac, 12% (19) received Janssen, 4% (6) received AstraZeneca, and 3% (5) received Moderna.

The biological Sinovac presented the highest percentage of non-reactivity (53%), while Janssen and Moderna had the lowest percentage of non-reactivity (Table 2).

Moderna's reactivity ratio was 1.0, indicating that 100% of the patients included in the study had antibodies against SARS-CoV-2 after immunization. Table 3 shows the crude reactivity ratio and the ratio adjusted for the sensitivity and specificity of each vaccine.

The comparison of BAU/ml values at each follow-up visit between those who showed reactivity (categorized into two groups) is shown in Figure 2: those showing hybrid immunity and those with non-hybrid immunity, i.e. those who only showed immunity through vaccination.

In the first follow-up ($n = 11$), it was observed that in the non-hybrid group ($n = 3$), the median value was 2,180 (range, 122–2,180). For the hybrid group ($n = 8$), the median value was 2,180 (range, 714–2,180).

In the second follow-up ($n = 37$), it was determined that in the non-hybrid group ($n = 18$), the median value was 1,397 (range, 90–2,180); for the hybrid group ($n = 19$), the median value was 2,180 (range, 494–2,180).

In the third follow-up ($n = 85$), it was observed that in the non-hybrid group ($n = 49$), the median value was 656 (range, 122–2,180); for the hybrid group ($n = 36$), the median value was 2180 (range, 2,180–2,180).

Figure 2 shows a comparison of BAU/ml values by follow-up among reactive individuals with hybrid and non-hybrid immunity.

Figure 3 shows a comparison of BAU/ml values in patients who had antibody titers to SARS-CoV-2. Those who were considered reactive ($n = 85$) were distinguished between those who had hybrid immunity and those who had only vaccine immunity (non-hybrids).

For individuals vaccinated with AstraZeneca ($n = 3$), no difference was observed between the medians of those who presented hybrid immunity and those who did not, with a median value of 2,180. The value of the adjusted proportion of reagents was 50%. For individuals vaccinated with Janssen ($n = 12$), it was observed that in the non-hybrid group ($n = 7$), the median value was 2,180 (range, 490.06–2,180). For the hybrid group, if ($n = 5$) the value of all was 2,180, the adjusted item ratio value was 66%.

For those vaccinated with Moderna ($n = 5$), it was observed that the value was 2,180 for the non-hybrid group ($n = 2$). For the hybrid group, if ($n = 3$) the value of all was 2,180, the value of the adjusted reactant ratio was 100%.

Among those vaccinated with Pfizer ($n = 48$), it was observed that in the non-hybrid group ($n = 29$), the median value was 341.39 (range, 113.58–2,180). For the hybrids, if ($n = 19$) the value of all was

2,180, the adjusted reagent ratio value was 52%. Finally, among those vaccinated with Sinovac (n = 17), it was observed that in the non-hybrid group (n = 9), the median value was 197.07 (range, 53.19–1181.12). For the hybrid group (n = 8), the value of the median was 355.56 (range, 57.55–2,180), and the value of the adjusted proportion of items was 46%.

On day 90, a crossover of each immunosuppressant given to the patients was done, with Belatacept gaining significance. This indicates a significant difference in the percentage of non-reactivity among the individuals receiving this medicine. Overall, 15% of the total study participants received Belatacept as part of their immunosuppressive therapy regimen. A multivariate logistic model was used to verify the association between Belatacept consumption and non-reactivity ($p < 0.05$). In total, 17% of participants from the AstraZeneca group, 5% from Janssen, 0% from Moderna, 13% from Pfizer, and 28% from Sinovac included this medicine in their immunosuppressive treatment plan out of the total number of patients who received any vaccination. Of those who received Belatacept, 100% of those vaccinated with AstraZeneca and Janssen were reactive, whereas of those vaccinated with Pfizer and Sinovac, 83% and 70% were non-reactive, respectively, and the remaining 17% and 30% were reactive.

DISCUSSION

Several studies, mostly using mRNA¹³⁻¹⁹ platforms, have found that kidney transplant recipients had a lower likelihood of developing a humoral immune response to immunization than the general population.

Our study evaluated seroconversion in kidney transplant recipients after 90 days of the first dose under different platforms. Table 1 shows that among 125 seronegative kidney transplant recipients who received various vaccinations, vaccination with an inactivated virus (Sinovac) resulted in the lowest rate of seroconversion 90 days after the first dose (28%). This was compared to platforms mRNA BNT162b2 (Pfizer-BionTech) 31%, mRNA 1273 (Moderna) 40%, and platforms with viral vectors ChAdOx1 nCoV-19 (Astra Zeneca) 33% and Ad26.CoV2.S (Janssen) 37%. Even if vaccination in kidney transplant recipients with the inactivated virus was associated with seroconversion, the antibody titers in BAU values/ml were lower than in kidney transplant recipients vaccinated under

other platforms. The antibody concentration is associated with protection against infection and disease in the presence of new variants²⁰.

Regarding vaccination with an inactivated virus (Sinovac), our results are similar to those of approximately 465 cases published in Thailand, Turkey, Uruguay, and Chile, with a percentage of seroconversion in seronegative kidney transplant recipients before the start of vaccination between 7.2% and 27.8% and a measurement time between 28 and 90 days after receiving the second dose (Table 3)²¹⁻²⁵. This percentage was significantly lower than that of the mRNA vaccination platforms in kidney transplant recipients²⁶⁻²⁸. Regarding vaccination through platforms with viral vectors, the data regarding seroconversion in kidney transplant recipients are scarce. A study on 131 seronegative patients, including 52 cases vaccinated with ChAdOx1 nCoV-19 (Astra Zeneca), 9 with Ad26.CoV2.S (Janssen), 68 with mRNA BNT162b2 (Pfizer-BionTech), and 8 with mRNA 1273 (Moderna) evaluating the presence of antibodies 2–4 weeks after the last dose, found a seroconversion rate of 33% in patients vaccinated with viral vectors. This was 58% in patients under the mRNA platform, indicating a statistically significant difference. We discovered a similar percentage of seroconversion in our study, despite having a very small patient population. In a cohort of 920 patients, another study comparing the immunogenicity of BNT 162b2 and ChAdOx1 discovered a seroconversion rate of 61.6% and 43.6%, respectively²⁹⁻³⁰.

In our study, the proportion of seronegative kidney transplant patients vaccinated with mRNA platforms had a lower seroconversion percentage than that reported in the literature³¹⁻³².

Several factors associated with a lower probability of humoral response have been described; this mainly includes immunosuppression with antimetabolites³³. However, a characteristic of our patients that could explain the lower seroconversion rate in our series is the use of immunosuppression with costimulation inhibitors (Belatacept) in 24 patients, representing 15% of the follow-up cohort. Our results suggest belatacept consumption is a risk factor for not developing antibodies.

We examined 160 kidney transplant recipients; of these, 24 (15%) received Belatacept. Under this immunosuppression regimen, vaccination against influenza has been described as being associated with significantly reduced total and specific IgG levels compared with those receiving tacrolimus³⁴.

Of the 24 cases in our study treated with Belatacept, 12 received vaccination with mRNA BNT162b2 (Pfizer-Biontech), 10 with an inactivated virus (Sinovac), 1 with ChAdOx1 nCoV-19 (Astra Zeneca) and 1 with Ad26. CoV2.S (Janssen). The overall seroconversion among those receiving Belatacept was 15%; 2/12 (16.6%) with mRNA BNT162b2 (Pfizer-Biontech) remained seronegative, 0/7 (0%) with an inactivated virus (Sinovac) and 1/1 (100%) with Ad26.CoV2. S (Janssen) on day 90 after the first dose.

Various studies have reported a seroconversion rate of 5%–17% in Belatacept-treated kidney transplant recipients after receiving two doses of vaccine with the mRNA platform. However, we believe this is the first description of behavior among different vaccination platforms, particularly the inactivated virus (Sinovac) platform with a lack of humoral response. This suggests that we should explore different options for those receiving immunosuppression according to this scheme³⁵⁻³⁸.

Finally, Table 2 shows 35 patients with the presence of antibodies and hybrid immunity, confirming that despite immunosuppression, kidney transplant recipients can develop a measurable humoral immune response and could achieve greater efficacy in response to vaccination, as in the general population was described³⁹.

The advantages of our study include monitoring kidney transplant recipients who have received different vaccination platforms and evaluating the behavior of non-mRNA vaccination platforms under immunosuppression schemes based on costimulation inhibitors.

Larger studies with a higher number of patients, which would allow us to adjust for comorbidities, are required to evaluate the potential adverse effect of Belatacept on the development of post-vaccine antibodies against Sars-CoV-2 and to establish their real effect on the development of symptomatic COVID-19 infections. Our findings suggest the need to continue evaluating the use of immunosuppressive drugs, such as Belatacept, on the immune response in patients administered these drugs, probably associated with the interaction of Belatacept with surface molecules CD80 and CD86 on antigen-presenting cells, blocking the co-stimulation of T lymphocytes mediated by CD28, altering their complete activation, which requires the triad constituted by antigenic presentation, soluble cytokine sensing, and co-stimulation.

The primary limitation of our study was the small sample, which did not allow us to draw definitive conclusions. In conclusion, the type of vaccination platform and the immunosuppression regimen impact the humoral response to vaccination against COVID-19 in kidney transplant recipients.

ACKNOWLEDGEMENTS

The authors would like to thank the study participants for their time and essential contribution. Our special thanks go to the staff of the participant clinical institutions and the members of the Donation and Transplantation Group of the National Institute of Health of Colombia.

CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest.

FUNDING

This research was funded by the National Institute of Health, project code CEMIN-19-2021, an investment project strengthening the coordination of blood banks and donation and transplant networks, national code BPIN -2018011000083, and resources of the hospitals with transplant programs participating.

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Table 1. General characteristics of the study population.

		Type of vaccine					
		ASTRAZENECA	JANSSEN	MODERNA	PFIZER	SINOVAC	Total
Age Groups	18 - 27	0 (0)	2 (10,5)	0 (0)	2 (2,1)	2 (5,6)	6 (3,8)
	28 - 37	0 (0)	8 (42,1)	2 (40)	16 (17)	2 (5,6)	28 (17,5)
	38 - 48	0 (0)	6 (31,6)	0 (0)	21 (22,3)	8 (22,2)	35 (21,9)
	48 - 58	3 (50)	1 (5,3)	2 (40)	36 (38,3)	8 (22,2)	50 (31,3)
	>58	3 (50)	2 (10,5)	1 (20)	19 (20,2)	16 (44,4)	41 (25,6)
Sex	Male	5 (83,3)	13 (68,4)	2 (40)	50 (53,2)	19 (52,8)	89 (55,6)
	Female	1 (16,7)	6 (31,6)	3 (60)	44 (46,8)	17 (47,2)	71 (44,4)
Socioeconomic level	I	0 (0)	2 (10,5)	0 (0)	5 (5,3)	1 (2,8)	8 (5)
	II	3 (50)	5 (26,3)	3 (60)	29 (30,9)	15 (41,7)	55 (34,4)
	III	2 (33,3)	9 (47,4)	1 (20)	35 (37,2)	15 (41,7)	62 (38,8)
	IV	1 (16,7)	3 (15,8)	0 (0)	17 (18,1)	2 (5,6)	23 (14,4)
	V	0 (0)	0 (0)	1 (20)	4 (4,3)	3 (8,3)	8 (5)
	VI	0 (0)	0 (0)	0 (0)	4 (4,3)	0 (0)	4 (2,5)
	SD	0 (0)	0 (0)	0 (0)	1 (1,1)	0 (0)	1 (0,6)
City	Atlántico	0 (0)	1 (5,3)	0 (0)	7 (7,4)	2 (5,6)	10 (6,3)
	Bogotá	4 (66,7)	16 (84,2)	4 (80)	67 (71,3)	30 (83,3)	121 (75,6)
	Cartagena	0 (0)	0 (0)	0 (0)	0 (0)	1 (2,8)	1 (0,6)
	Bogota	2 (33,3)	2 (10,5)	1 (20)	18 (19,1)	3 (8,3)	26 (16,3)
	Surrounding towns						
	Neiva	0 (0)	0 (0)	0 (0)	1 (1,1)	0 (0)	1 (0,6)
School grade	Ninguna	1 (16,7)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0,6)
	Primary school	1 (16,7)	2 (10,5)	1 (20)	6 (6,4)	3 (8,3)	13 (8,1)
	High School	1 (16,7)	8 (42,1)	2 (40)	25 (26,6)	13 (36,1)	49 (30,6)
	Technician or technologist	2 (33,3)	6 (31,6)	2 (40)	21 (22,3)	8 (22,2)	39 (24,4)
	Undergraduate	1 (16,7)	3 (15,8)	0 (0)	25 (26,6)	8 (22,2)	37 (23,1)
	Postgraduate	0 (0)	0 (0)	0 (0)	17 (18,1)	4 (11,1)	21 (13,1)
Transplant years	Minimum	3,00	1,00	1,00	2,00	1,00	1,00

	Maximum	10,00	16,00	13,00	23,00	24,00	24,00
	Median	8,00	9,00	5,00	7,00	9,00	8,00
	25th percentile	4,00	6,00	2,00	5,00	5,00	5,00
	75th percentile	10,00	14,00	5,00	13,00	13,50	13,00
Hypertension	No	0 (0)	6 (31,6)	1 (20)	47 (50)	17 (47,2)	71 (44,4)
	Yes	6 (100)	13 (68,4)	4 (80)	47 (50)	19 (52,8)	89 (55,6)
Diabetes	No	5 (83,3)	14 (73,7)	4 (80)	80 (85,1)	28 (77,8)	131 (81,9)
	Yes	1 (16,7)	5 (26,3)	1 (20)	14 (14,9)	8 (22,2)	29 (18,1)
Chronic obstructive pulmonary disease	No	6 (100)	19 (100)	4 (80)	91 (96,8)	36 (100)	156 (97,5)
	Yes	0 (0)	0 (0)	1 (20)	3 (3,2)	0 (0)	4 (2,5)
Hypothyroidism	No	5 (83,3)	14 (73,7)	5 (100)	86 (91,5)	32 (88,9)	142 (88,8)
	Yes	1 (16,7)	5 (26,3)	0 (0)	8 (8,5)	4 (11,1)	18 (11,3)
Heart disease	No	6 (100)	14 (73,7)	5 (100)	91 (96,8)	35 (97,2)	151 (94,4)
	Yes	0 (0)	5 (26,3)	0 (0)	3 (3,2)	1 (2,8)	9 (5,6)

Table 2. Reactivity by type of vaccine and immunity.

Type of vaccine	Non-reactive		Reactive					
			vaccine immunity		Hybrid immunity		% Total reactive	
	n	%	n	%	n	%	n	%
AstraZeneca	3	50%	2	33%	1	17%	3	50%
Janssen	7	37%	7	37%	5	26%	12	63%
Moderna	0	0%	2	40%	3	60%	5	100%
Pfizer	46	49%	29	31%	19	20%	48	51%
Sinovac	19	53%	10	28%	7	19%	17	47%
Totals	75	47%	50	31%	35	22%	85	53%

Table 3. Proportion of reactivity to each type of vaccine at day 90 post immunization.

Vaccine	% Crude	%
		Adjusted
AstraZeneca	0.50	0.50
Janssen	0.63	0.66
Moderna	1.00	1.00
Pfizer	0.51	0.52
Sinovac	0.47	0.46

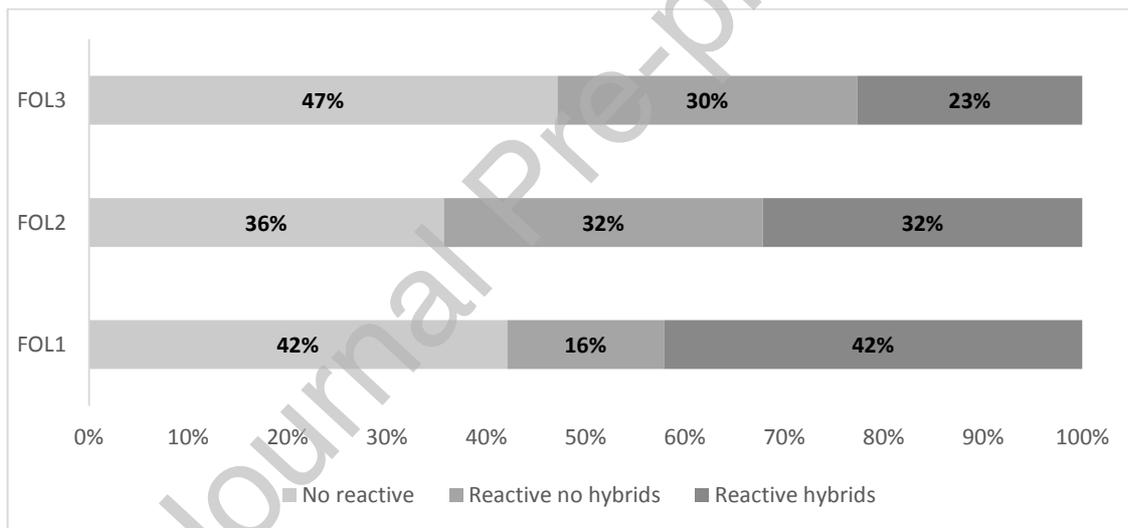
FIGURE 1

Figure 1. SARS-CoV-2 antibody detection based on follow-up examination.

FIGURE 2

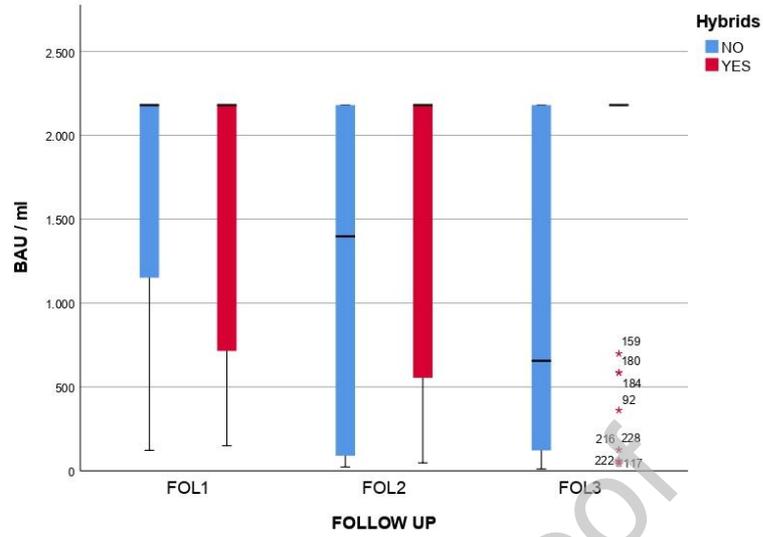


Figure 2. Comparison of BAU/ml values by follow-up between reactive individuals with hybrid and non-hybrid immunity.

FIGURE 3

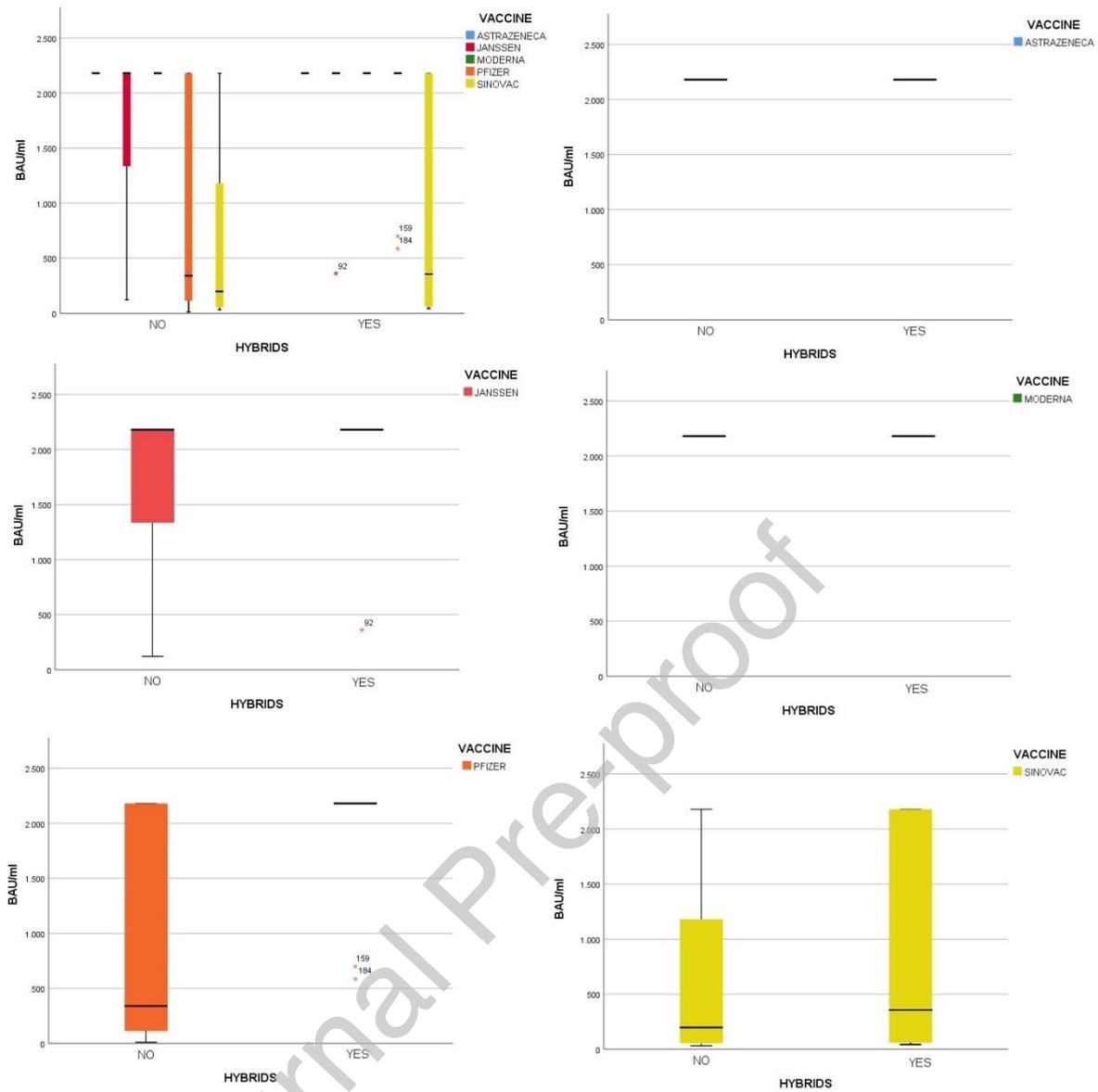


Figure 3. Comparison of BAU/ml values of reactive patients at third follow-up by vaccine type between hybrids and non-hybrids.