Reduced immune response to inactivated SARS-CoV-2 vaccine in a cohort of immunocompromised patients in Chile

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Summary: Inactivated-SARS-CoV-2 vaccine induced lower NAb positivity in solid organ transplant, rheumatic diseases, cancer, and HIV infected groups compare to controls. Specific cellular response did not differ significantly between groups. A boosting vaccination strategy should be considered in these vulnerable patients.

Abstract

Background: Inactivated SARS-CoV-2 vaccines have been widely implemented in low- and middle-income countries. However, immunogenicity in immunocompromised patients has not been established. Herein, we aimed to evaluate immune response to CoronaVac vaccine in these patients.

Methods: This prospective cohort study included 193 participants with five different immunocompromising conditions and 67 controls, receiving two doses of CoronaVac 8-12 weeks before enrollment. The study was conducted between May and August 2021, at Red de Salud UC-CHRISTUS, Chile. Neutralizing antibodies (NAb) positivity, total anti-SARS-CoV-2 IgG antibodies (TAb) concentration, and T cell response were determined.

Results: NAb positivity and median neutralizing activity were 83.1% and 51.2% for the control group versus 20.6% (p<0.0001) and 5.7% (p<0.0001) in the solid organ transplant (SOT) group, 41.5% (p<0.0001) and 19.2% (p<0.0001) in the autoimmune rheumatic diseases group, 43.3% (p=0.0002) and 21.4% (p=0.0013) in the cancer patients with solid tumors group, 45.5% (p<0.0001) and 28.7% (p=0.0006) in the HIV infected group, 64.3% (p=n.s.) and 56.6% (p=n.s.) in the hematopoietic stem cell transplantation (HSCT) group, respectively. TAb seropositivity was also lower for the SOT (20.6%, p<0.0001), rheumatic diseases (61%, p=0.0001) and HIV groups (70.9%, p=0.0032), compared to control group (92.3%). On the other hand, the number of IFN-γ Spot Forming T Cells specific for SARS-CoV-2 tended to be lower but did not differ significantly between groups.

Conclusions: Diverse immunocompromising conditions markedly reduce the humoral response to CoronaVac vaccine. These findings suggest a boosting vaccination strategy should be considered in these vulnerable patients.

Keywords: SARS-CoV-2; COVID-19; vaccine; CoronaVac; inactivated vaccine; Immunocompromised Patient

Clinical Trials registration: NCT04888793

Introduction

The COVID-19 pandemic has ravaged across the globe claiming >4 million lives (1). New vaccine platforms such as adenovirus vectored and nucleic acid vaccines have succeeded in inducing robust cellular and humoral immune responses (2). Novel mRNA vaccines such as the BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) have reported a stunning >94% efficacy against COVID-19 (3, 4). However, many low- and middle-income countries have had access to traditional inactivated vaccines approved under emergency use, such as CoronaVac (Sinovac), BBIBP-CorV (Sinopharm Beijing), or BBV152 (Bharat Biotech) SARS-CoV-2 vaccines (5). Inactivated vaccines have demonstrated relatively lower levels of neutralizing antibodies (NAb) and T-cell responses versus other vaccines, and require to be assisted by adjuvants with one or more boosters to establish immunological memory (2). A preliminary study in healthy individuals showed lower NAb concentrations obtained by CoronaVac compared to mRNA-based vaccine (6). This is relevant since neutralization antibodies could predict immune protection following SARS-CoV-2 vaccination and in-vitro neutralization titers remain a correlate of protection from SARS-CoV-2 variants (7, 8).

In Chile, COVID-19 was first detected in March 2020. Eighteen months later official numbers reached > 1.6 million confirmed cases and >37,000 deaths. As of January 2nd 2021, over 90% of its target population has received two vaccine doses and CoronaVac has been the main vaccine utilized in over 70% of cases (9). Phase III trial in 18-59-year-old subjects indicated 83.5% of CoronaVac efficacy against symptomatic COVID-19 (10). Locally, the reported prevention and mortality effectiveness were 65.9% and 86.3% respectively (11).

Immunocompromised patients represent a vulnerable population at higher risk of severe COVID-19 and death from COVID-19, and there are very limited data on efficacy of SARS-CoV-2 vaccines in these patients. The present study aimed to evaluate the immune response induced by an inactivated anti-SARS-CoV-2 vaccine CoronaVac in adults with different acquired immunosuppressing conditions, as compared with healthy volunteers.

Methods

Study population and design

Adult patients with pre-defined acquired immunosuppressive conditions under medical care at Red de Salud UC-CHRISTUS (Santiago, Chile) and collaborating centers (Hospital Clínico Universidad de

Chile, Santiago, Chile) having received two doses of CoronaVac vaccine separated by 4 weeks (standard schedule), with the second dose administered 8-12 weeks before enrollment, were invited to participate between May 12th and August 6th, 2021. In addition, participants without immunosuppression vaccinated with two doses of CoronaVac at the same time-period, were selected for the control arm. Patients reporting previous SARS-CoV-2 infection or having received plasma or intravenous immunoglobulin therapy in the previous 60 days were excluded.

Specific inclusion criteria for each cohort were the following: **1.** Cancer cohort: diagnosis of solid tumor (excludes leukemias, lymphomas, or multiple myelomas) and currently receiving chemotherapy. **2.** Hematopoietic stem cell transplantation (HSCT) cohort: allogeneic with active immunosuppressive treatment or autologous transplantation, in the last 5 years. **3.** Solid organ transplant (SOT) cohort: liver, kidney or heart transplant in the last 5 years, and active immunosuppressive treatment. **4.** HIV cohort: HIV infection under antiretroviral therapy with $CD4^+$ cell count ≤ 500 cells/mm^3 and HIV viral load <200 copies/ml. **5.** Autoimmune rheumatic diseases cohort: rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, relapsing polychondritis, Behcet's disease or juvenile idiopathic arthritis, receiving chronic immunomodulatory treatment with anti-TNF, anti-IL6 or anti-IL17 agents.

Blood sampling: A single blood sample was taken between 8-12 weeks (+/-72h) after the second dose of CoronaVac vaccine.

Outcomes: The primary outcome was humoral immunogenicity assessed by the proportion of participants with positive SARS-CoV-2 NAb 8-12 weeks after CoronaVac vaccine. Secondary immunogenicity outcomes were the percentage of neutralizing activity, expressed as inhibition percentage of NAb, IgG seropositivity measured as total IgG anti- spike protein (S1) domain of SARS-CoV-2 (TAb), geometric mean concentration (GMC) of anti-S1 IgG, and specific T cell immune response to SARS-CoV-2 antigens. The study was registered with ClinicalTrials.gov (NCT04888793).

Laboratory assessments

Determination of anti-SARS-CoV-2 IgG antibodies

A commercial ELISA (SARS-CoV-2 QuantiVac, Euroimmun, Lübeck, Germany) was used for quantitative *in vitro* determination of human TAb in serum samples. Data were expressed in Relative Units per ml (RU/ml) and values ≥11 RU/ml were interpreted as positive according to manufacturer instructions.

Determination of neutralizing antibodies against SARS-CoV-2

The presence of NAbs against SARS-CoV-2 was determined using a SARS-CoV-2 Surrogate Virus Neutralization Test (sVNT) Kit (GenScript, New Jersey, USA), according to the manufacturer instructions. The test assesses the presence/absence of NAb and allows the interpretation of the inhibition rate as Inhibition = [1 – (OD value of Sample/OD value of Negative Control)] × 100%. A percentage of neutralization ≥30 at a 1:10 sample dilution was considered positive.

The assessment of Variant of Concern neutralization was performed using an sVNT developed based on previous reports (12). RBD unconjugated proteins from SARS-CoV-2 variant D614G was obtained from GenScript (#Z03483) and P.1-Gamma variant was obtained from SinoBiological (#40592-V08H86). The percentage of inhibition was defined as: [OD_{450nm} value of negative control-OD_{450nm} value of sample] / [OD_{450nm} value of negative control*100].

Cellular immunity assessments

The presence of IFN-γ Spot Forming T Cells (SFC) specific for SARS-CoV-2 was determined with human IFN-γ/IL-4 double-color ELISPOT assay (Immunospot), using isolated Peripheral Blood Mononuclear Cells (PMBCs), obtained as previously described (13). T cells were stimulated with Mega Pools (MPs) of peptides derived from the SARS-CoV-2 proteome, which include 2 sets of 15-mer peptides derived from the Spike protein (MP-S) and the remaining proteins (MP-R) and 2 sets of 8- to 9-mer peptides derived from the whole proteome as previously described (14). A total of $3x10^5$ cells were incubated with each respective stimulus and incubated for 48 h at 37ºC, 5% CO_2, (13). As positive controls, PBMCs were stimulated with Concanavalin A and MPs of peptides derived from Cytomegalovirus (CMV) and stimulation with DMSO 1% was included as negative control to determine unspecific response. IFN-γ/IL-4 production was measured as indicated by the manufacturer and SFCs were counted on an ImmunoSpot® S6 Micro Analyzer. SFC obtained in DMSO stimulation were subtracted to the SFC obtained for each MP stimulation and expressed as SFC per $3x10^5$ cells.

Statistical analyses

The sample size was calculated with a significance level of 5% and a statistical power of 90% to detect differences of 15% in post-vaccine NAb seropositivity for immunocompromised patients compared to the control group. The seropositivity in the immunocompetent population was estimated to be 97% according to the results of the Phase I/II study of the CoronaVac vaccine at 28

days post vaccination (15). The total number of patients to be recruited was 86 for each study arm with total participants 516. Dichotomous variables were compared with the chi-square test or Fisher exact test, and continuous variables with t-test or Mann-Whitney test. Confounding effects and effect modifier of potential covariates such as age, body mass index and time from vaccination were explored using generalized linear models. Binary variables such as seropositivity in NAb or TAb were analyzed with logistic regression, whereas NAb inhibition percentage was examined using a beta regression model. The quantitative measurement of anti-SARS-Cov2 IgG antibodies was expressed in geometric means and analyzed with generalized linear models with gaussian family and identity link functions, respectively. Exponentiated coefficients of the log transformed dependent variable provided the effects of the covariates on the geometric mean. These models were chosen based on the characteristics of the dependent variables as well as their goodness of fit using the Akaike information criterion (AIC). Analyses and graphs were performed using STATA version 14 and GraphPad Prism 9.0.1.

Ethics

This study was approved by the institutional review board of the Pontificia Universidad Católica de Chile. Informed consent was obtained from all patients.

Results

Description of cohorts

A total of 260 healthy individuals and patients with immunocompromising conditions consented to this study. We excluded a total of 21 participants that were found not to fulfil protocol inclusion/exclusion criteria. Thus, final groups of analysis included 65 healthy controls, 34 SOT patients, 41 rheumatic diseases patients, 30 solid tumors cancer patients, 55 HIV infected patients and 14 HCST patients (Figure 1). Clinical and epidemiological characteristics of enrolled patients are described in Table 1.

Humoral immune response

The proportion of individuals with positive NAb and positive TAb were 40.8% and 63.8% respectively, for all immunocompromised patients, vs 83.1% and 92.3% in the control group ($p<0.001$). The proportion of patients who reached NAb positivity and the amount of neutralizing activity were significantly lower in all immunocompromised cohorts compared to the control group, except for the

HSCT group (Figure 2a-b). Neutralizing response was particularly impaired in SOT group with only 20.6% of participants reaching NAb positive response and a median neutralizing activity of 5.66% (IQR 3.7-11.7) versus 51.21% (IQR 34.6-68.6) in the control group (p<0.0001). Multivariable analysis adjusting for age, body mass index, and time from vaccination to blood sampling did not modify these findings (Table 2). TAb positivity and concentration were also significantly lower in the SOT (20.6% and GMC 5.6 AU ml^{-1}, both p<0.0001), rheumatic diseases (61% and GMC 15.2 AU ml^{-1}, both p<0.001) and HIV (70.9% and GMC 21.2 AU ml^{-1}, both p<0.005) groups, compared to the control group (92.3% and GMC 36.8 AU ml-1) (Figure 2c-d). Neither TAb seropositivity in cancer group nor in HSCT group differ from the control group. These findings were consistent in multivariable analysis (Table 2). As an exploratory analysis, we evaluated other co-variables that would impact the humoral response. We found that a negative NAb was strongly associated with the use of prednisone (87.32% vs. 12.68%, p=0.001) and mycophenolate (71.43% vs. 28.57%, p= 0.007). For all study participants, we found a strong correlation between TAb concentration and NAb neutralizing activity expressed as inhibition percentage (r = 0.864, p<0.0001) with an AUC of 0.965 (95% CI 0.943-0.988) and a cut-off of TAb ≥26 RU/ml best predicting NAb seropositivity (92% sensitivity and 94% specificity) (Figure S1).

The neutralization capacity against the SARS-CoV-2 variants D614G and Gamma was tested for 9-13 sera from control and immunosuppressed patients having resulted with a positive NAb response in previous assays. These studies were performed using a sVNT that evaluated the capacity of sera to inhibit the binding of RBDs from these SARS-CoV-2 variants to the recombinant ACE2 receptor. As shown in Figure S2A, a significant reduction of neutralization of D614G variant was observed for the rheumatic disease and cancer groups, as compared to control. For neutralization of Gamma variant, a higher level was observed in the SOT group as compared to the control group (Figure S2B). Inhibition levels for the Gamma variant show a significant reduction as compared to the inhibition level observed for the D614G for all the groups, except for the SOT group (Figure S2C).

Cellular immune response

Subgroups of enrolled patients were evaluated for IFN-γ SFC upon stimulation with MP of SARS-CoV-2 derived peptides. As shown in Figure 3, the IFN-y response in the immunocompromised groups when stimulated with 15-mer peptides (MP-S+MPR, Figure 3A) or 8-9 mer peptides (CD8A+CD8B, Figure 3B) tended to be lower but did not differ significantly as compared to the healthy controls. Similarly, no significant differences were observed between groups for IL-4 SFC (Figure S3).

Patients' follow-up

Four non-severe breakthrough COVID-19 cases occurred in enrolled participants (1.5%) from different groups after a mean period of 14 weeks elapsed from full vaccination. Two of these breakthrough cases occurred in patients with negative TAb and NAb.

Discussion

Our study demonstrates that humoral immune response induced by inactivated SARS-CoV-2 vaccine CoronaVac is significantly reduced in patients with immunocompromising conditions. As reported with other currently available vaccines, our findings are coherent with a higher-than-expected rate of breakthrough SARS-CoV-2 infections reports in immunocompromised patients (16). Given these findings, vaccinated immunocompromised patients should consider continuing nonpharmaceutical interventions such as mask wearing; social distancing in personal, work, and clinical settings; and avoiding crowded settings (17).

Vaccine responses were markedly reduced in SOT recipients with only 20% attaining a positive

neutralizing response. These patients - that require life-long immunosuppression regimens and sometimes highly immunosuppressive induction therapy – also develop a weak humoral and cellular response after two doses of mRNA vaccine, with described seropositivity of anti–SARS-CoV-2 IgG TAb ranging between 19% and 50% (18-20). A previous study found that less than 10% reached a positive neutralizing response with two doses of mRNA vaccine (21). Accordingly, recent cohort and population studies describe higher rate for COVID-19 breakthrough infection and worse outcomes compared with persons without immune dysfunction; with up to 27% of vaccinated SOT recipients requiring hospitalization, >10% required admission to the intensive care unit, and >5% dying (17, 22, 23).

Oncological patients have also been reported to be at high risk of severe COVID-19 with an estimated fatality rate of 25.6% versus 2.7% in the general population (24). Studies in patients undergoing chemotherapy show reduced immunogenicity after two doses of the BNT162b2 mRNA vaccine (25). Our study shows that cancer patients with solid tumors receiving chemotherapy despite having comparable TAb response, attain a lower neutralizing capacity versus control group

with this vaccine. Conversely, in HSCT patients, humoral response did not differ from control, although low number of participants, heterogeneity in underlying disease and in type of transplant in this group may preclude concluding.

Immune function in people living with HIV (PLHIV) is impaired due to depletion of the CD4 T-cells and dysfunction of cellular and humoral immunity leads to weakening in vaccine response (26). SARS-CoV-2 vaccine response in PLHIV has been scarcely assessed, with no study reporting so far on inactivated vaccines. Two studies have described that ChAdOx1 nCoV-19 elicits similar humoral, and cell mediated immune response compared to healthy individuals (27, 28). Subsequently, PLHIV vaccinated with mRNA-1273 or BNT162b2 exhibited robust immune responses comparable to those in healthy subjects (29). On the contrary, our study indicates that in PLHIV, humoral response to this inactivated SARS-CoV-2 vaccine is significantly impaired, a finding that may relate to the fact that we only included participants with CD4 cell count ≤500 cell/mm^3.

In inflammatory arthritis, both the disease and biologic immunomodulators used in its treatment can affect cellular and humoral immunity (30). We found a significant weaker humoral response in patients with autoimmune rheumatic diseases on biologic agents. An impairment in humoral response has also been described with BNT162b2 vaccine in other autoimmune rheumatic diseases, associated with older age and the use of methotrexate, steroids, mycophenolate, abatacept and rituximab (31, 32). A recent meta-analysis involving various autoimmune inflammatory diseases found over 90% seroconversion rates for mRNA vaccines for patients on anti-TNF, but combination of anti-TNF with immunomodulators resulted in an attenuated vaccine response as compared to anti-TNF monotherapy (33). CoronaVac was recently evaluated in rheumatic diseases patients in two studies conducted in Brazil: in the first, patients with immune mediated diseases were less likely to have detectable anti-S1 IgG TAb versus healthy controls (34), whereas in the second lower anti-S1 IgG TAb seroconversion (70.4% vs 95.5%, $p < 0.001$) and NAb positivity (56.3% vs 79.3%, $p< 0.001$) were detected 6 weeks after vaccination in the autoimmune rheumatic diseases group versus the control group (35).

The development of vaccines to prevent SARS-CoV-2 infection has mainly relied on the induction of NAb to the Spike protein of SARS-CoV-2, but there is growing evidence that T-cell immune response can contribute to protection as well. We know that mRNA vaccines elicit Spike-targeted T-cell responses, intracellular cytokine staining, and cytokine profile (36). We observed no differences when each subgroup was compared to control group. These results could be explained either by the reduced number of patients, or because CoronaVac is still able to promote to some extent the expansion of IFN-γ secreting T-cells in immunocompromised population.

The present study suggests that the current scheme of two doses CoronaVac is insufficient to induce an acceptable immune response in immunocompromised subjects, thus, booster doses or primary vaccination with more than two doses are needed. Multiple vaccine doses can boost the primary immune response by providing supplementary innate immune activation signals, and promoting further expansion of previously activated T- and B-cell clones (37). A third dose in immunocompromised patients is already being recommended in France, Israel, Chile, United States, and several other countries. Significant improvement in immunogenicity after administration of a third dose of the BNT162b2 vaccine to SOT recipients has been shown in one study (38). However, a second study reported that 51% of the kidney transplant recipients who did not respond after two doses of mRNA-1273 vaccine did not develop anti–SARS-CoV-2 antibodies after the third dose, especially those receiving triple immunosuppression (39). Multiple doses strategies must be followed with long term effectiveness and immunogenicity studies.

As study limitations, we did not evaluate the prevalence of anti–SARS-CoV-2 antibodies before vaccination. However, we excluded participants reporting a previous positive SARS-CoV-2 RT-qPCR, specific antibodies, or a clinical history of COVID-19. Secondly, we did not attain the pre-specified sample size, given the strict enrollment period and all participants having been vaccinated nationally rapidly and in a very short period. However, the differences in humoral response between the immunocompromised and control groups were higher than expected, which allowed reducing the number needed to demonstrate significance. Furthermore, adjustment for other relevant covariates such as age did not modify the findings. Thirdly, we did not evaluate immune response to other relevant SARS-CoV-2 variants such as Delta. However, our previous data in immunocompetent subjects showed that NAb against Delta were equivalent to the levels reached for the Gamma variant with CoronaVac vaccine (40).

Strengths of our study include the inclusion of an immunocompetent control group, and assessment of both full humoral and memory T-cell responses. Also, this is the first study to report the response to two doses of CoronaVac inactivated SARS-CoV-2 vaccine in PLHIV and SOT.

Lastly, systematic assessing of immune response in all vaccine recipients to verify immunogenicity status is currently not recommended since no validated biomarkers for both humoral and cellular immunity correlate with protection, as suggested by previous analyses of the immune response of CoronaVac breakthrough cases in immunocompetent adults (41). Here, we observed that a substantial proportion of immunocompromised recipients have no detectable NAb at all, and probably remain at a high risk for COVID-19 even after vaccination. Our results, fully support the

necessity of additional vaccine doses in primary vaccination schemes in the immunocompromised population.

NOTES

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Legends to tables and figures

Table 1. Baseline characteristics of enrolled participants from immunocompromised and control.

Table 2. Frequency of neutralizing antibodies (NAb); median neutralizing activity expressed in inhibition percentage; frequency of total anti SARS-CoV-2 IgG antibodies (TAb) and TAb GMC, 8-12 weeks after the second dose of CoronaVac vaccination in patients with immunosuppression conditions in comparison to control group

Figure 1. Study flow-chart

Figure 2. Humoral response against SARS-CoV-2 in healthy and immunocompromised individuals 8-12 weeks after vaccination with CoronaVac. Distribution for (a) neutralizing antibodies (NAb) positivity (≥30% of inhibition rate) (b) neutralizing activity (median (IQR) of percentage of inhibition), (c) frequency of total IgG anti S1 positivity (≥11 relative units per ml, RU/ml) and (d) total IgG anti S1 GMC (95%CI), RU/ml). Healthy control (n=65), solid organ transplant (SOT) (n=34), rheumatic diseases (n=41), cancer (n=30), HIV-infected (n=55) and hematopoietic stem cell transplant (HSCT) (n=14)). Dotted line in 2b, d show seropositivity cutoff. Statistical significance was calculated with Fisher test (1a-b), Mann-Whitney (1c-d), and two-tailed p values are indicated when significant. *p ≤0.05, **p≤ 0.01, ***p≤0.001 and ****p≤0.0001.

Figure 3. Evaluation of IFN-g secreting Spot Forming T cells in healthy controls and immunosuppressed patients after vaccination with CoronaVac. PBMCs ($3x10^5$ cells) obtained between 8-12 weeks after a second dose of CoronaVac from heathy controls (n=29), solid organ transplant (SOT) (n=30), cancer (n=25), rheumatic diseases (n=27), HIV-infected (n=26) and hematopoietic stem cell transplant (HSCT) (n=11) were stimulated with 15-mer megapool of peptides (MP-S+MP-R) (a), or 8-9-mer megapool of peptides (CD8A+CD8B) **(b)** from SARS-CoV-2 proteins. IFN-g-secreting spot forming T cells (SFC) were quantified by ELISPOT. Medians with IQR are shown.

Table 1. Baseline characteristics of enrolled participants from immunocompromised and control group.

Total (n=239)	**Control** group (n=65)	**Solid organ transplant** group (n=34)	**Rheumatic diseases** group (n=41)	**Cancer** group (n=30)	**HIV infected** group (n=55)	**Hematopoietic stem cell transplant** group (n=14)
Demographics						
Mean age (range)	44.3 (51.0)	54.0 (54.0)	51.7 (45.0)	57.7 (46.0)	46.8 (52.0)	47.4 (49.0)
Female (n, %)	44 (67.7)	16 (47.1)	30 (73.2)	17 (56.7)	2 (3.6)	4 (28.6)
Current smoking (n, %)	12 (18.5)	1 (2.9)	8 (19.5)	2 (6.7)	17 (30.9)	0 (0.0)
BMI (mean, SD)	24.7 (4.2)	28.1 (6.6)	29.5 (4.9)	25.7 (3.4)	26.9 (3.7)	28.8 (6.0)
Comorbidities						
Hypertension (n, %)	4 (6.2)	14 (41.2)	15 (36.6)	8 (26.7)	9 (16.4)	2 (14.3)
Diabetes (n, %)	1 (1.5)	10 (29.4)	6 (14.6)	8 (26.7)	6 (10.9)	2 (14.3)
Asthma or COPD (n, %)	5 (7.7)	0 (0.0)	4 (9.8)	1 (3.3)	3 (5.5)	0 (0.0)
Chronic renal disease (n, %)	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Chronic liver disease (n, %)	0 (0.0)	3 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Current immunosuppressive or immunomodulator therapy						
Prednisone (n, %)	-	23 (67.6)	22 (53.7)	0 (0.0)	1 (1.8)	0 (0.0)
Prednisone dose >15 mg/d (n, %)	-	3 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hydroxichloroquine (n, %)	-	0 (0.0)	8 (19.5)	0 (0.0)	0 (0.0)	0 (0.0)
Sulphasalazine (n, %)	-	0 (0.0)	7 (17.1)	0 (0.0)	0 (0.0)	0 (0.0)
Leflunomide (n, %)	-	1 (2.9)	10 (24.4)	0 (0.0)	0 (0.0)	0 (0.0)
Methotrexate (n, %)	-	0 (0.0)	20 (48.8)	0 (0.0)	0 (0.0)	3 (21.4)
Mycophenolate mofetil (n, %)	-	25 (73.5)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
Tacrolimus (n, %)	-	30 (88.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (14.3)

				)		
Cyclosporine (n, %)	-	3 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)
TNF inhibitors[1] (n, %)	-	-	40 (97.6)	-	-	-
Anti-IL6 (tocilizumab) (n, %)	-	-	1 (2.4)	-	-	-
Anti-IL17 (secukinumab) (n, %)	-	-	0 (0.0)	-	-	-
Cancer chemotherapy (n, %)	-	-	-	30 (100)	-	-
Induction immunosuppressive therapy						
Basiliximab (n, %)	-	19 (55.9)	-	-	-	-
Anti-thymocyte globulin (n, %)	-	4 (11.8)	-	-	-	-
Antibody-mediated rejection therapy	-	-	-	-	-	-
Anti-CD20 (rituximab) (n, %)	-	2 (5.9)	-	-	-	-
Anti-thymocyte globulin (n, %)	-	1 (2.9)	-	-	-	-
Years since transplant						
<=1	-	29 (85.3)	-	-	-	10 (71.4)
1->=3	-	4 (11.8)	-	-	-	4 (28.6)
>3-5	-	1 (2.9)	-	-	-	0 (0.0)
Type of cancer						
Colorectal (n,%)	-	-	-	14 (46.6)	-	-
Breast (n, %)	-	-	-	6 (20.0)	-	-
Páncreas (n, %)	-	-	-	2 (6.7)	-	-
Lung (n, %)	-	-	-	2 (6.7)	-	-
Other2 (n, %)	-	-	-	6 (19.8)	-	-
Rheumatic disease						
Rheumatoid arthritis (n, %)	-	-	31 (75.6)	-	-	-
Psoriatic arthritis (n, %)	-	-	9 (22.0)	-	-	-
Juvenile idiopathic arthritis (n, %)	-	-	1 (2.4)	-	-	-
Type of transplant						
Liver (n, %)	-	20 (58.8)	-	-	-	-
Kidney (n, %)	-	11 (32.4)	-	-	-	-
Liver & kidney (n, %)	-	2 (5.9)	-	-	-	-
Kidney & páncreas (n, %)	-	1 (2.9)	-	-	-	-

HSCT[3] allogeneic (n, %)	-	-	-	-	-	5 (35.7)
HSCT[3] autologous (n, %)	-	-	-	-	-	9 (64.3)
CD4 cell count (mean, SD)	-	-	-	-	358.8 (100.0)	-

1. *TNF inhibitors: infliximab, golimumab, adalimumab, etanercept, certolizumab pegol*
2. *Other cancers: peritoneum, gastric, liver, ovarium, testicular and small bowel*
3. *HSC: hematopoietic stem cell transplant*

Table 2. Frequency of neutralizing antibodies (NAb); median neutralizing activity expressed in inhibition percentage; frequency of total anti SARS-CoV-2 IgG antibodies (TAb) and TAb GMC, 8-12 weeks after the second dose of CoronaVac vaccination in patients with immunosuppression conditions in comparison to control

	NAb positivity[1]			Neutralizing activity			TAb positivity[2]		TAb quantification	
	n (%)	OR (95% CI)[3], *p value*	$_{ad}$OR (95% CI)[3], *p value*	Median %, (IQR)	ß regression[3], *p value*	$_{ad}$ß regression[3], *p value*	*n* (%)	OR (95% CI)[3], *p value*	GMC (RU ml^{-1}), 95%CI	ß *regression*[3], *p value*
Control (n=65)	54 (83.1)	--	--	51.21 (34.6-68.6)	--	--	60 (92.3)	--	36.77 (30.0-45-05)	--
Solid organ transplant (n=34)	7 (20.6)	0.05 (0.02-0.15), p<0.001	0.07 (0.02-0.19), p<0.001	5.65 (3.67-11.7)	-1.23, p<0.001	-0.28, p<0.001	7 (20.6)	0.02 (0.01-0.07), p<0.001	5.64 (3.45-9.24)	0.15, p<0.001
Rheumatic diseases (n=41)	17 (41.5)	0.14 (0.06-0.35), p<0.001	0.19 (0.07-0.49), p=0.001	19.23 (11.27-38.98)	-0.82, p<0.001	-0.19, p<0.001	25 (61.0)	0.13 (0.04-0.39), p<0.001	15.17 (10.36-22.22)	0.41, p<0.001
Cancer (n=30)	13 (43.3)	0.15 (0.06-0.41), p<0.001	0.18 (0.06-0.49), p=0.001	21.44 (12.86-52.34)	-0.60, p=0.002	-0.14, p=0.002	28 (93.3)	1.17 (0.21-6.39), p=0.859	24.71 (17.04-35.82)	0.67, p=0.062
HIV+ (n=55)	25 (45.5)	0.17 (0.07-0.39), p<0.001	0.19 (0.08-0.44), p<0.001	28.72 (15.74-54.13)	-0.39, p=0.029	-0.09, p=0.027	39 (70.9)	0.20 (0.07-0.60), p=0.004	21.20 (15.98-28.13)	0.58, p=0.002
HSCT (n=14)	9 (64.3)	0.37 (0.10-1.31), p=0.122	0.45 (0.12-1.71), p=0.241	56.57 (21.46-85.71)	0.11, p=0.742	0.02, p=0.742	12 (85.7)	0.50 (0.09-2.89), p=0.438	34.98 (17.75-68.97)	0.95, p=0.887

[1]Number of participants reaching the cut-off (≥30%) in SARS-CoV-2 neutralizing antibodies (NAb) for test positivity. [2]Number of participants reaching the total anti-SARS-CoV-2 S1 IgG antibodies (TAb) cut-off (≥11 UR/ml). [3]All comparisons are versus Control Group. Abbreviations: OR: Odds Ratio; CI: Confidence interval; IQR: Inter Quartile Range; GMC: Geometric mean concentration: RU: Relative units; HIV: human Immunodeficiency Virus; HSCT: Hematopoietic Stem Cell Transplant

Figure 1

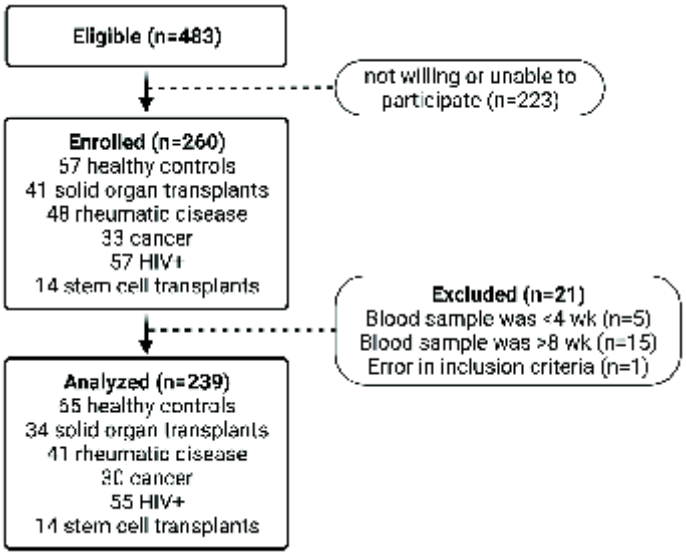

Figure 2

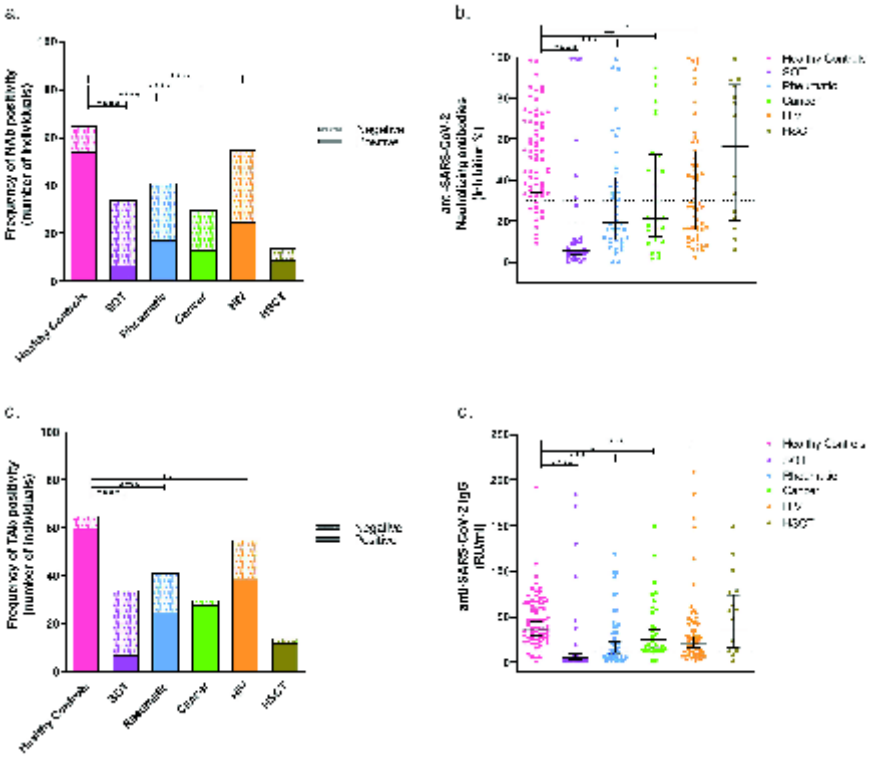

Figure 3