Specific Cellular and Humoral Immune Responses to the Neoantigen S1 of SARS-CoV-2 in Patients with Primary and Secondary Immunodeficiency

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Research Article

Abstract

Patients with antibody deficiency disorders, such as common variable immunodeficiency (CVID), or secondary immunodeficiency (SIDs) to B-cell lymphoproliferative disorder (B-CLPD), are two vulnerable groups of developing severe or chronic form of coronavirus disease caused by SARS-CoV-2 (COVID-19). Data on adaptive immune responses against SARS-CoV-2 is well described in healthy donors, but still limited in patients with antibody deficiency of different cause. Herein, we analyzed Spike-specific IFN-γ and anti-Spike IgG antibody responses at 3 and 6 months after exposure to SARS-CoV-2 derived from vaccination and infection in two cohorts of immunodeficient patients (CVID vs. SID) compared to healthy controls (HC). Baseline cellular responses before vaccine administration were measured in 10 CVID patients. Adequate specific cellular responses was observed in 18 out of 20 (90%) CVID patients, in 14 out of 20 (70%) out of 20 SID patients and in 74 out of 81 (96%) HC. Specific IFN-γ response was significantly higher in HC respect to CVID (1,908.5 mUI/ml versus 1,694.1 mUI/ml; p = 0.005). Pre-vaccine anti-SARS-CoV-2 cellular responses were detectable in 4 out of 10 CVID patients, who had COVID-19 prior to vaccination, noticing an increase in cellular responses after vaccination (p < 0.001). Whereas all SID and HC mounted a specific humoral immune response, only 80% of CVID patients showed positive anti-SARS-CoV-2 IgG. The titer of anti-SARS-CoV-2 IgG was significantly lower in SID compared with HC (p = 0.040), without significant differences between CVID and HC (p = 0.123) and between CVID and SID (p = 0.683). High proportions of CVID and SID patients showed adequate specific cellular responses to S1 neoantigen, with divergence between cellular and humoral immune responses in CVID and SID patients. Our data might support the relevance of these immunological studies to determine the correlate of protection to severe disease and for deciding the need of additional boosters. Follow-up studies are required to evaluate the duration and variability of the immune response to COVID-19 vaccination or infection.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has posed a threat to public health, especially in specific groups of risk including immunodeficient patients. Clinical presentations of COVID-19 vary quite widely in immunodeficient patients, ranging from asymptomatic to severe acute respiratory syndrome (SARS) [1–2]. The most clinically prevalent primary immunodeficiency (PID) is common variable immunodeficiency (CVID), a predominantly antibody deficiency estimated in 1 of 25,000 to 50,000 individuals [3]. According to the European Society for Immunodeficiencies (ESID) criteria, CVID is characterized by marked reduction in immunoglobulin IgG and IgA with or without reduced IgM levels as well as reduced frequencies of switched memory B cells and/or diminished vaccine antibody responses [4–5].

On the other hand, patients with hematological cancer have been defined as the most vulnerable group for severe COVID-19-related morbidity and mortality [6]. In this secondary immunodeficiency (SID) of predominantly antibody defect, both the underlying disease and the immunosuppressive treatment contribute to the immunodeficiency. Disease-related factors that contribute to immunodeficiency include

B-cell dysfunction leading to hypogammaglobulinemia, advanced age and comorbidities, which are known factors for severe COVID-19 [7–8].

Failure to produce specific antibody responses to pathogens in PID and SID has raised concerns on the risk for severe or prolonged infection with SARS-CoV-2 and the potential benefits of immunization against SARS-CoV-2 in terms of protective specific T cell responses in these patients' populations [9, 10]. The interferon (IFN)-γ, is a key player in driving antiviral cellular immunity, through the activation, for instance, of macrophages and triggering specific cytotoxic immunity [11]. In vitro production of IFN-γ can be used as a reliable read-out of specific memory T cells in circulation [12].

As with many other infections, both natural immunization through infection or vaccination can develop long-term immunity against SARS-CoV-2 [13, 14]. With the ongoing rollout of COVID-19 vaccinations, B and T cell responses to SARS-CoV-2 in healthy convalescent or vaccinated donors are well described to date, whereas few data exist in PID and SID patients [15–17]. Reliable diagnostic assays are critical for evaluating the relation of specific cellular and humoral responses to SARS-CoV-2 vaccines in immunodeficient patients and to establish their correlates of protection [18].

The purpose of this study was to compare cellular and humoral responses in primary (CVID) patients and in SID patients to hematological cancer with a group of healthy controls, and to better define the overall efficacy of host immune responses after new exposure to SARS-CoV-2 infection.

Material And Methods

Study design

The total study population was composed 121 subjects: 20 CVID patients (aged 17 to 74 years, 14/20 females), 20 SID patients to hematological cancer (aged 49 to 85 years, 15/20 females) and 81 healthy controls (aged 23 to 83 years, 60/81 females) who were consecutively studied. Samples were collected before the administration of the first vaccine dose in 10 of the CVID patients. Patients and HC were vaccinated at week 0 and 4. Additionally, for all patients, samples were collected between 3 and 6 months after the second vaccine dose or after recovering from COVID-19 as part of follow-up of patients in the Clinical Immunology Unit. In patients on immunoglobulin replacement therapy (IgRT), we established the vaccination before at least 2 weeks of IgRT administration. The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board. The study was approved by the Ethics Committee of the Hospital Clínico San Carlos (20/243-E_BS). Written informed consent for clinical data and blood sample collection was waived given the emergency of the current pandemic. All participating donors were included in this report and no subject was excluded.

Evaluation of SARS-CoV-2 cellular response

T Cell response to SARS-CoV-2 was measured using IFN-γ ELISA kit (Euroimmun, Lübeck, Germany) within 16-hours of blood withdrawal and was analyzed on a Triturus analyzer (Grifols S.A., Barcelona,

Spain). Human lithium-heparin plasma, obtained after stimulation using the SARS-CoV-2 IGRA stimulation tube set, were diluted 1:5 in the sample buffer. Afterwards, 100 µL of each calibrator, controls and diluted samples were added to high-binding 96 well ELISA plates pre-coated with monoclonal anti-IFN-γ antibodies. After 2 hours of incubation at room temperature (RT), plates were washed 5 times with 350 µL of wash buffer. Subsequently, 100 µL of biotin-labeled anti-interferon-gamma antibody was added into each of the microplate wells and incubated for 30 minutes at RT. After following washes as described above, 100 µL peroxidase-labeled streptavidin was added and incubated for 30 minutes at RT. After five additional washes with wash buffer, 100 µL of 3,3',5,5'-tetramethylbenzidine/peroxide (TMB/H_2O_2) was added to each well incubating it during 20 minutes and the absorbance was read at 450 nm after 30 minutes of adding the stop solution (sulphuric acid). The interpretation of SARS-CoV-2 IFN-γ antibody testing was as follows: <100 mUI/ml = negative, ≥ 100 to < 200 = borderline, ≥ 200 = positive.

Evaluation of SARS-CoV-2 humoral response

Humoral immune response was assessed by a highly sensitive and specific chemiluminescent microparticle immunoassay (SARS-CoV-2 IgG II Quant assay on an ARCHITECT analyzer; Abbott Laboratories, Chicago, USA), according to the manufacturer's instructions. The assay detects IgG antibodies against the receptor binding protein (RBD) of the S1 subunit of the spike protein of SARS-CoV-2. A value ≥ 50 arbitrary units per milliliter (AU/ml) was considered evidence of vaccination response.

Statistical analysis

Microsoft Excel (v.14.1.0), GraphPad Prism software (version 8.1.0), and R software (version 4.0.4) was used for descriptive and statistical data analysis. Categorical variables were compared using Fisher's exact test or chi-squared test, as appropriate. The difference in IFN-γ levels between clinical groups (PID, SID, HC) was analyzed with both bivariable (Kruskall-Wallis and Mann-Whitney U) and multivariable (logistic regression) tests. The dependent variable in logistic regression was coded as values greater than or less than the median of IFN-γ levels. The characteristics of the variables did not allow us using linear regression. Values were expressed as mean ± standard deviation (SD) or median (IQR) and p values of less than 0.05 were considered significant.

Results

Epidemiological and Immunological Characteristics of the Study Population

To understand immune responses to SARS-CoV-2 in patients with predominantly antibody deficiencies, 20 patients who fulfilled CVID diagnosis according to ESID criteria, 20 patients with SID to B- cell lymphoproliferative disorder (B-CLPD) and 81 healthy controls (HC) were consecutively assessed. The study population characteristics are shown in Table 1. All CVID patients had suffered from recurrent respiratory tract infections and had decreased IgG, IgA and/or IgM levels before IgRT. Six out of 20 CVID patients (30%) had lymphoproliferative manifestations, one with a current clinical course of large

granular lymphocytic (LGL) leukemia and 5 cases (25%) had clinical signs of autoimmune disease. Five CVID patients (25%) had lymphopenia, one of which after rituximab treatment years after CVID diagnosis. All but 1 patient were receiving IgRT with improvement in infections, 6 patients (30%) were treated with subcutaneous (SC) IgRT and 13 patients (65%) with intravenous (IV) IgRT.

Among patients diagnosed with SID to B-CLPD, the most frequent cancer was non-Hodgkin's lymphoma (n = 12, 60%), chronic lymphocytic leukemia (n = 5, 25%), monoclonal gammopathy of undetermined significance (n = 2, 10%) and multiple myeloma (n = 1, 5%). Fifteen out of 20 patients (75%) with SID were on IgRT (all IV).

Table 1
Epidemiological features of the three study groups.

	CVID No. = 20	SID No. = 20	Healthy controls No. = 81
M/F	6/14 (30%/70%)	5/15 (25%/75%)	21/60 (26%/74%)
Age (years)	49.8 ± 16.4	67.9 ± 8.8	48.1 ± 15.6
IgG at diagnosis (mg/dL)	464 ± 276 499 (269−595)	720 ± 1106 369 (162−816)	NA
IgA at diagnosis (mg/dL)	41 ± 44 40 (0−51)	56 ± 64 25 (12−104)	NA
IgM at diagnosis (mg/dL)	64 ± 112 17 (5−52)	32 ± 45 11 (8−43)	NA
CD4 + T-lymphocytes (/uL)	659 ± 288 598(431−870)	900 ± 650 725(436−1222)	NA
CD8 + T T-lymphocytes (/uL)	574 ± 414 530(257−682)	751 ± 370 709(440−1047)	NA
IgRT	SCIG 6/20 (30%) IVIG 13/20 (65%)	IVIG 15/20 (75%)	NA
Prior COVID-19 to vaccine	5/20 (25%)	3/20 (15%)	31/81 (38%)
M: male; F: female. Results are expressed as No. (%) or mean + ESM, median (IQR).			

SARS-CoV-2 History

CVID patients were vaccinated with the first and second vaccine dose between April to June, 2021 depending on the vaccine brand received. According to the Spanish SARS-CoV-2 vaccine schedule, 17 patients (85%) received two doses of the mRNA-1273 vaccine (Moderna), 2 patients (10%) the mRNA vaccine BNT162b2 (Pfizer/Biontech) and 1 patient (5%) the adenovirus-vectored vaccine ChAdOx1 nCoV-19 (AstraZeneca). Five CVID patients (25%) had already presented COVID-19, with asymptomatic (n = 2), mild (n = 2) and severe (n = 1) clinical courses.

Among patients with SID, 11 cases (55%) received the mRNA-1273 vaccine (Moderna) and the remaining 9 patients (45%) the mRNA vaccine BNT162b2 (Pfizer/Biontech). They received the two doses between January to June, 2021. Three of the 20 SID patients had presented COVID-19, with mild (n = 2) and severe (n = 1) clinical courses.

With respect to the population of 81 HC, 70 controls (86.4%) were vaccinated with the first and second dose between January to June, 2021, according to the Spanish SARS-CoV-2 vaccine calendar. Fifty-one HC (72.9%) received the mRNA vaccine BNT162b2 (Pfizer/Biontech), 12 (17.1%) the mRNA-1273 vaccine, and 5 (7.1%) the adenovirus-vectored vaccine ChAdOx1 nCoV-19 (AstraZeneca) and 2 cases (2.9%) received a single dose of the adenovirus-vectored vaccine Ad.26.COV2.S (Janssen). The remaining 11 HC had not received any vaccine at the time of study, 8 out 11 had experienced COVID-19 and 3 were neither vaccinated or with known COVID-19, to determine the specificity of the test. Globally, 31 HC (39.2%) had presented the COVID-19, with asymptomatic (n = 3), mild (n = 23) and severe (n = 5) clinical courses.

SARS-CoV-2 T Cell Responses in PID and SID

Post-vaccine results showed positive cellular response in 18 out of 20 (90%) CVID patients, with median (IQR) IFN-γ levels of 1,694.1 (651.5-1,856.5) mUI/ml; and in 74 out of 81 (96%) HC, with median (IQR) IFN-γ levels of 1,908.5 (1,149.5-2,001) mUI/ml, with significant differences (p = 0.005) (Fig. 1a). Specific anti-SARS-CoV-2 IFN-γ responses in the remaining two CVID patients (PID#6 and PID#11) were borderline, both had lymphopenia. PID#6 displayed panhypogammaglobulinemia with upper respiratory tract infections since she was 6 months-old, chronic gastritis due to *H. pylori* treated and eradicated in 2013, and mild T CD8 + lymphopenia (195 cell/uL). PID#11 showed a low increase of IFN-γ production (from 0 to 99 mUI/ml) post-vaccine. PID#11 had panhypogammaglobulinemia and lymphoid granulomatosis with interstitial lung involvement in 2016, which was treated with rituximab until 2017 with complete remission. She developed lymphopenia T CD8+ (196 cell/uL) secondary to treatment.

Cellular responses before vaccine administration were measured in 10 CVID patients with median (IQR) increase of IFN-γ levels of 80.5 (0-270) mUI/ml, statistically significant with respect to post-vaccination levels (p < 0.001) (Fig. 1b). Four of these ten patients (PID#1, PID#3, PID#7 and PID#9), who had passed COVID-19 prior to vaccination (one with bilateral pneumonia and the rest with mild symptoms), showed higher specific anti-SARS-CoV-2 IFN-γ production than those without previous disease, as expected 270 (68.7-1,375) mUI/ml versus 1.1 (0−17) mUI/ml. PID#2, whose parents in close contact had had COVID-19 showed baseline borderline results, suggesting asymptomatic COVID-19.

With respect to the 20 SID patients, specific cellular responses showed median (IQR) IFN-γ levels of 1,877.9 (167-1,937) mUI/ml without differences with HC (p = 0.215). Also, no differences were observed between PID and SID groups (p = 0.371). Positive T cell responses were observed in 14 out of 20 (70%) SID patients. Three patients (SID#5, SID#8 and SID#11) displayed borderline specific anti-SARS-CoV-2 IFN-γ responses and no response in the remaining three patients (SID#1, SID#2 and SID#6). SID#5 showed panhypogammaglobulinemia secondary to CLL diagnosed in 2002 without treatment to date. SID#8 had a NHL diagnosed in 2003 in complete remission (CR) and CD8 + T lymphocytopenia. SID#11 had a NHL treated with bendamustine and rituximab (BR) until 2018. With respect to SID patients with no response: SID#1 was diagnosed with pulmonary lymphoma in 2021, and she is currently under radiotherapy combined with chemotherapy. At the time of the study she presented marked B and NK lymphopenia (27 cell/uL and 32 cell/uL). SID#2 had a follicular lymphoma in 2003 treated with fludarabine, cyclophosphamide and rituximab (FCR) with CR since 2008 and showed panhypogammaglobulinemia. SID#6 had CLL diagnosed in 2003 and panhypogammaglobulinemia without anticancer treatment, serious recurrent respiratory infections, UTIs and asthma.

The difference in IFN-γ levels between clinical groups (PID, SID, HC) remained statistically significative after adjusting for age, sex, time since last exposition to SARS-CoV-2 antigens (vaccination or natural infection) and past history of natural SARS-CoV-2 infection with logistic regression (LR test, p = 0.016). The inspection of the model showed that this difference depended on the difference between the PID and HC groups (Wald test, p = 0.013), while it was not significative for the contrast between the SID and HC groups (Wald test, p = 0.760).

SARS-CoV-2 specific T Cell Responses in Healthy Donors

As mentioned previously, 74 out of 81 (96%) HC had positive cellular response. Among 7 patients who had not achieved positive IFN-γ production, 3 were not-vaccinated and without known COVID-19, to ensure the specificity of the study. The remaining 4 presented borderline cellular responses, without medical history suggestive of immunodeficiency. HC were divided into three subgroups: SARS-CoV-2 vaccination (HC-vaccine); naturally immunized by infection (HC-nat-immun); or both (HC-hybrid), respectively. Regarding the cellular immune responses, 39 out of 42 (93%) HC-vaccine, all 8 HC-nat immun (100%) and 27 out of 28 (96.4%) of HC-hybrid showed positive IFN-γ levels. Median (IQR) IFN-γ levels are as follows: 1,863 (1,064 – 1,995) mUI/ml for HC-vaccine, 1,601.1 (945.8-1.944,6) mUI/ml for HC-nat-immun and 1,964.5 (1,879.9-2,059.6) mUI/ml for HC-hybrid, respectively (Fig. 2). Specific anti-SARS-CoV-2 IFN-γ levels were higher in hybrid HC subgroups without significant differences with the other subgroups, but a trend was observed (p = 0.097). The greater variability in specific anti-SARS-CoV-2 cellular responses was observed in the HC-vaccine subgroup, despite the narrow time frame (3 – 6 months) with respect to HC-nat-immun (3 – 18 months).

SARS-CoV-2 Antibody Responses

SARS-CoV-2 antibody testing displayed adequate B-cell antibody responses in 80% of CVID patients with median (IQR) anti-spike IgG levels of 2,015.6 (51.9-5,611.4) UA/ml. PID#6 was the only patient who failed

to produce positive both humoral and cellular responses. As mentioned previously, she had B (31 cells/µl) and T CD8 lymphopenia. All SID patients tested for antibodies (17/20, 85%) developed positive humoral responses with median (IQR) of 465.7 (238.6-1,984.9). All HC tested for humoral response (14/81, 17%) presented adequate humoral responses with a median (IQR) of 4,392.8 (2,528.2–13,384) UA/ml, significantly higher than SID ($p = 0.040$), and without significant differences between PID and HC ($p = 0.123$) and PID and SID ($p = 0.683$) (Fig. 3). Interestingly, no correlation was observed between specific cellular responses and to specific humoral responses to SARS-CoV-2.

SARS-CoV-2 Infection Follow-Up

Our study population was followed-up 4 months after the cellular and humoral assay to evaluate whether high cellular IFN-γ responses correlated with protection against a subsequent exposure to SARS-CoV-2 infection. Three out of 20 CVID patients (PID#1, PID#7 with previous COVID-19 plus 2-dose of vaccine and PID#11, with borderline IFN-γ levels after 2-dose vaccine) were exposed to SARS-CoV-2 during the sixth wave of the coronavirus in Spain, all of them related to mild symptoms. Among SID patients, only one patient (SID#20) experienced asymptomatic COVID-19 after a routine RT-PCR testing that resulted positive. Nine out of 81 (11%) HC referred exposure to SARS-CoV-2, 6 with mild symptoms, 1 with moderate course and the remaining 2 of the HC-vaccine group (HC#39 and HC#51) (2.5%) with bilateral pneumonia despite IFN-γ titers of 2,083 mUI/ml and 1,958 mUI/ml, respectively. None of them required hospitalization and are currently without sequels of the disease.

Discussion

To the best of our knowledge, this is the first study assessing the immunogenicity of COVID-19 infection and vaccination in CVID and SID, and compared to a large healthy control group. We show a detectable specific SARS-CoV-2 cellular response in 90% of CVID patients, 70% of SID patients and 96% of HC. Specific humoral response was detected in all SID and HC, whereas only 80% of CVID displayed positive S1-specific antibodies, much greater than expected in primary antibody-production deficiencies. This latter result is in line with other cohort reports showing that the majority of CVID patients are able to respond to SARS-CoV-2 vaccines or infection [19–22]. However, other authors have reported low humoral responses in CVID patients after SARS-CoV-2 vaccine [23]. Our findings in SID patients are in agreement with a study by Mairhofer et al [24]. The authors found detectable antibody levels in 57.8%, while 100% in our series, which might be due to their patients were under cancer treatment, whereas our patients were not on active anticancer treatments. Differences in responses between CVID and SID maybe due to deeper cellular immunodeficiency in SID patients. Titers of specific antibody responses were low in SID patients for the same reason, despite the fact of patients being previously immunocompetent and may show secondary responses to coronavirus.

This study has several limitations that should be considered, regarding its relatively small sample size for the immunodeficiency groups and the intrinsic heterogeneity of the SID group, although all classified as B-CLPD. Another potential limitation was the lack of corresponding data on humoral immunity of all patients due to availability issues, to better clarify the correlation with cellular responses. Additionally, the

IGRA test does not differentiate between CD4- and CD8-SARS-CoV-2-specific T cells. Further studies are needed to understand the degree of each cell subset participation in the response after infection or vaccination. Therefore, we present the work as a pilot exploratory analysis.

Even with those limitations, several points can be made. Although our CVID patients had failed to produce antibody responses to polysaccharide or tetanus vaccines, they mostly showed adequate humoral responses to RNA-based SARS-CoV-2 vaccines and infection. From the CVID diagnosis perspective, S1 ARN immunization does not seem to reliable discriminate between patients and controls. Furthermore, the cellular response observed in CVID patients with antibody deficiency was reassuring and supports vaccination in this population. Similar IFN-γ T cell results of patients with PID to influenza vaccine have been described before [25, 26]. In those CVID patients whose T cell response was measured before vaccination, the vaccine enhanced cellular responses induced by natural infection, which suggests a prominent boosting effect of vaccination in all convalescent CVID patients [27]. Despite the high percentage of CVID responders, IFN-γ levels were significantly lower than HC. We noticed that individuals who had borderline or negative cellular responses had T lymphopenia, which could probably explain in part their in vitro low IFN-γ production [28].

In the case of HC, the hybrid subgroup presented the highest specific anti-SARS-CoV-2 IFN-γ levels, which might indicate that the cellular response induced by natural infection was significantly enhanced by subsequent vaccination [29]. All naturally immunized HC disclosed positive and long-lasting cellular responses (up to 18 months now), highlighting the relevance of monitoring anti-SARS-CoV-2 IFN-γ production to help immunizations decisions. According to Krüttgen et al, we observed an interindividual variability in cellular responses among the vaccination HC subgroup: we can distinguish high responders and low responders to the different types of SARS-CoV-2 vaccines [30]. Low responders might need additional booster doses, as established for other vaccines [31]. Parallel to the differences observed in cellular responses, we also observed high heterogeneity in specific antibody levels. Our results warrant further studies in larger series of patients to evaluate whether there exists a correlation between cellular and humoral responses, and the best correlate of protection.

In summary, the two-dose SARS-CoV-2 vaccine appears to be beneficial in primary and secondary immunodeficient patients. Our observations underline the need of additional booster in low responders to SARS-CoV-2 vaccines to achieve a better immune response against the virus. Two HC from the vaccinated group with normal cellular responses presented with bilateral pneumonia after SARS-CoV-2 exposure. Immunization after natural infection seems to elicit positive and long-lasting adaptive immunity responses, without severe infection after re-exposure. Further analysis is ongoing to assess in the near future the duration of these immune responses to SARS-CoV-2, the effects of the third dose in immunodeficient patients and to determine the best correlate for protection after infection and after vaccination in our study populations.

Abbreviations

PID: primary immunodeficiency; SID: secondary immunodeficiency; CVID: Common variable immunodeficiency; HC: Healthy control; COVID19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; ESID: European Society for Immunodeficiencies; IgRT: Immunoglobulins replacement therapy; IgA: Immunoglobulin A; IgG: Immunoglobulin G; IgM: Immunoglobulin M.

Declarations

Data Availability The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Code Availability This work complies with feld standards.

Ethics Approval This study was approved by the Ethics Committee of the Hospital Clinico San Carlos (20/243-E_BS).

Consent to Participate See above.

Consent for Publication All authors concur with the submission of this manuscript, and the material submitted for publication is original research and has not been previously reported and is not under consideration for publication elsewhere.

Conflict of Interest The authors declare no competing interests.

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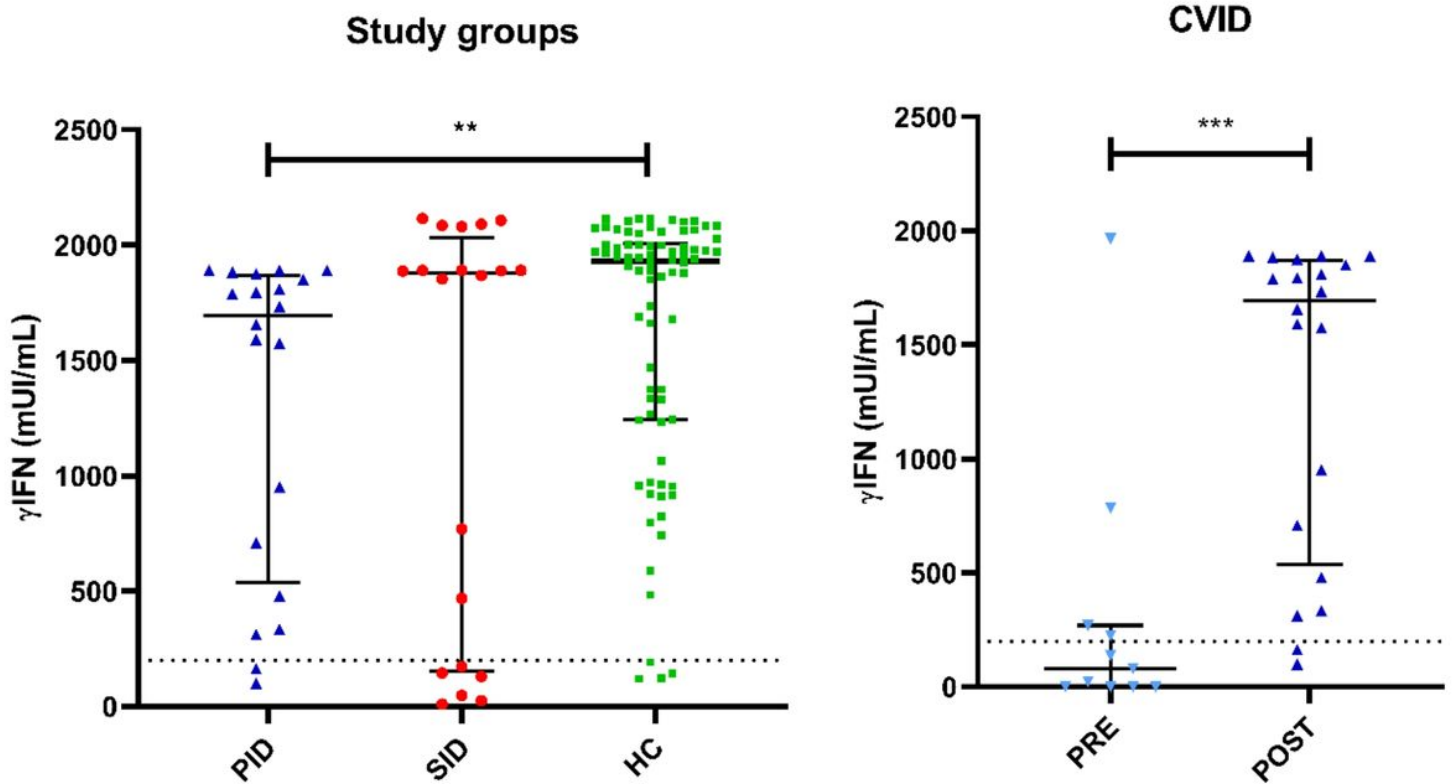
Figures

Figure 1

Specific anti-SARS-CoV-2 IFN-γ responses measured by IGRA. **(a)** Patients with PID in blue and SID in red compared to immunocompetent controls in green. PID mounted significantly lower IFN-γ anti-SARS-CoV-2 titers than healthy controls (*p*=0.005) **(b)** Anti-SARS-CoV-2 IFN-γ levels pre-vaccine and post-vaccine in PID with titers significantly lowers before the vaccine administration with respect to post-vaccination levels (*p* < 0.001).
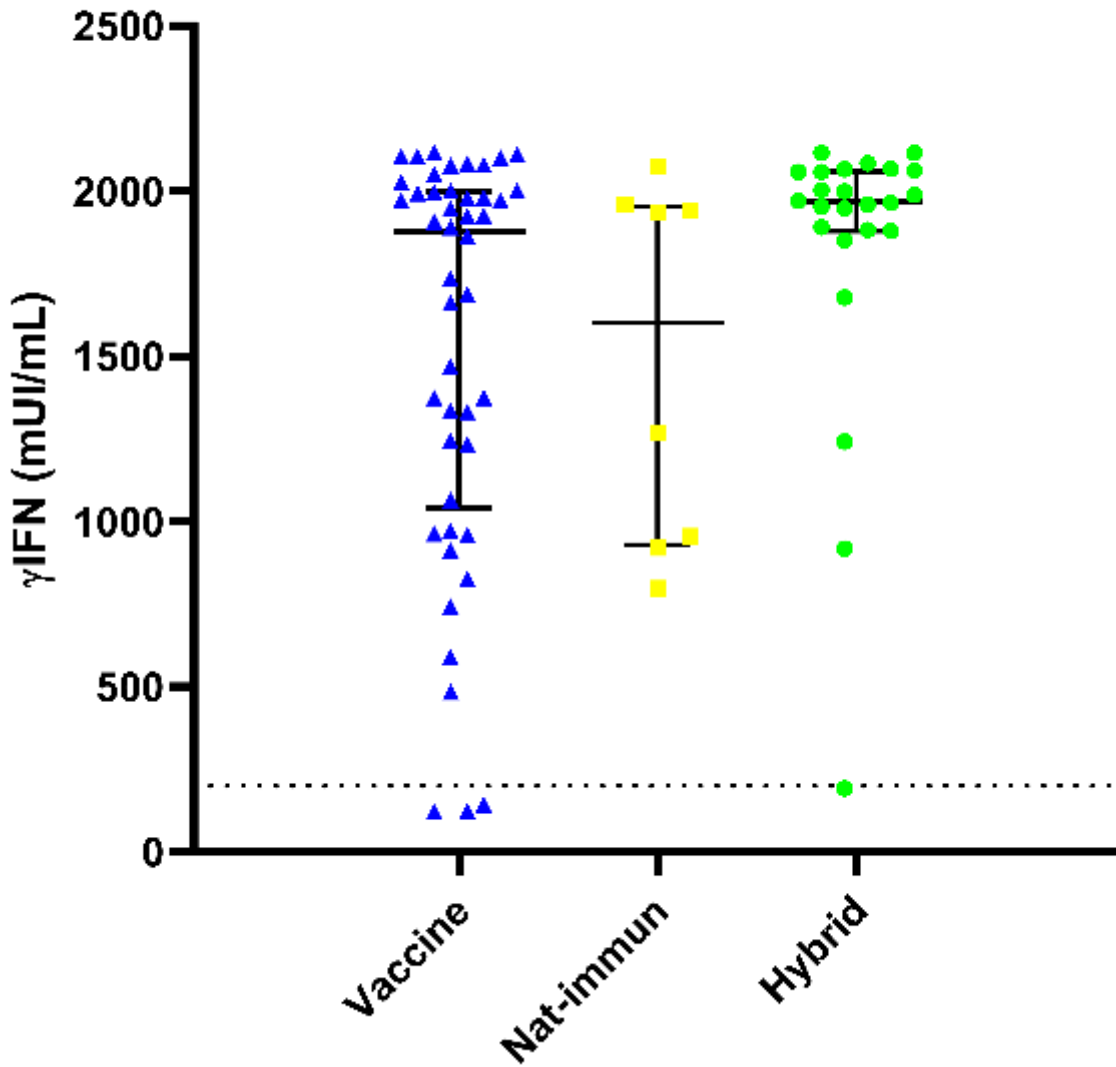
Healthy Controls

Figure 2

Specific anti-SARS-CoV-2 IFN-g responses in healthy control subgroups (vaccine, natural immune response, and hybrid) measured by IGRA. There was a great variability in HC vaccine in comparison with the other subgroups and the highest levels were achieved in the HC hybrid subgroup.
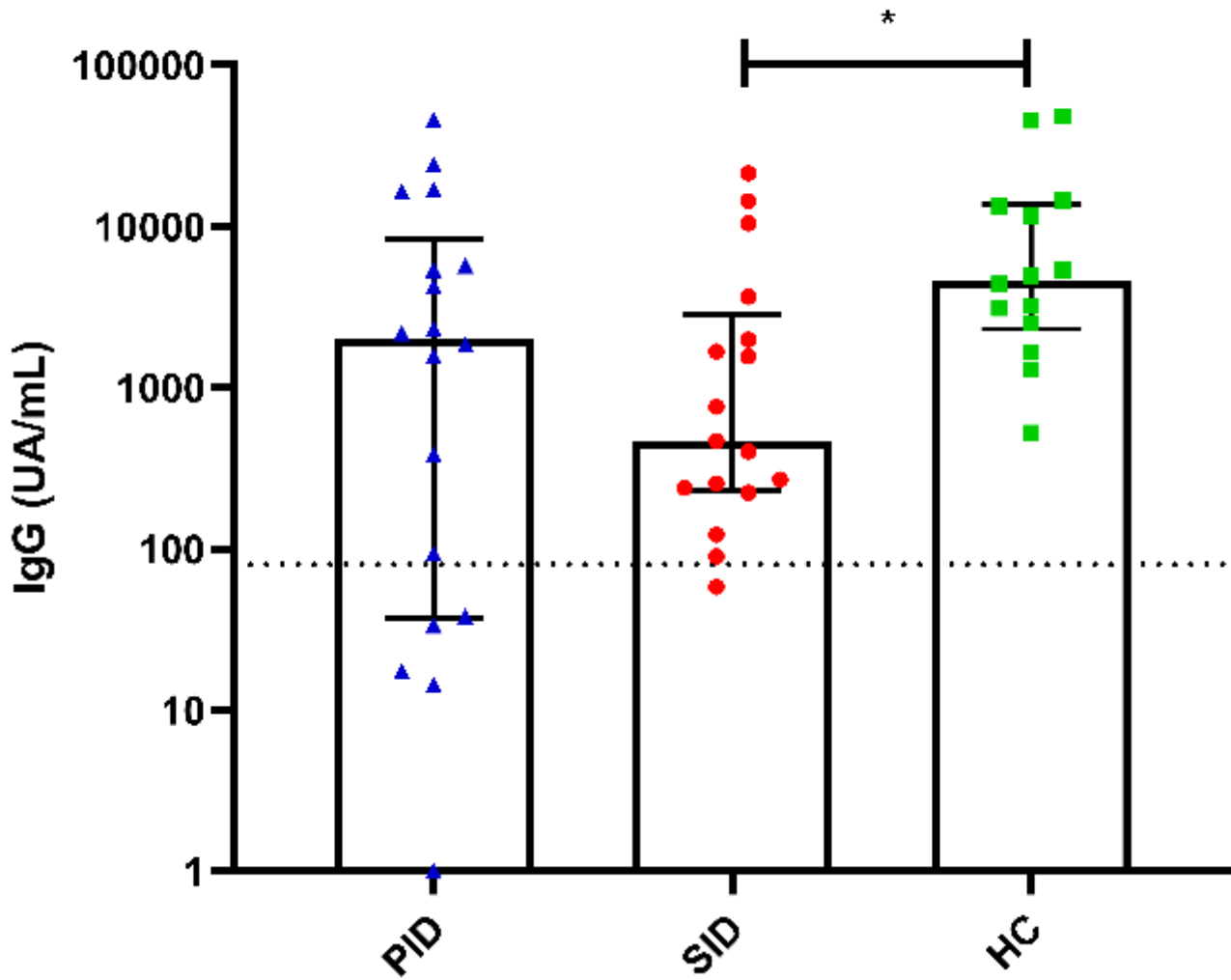
Figure 3

Antibody responses as measured by chemiluminescent microparticle immunoassay in the three study groups. SID to BCLD mounted significantly lower IgG anti-SARS-CoV-2 titers than healthy controls. *Significant differences (p < 0.05)