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RESEARCH ARTICLE

SARS-CoV-2-reactive antibody detection after SARS-CoV-2 vaccination in hematopoietic stem cell transplant recipients: Prospective survey from the Spanish Hematopoietic Stem Cell Transplantation and Cell Therapy Group

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Abstract

This is a multicenter prospective observational study that included a large cohort ($n = 397$) of allogeneic (allo-HSCT; ($n = 311$) and autologous (ASCT) hematopoietic stem cell transplant ($n = 86$) recipients who were monitored for antibody detection within 3–6 weeks after complete severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination from February 1, 2021, to July 20, 2021. Most patients ($n = 387$, 97.4%) received mRNA-based vaccines. Most of the recipients (93%) were vaccinated more than 1 year after transplant. Detectable SARS-CoV-2-reactive antibodies were observed in 242 (78%) of allo-HSCT and in 73 (85%) of ASCT recipients. Multivariate analysis in allo-HSCT recipients identified lymphopenia $< 1 \times 10^9$/ml (odds ratio [OR] 0.33, 95% confidence interval [95% CI] 0.16–0.69, $p = .003$), active graft versus host disease (GvHD; OR 0.51, 95% CI 0.27–0.98, $p = .04$) and vaccination within the first year of transplant (OR 0.3, 95% CI 0.15–0.9, $p = .04$) associated with lower antibody detection whereas. In ASCT, non-Hodgkin's lymphoma (NHL; OR 0.09, 95% CI 0.02–0.44, $p = .003$) and active corticosteroid therapy (OR 0.2, 95% CI 0.02–0.87, $p = .03$) were associated with lower detection rate. We report an encouraging rate of SARS-CoV-2-reactive antibodies detection in these severe immunocompromised patients. Lymphopenia, GvHD, the timing of vaccine, and NHL and corticosteroids therapy should be considered in allo-HSCT and ASCT, respectively, to identify candidates for SARS-CoV-2 antibodies monitoring.

1 | INTRODUCTION

The coronavirus infectious disease 2019 (COVID-19) pandemic caused by the new zoonotic coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) is causing a massive impact globally, including patients with hematological malignancies and recipients of hematopoietic stem cell transplantation (HSCT) whose overall mortality exceeds 25%.[1–6]

Vaccination is expected to mitigate the severe course of COVID-19 in immunocompromised patients such as recipients of autologous stem cell transplantation (ASCT) and allogeneic HSCT (allo-HSCT) recipients. However, prior experience with influenza vaccines indicated a lower serological response in immunocompromised patients compared to healthy individuals.[7–10] Despite these observations, influenza vaccination showed clinical benefit in allo-HSCT recipients.[11] New vaccine technologies led to the development of mRNA vaccines which could improve efficacy and robustness of serological response in immunocompromised patients as seen in the general population (> 90% seroconversion rates).[12–14] Initial reports on antibody response after full SARS-CoV-2 vaccination in hematological patients confirm the lower antibody response rates compared to the general population.[15–21] Although antibody detection monitoring after SARS-CoV-2 vaccination is not currently recommended in daily clinical practice,[22] the identification of poor responsive patients could have several important implications for immunocompromised patients such as the design of more efficacious vaccination programs, the identification of booster dose candidates, annual revaccination counseling, or inclusion in studies using anti-SARS-CoV-2 antibody-based therapies. Additionally, the identification of predictive factors of poor antibody production in immunocompromised patients could be useful to focus serological monitoring only on those predicted to have a poor vaccine serological immunogenicity.

The current study analyzes the SARS-CoV-2-reactive IgG antibodies detection at 3–6 weeks after a full course of SARS-CoV-2 vaccination and explored predictive factors for poor response in over 390 recipients of allo-HSCT and ASCT. This prospective study was conducted by the Spanish Hematopoietic Stem Cell Transplantation and Cell Therapy Group (GETH-TC).

2 | PATIENTS AND METHODS

2.1 | Study population

This is a prospective observational multicenter registry study conducted by the Infectious Complications Subcommittee (GRUCINI) of

the GETH-TC in collaboration with the Spanish Society of Hematology and Hemotherapy. The local ethical committee of the Hospital Clínico Universitario of Valencia approved the registry and study protocol (reference code 35.21).

2.2 | Inclusion criteria and cohort selection

This multicenter registry included consecutive adult patients with a prior history of hematological malignancies who were vaccinated against SARS-CoV-2 from December 30, 2020, to June 30, 2020, in 21 participating Spanish centers. All patients included in this registry gave their signed informed consent according to the declaration of Helsinki. The primary objectives of the current registry are (i) the assessment of antibody detection at 3–6 weeks, and its durability at 3, 6, and 12 months after full dose vaccination with any type of SARS-CoV-2 vaccines; (ii) to clinically monitor these patients for the occurrence of symptomatic COVID-19 after vaccination; (iii) and, finally, to assess the timing and the side effects of these vaccines in this immunocompromised population in Spain. Adult patients with a history of hematological malignancy were prioritized for early vaccination with any available SARS-CoV-2 vaccine type by the Spanish health authorities on March 11, 2021.

The status of all included patients was updated on July 30, 2021. During the study period, hematological patients vaccinated against COVID-19 from participating centers were prospectively registered through REDCap online platform in the GETH database by completing an essential medical data form, including patient and disease characteristics, date of vaccination, type of vaccination, self-reported adverse events (AEs) after vaccination, prior history of COVID-19, serological status before vaccination, the serological response at 3 week and at 3, 6, and 12 months after complete vaccination, and data regarding characteristics of later COVID-19 when applicable. Details on the treatment(s) of the underlying malignancy, conditioning regimens, type of donor, graft versus host disease (GvHD) prophylaxis, immunosuppressive drugs, GvHD status, and status disease at the time of vaccination were also registered. Also baseline laboratory variables before SARS-CoV-2 vaccination (absolute lymphocyte and neutrophil counts) were also collected.

As of July 30, 2021, 1546 patients with hematological malignancies who had been fully vaccinated against COVID-19 were registered in the GETH-TC database. With the aim of assessing antibody detection rates and its predictive factors in HSCT recipients, we first identified 457 such patients in our database. Sixty patients were finally excluded since they did not have a serological assessment at 3–6 weeks after complete vaccination. Thus, only recipients with available serological testing 3–6 weeks after full vaccination were included ($n = 397$). CAR-T recipients were excluded from this study.

2.3 | Definitions and technical considerations

The protective threshold levels of anti-SARS-CoV-2 antibodies below which the humoral defense against different SARS-CoV-2 variants is suboptimal have not been established yet. We defined antibody detection or seropositivity when SARS-CoV-2-reactive IgG antibodies recognition at any level was above the lower limit level of detection for each of the tests used. The rate of SARS-CoV-2-reactive IgG antibodies seroconversion was analyzed in the subgroup of patients with documented negative SARS-CoV-2 serostatus within 2 weeks prior to the first vaccine dose.

We assessed seropositivity using serological ELISA or chemiluminescence immunoassay assays following manufacturer instructions according to their availability at the microbiology services of each participating center. Table S1 summarizes the technical characteristics of serological tests used. All test used in the microbiology departments in the participating Spanish centers were able to detect SARS-CoV-2-reactive IgG antibodies. Overall results were reported as positive or negative detection. However, in a relevant number of cases ($n = 163$), antibody assessment was performed by chemiluminescence immunoassay techniques detecting anti-S-IgG normalized to the first World Health Organization (WHO) standard, and results were reported as anti-S1 IgG binding antibody units per milliliter (BAU/ml), and their results were analyzed separately. The lower limit of BAU/ml defined as a positive result was 350 BAU/ml following the latest WHO recommendations (NIBSC 20/136).

Prevaccination SARS-CoV-2 infection was defined as patients with prior history of polymerase chain reaction (PCR)-proven COVID-19 and/or positive SARS-CoV-2 serostatus (IgG and/or IgM) before the first vaccine dose.

2.4 | Endpoints and statistical analysis

The primary objective of the study was to assess seropositivity rates in HSCT recipients at 3–6 weeks after full COVID-19 vaccination. We also analyzed potential predictive factors for SARS-CoV-2-reactive IgG antibodies detection in each subgroup of recipients.

The main characteristics of patients were reported by descriptive statistics on the total of the available information, median and range were used for continuous variables, while absolute and percentage frequency were used for categorical variables. Variables of interest were tested using logistic regression models. Variables with a p-value < .1 in the univariate model were included in the multivariate analysis. A p-value < .05 was considered statistically significant. All p-values are two-sided. A median test subanalysis to check variables associated with the amount of antibodies production was carried out in patients with available quantitative anti-S1 IgG titers expressed as BAU/ml. All the analyses were performed using the statistical software SPSS v. 25.

3 | RESULTS

3.1 | Patient characteristics

We included 397 recipients (311 allo-HSCT and 86 ASCT recipients) with full vaccination schedule and available serological test at 3–6 weeks after the last vaccine dose. Detailed clinical and laboratory characteristics by patient's category (allo-HSCT, and ASCT recipients)

TABLE 1 Patients' characteristics

Characteristics	Allo-SCT ($n = 311$)	ASCT ($n = 86$)	p value
Type of vaccine, *n* (%)			.1
Moderna mRNA-1273	261 (84)	67 (78)	
Pfizer-BioNTech BNT162b2	47 (14)	12 (14)	
AstraZeneca/Oxford COVID-19 AZD1222	2 (0.6)	7 (8)	
Janssen Ad26.COV2. S	1 (0.3)	0	
Age (years), median (range)	56.7 (18–80)	64.6 (19–78)	.001
17–30 years, *n* (%)	32 (10)	2 (2)	
31–40 years, *n* (%)	33 (11)	4 (5)	
41–50 years, *n* (%)	54 (17)	10 (12)	
51–60 years, *n* (%)	79 (25)	18 (21)	
61–70 years, *n* (%)	88 (28)	40 (47)	
>71 years, *n* (%)	25 (8)	12 (14)	
Male, *n* (%)	185 (60)	49 (57)	.8
Baseline disease, *n* (%)			.001
AML	111 (36)	1 (1)	
MDS	43 (14)	1 (1)	
NHL	42 (13)	16 (19)	
MM	9 (3)	57 (66)	
CLL	7 (2)	0	
HD	29 (9)	11 (13)	
MPN	17 (5)	0	
ALL	42 (14)	0	
Others	11 (4)	0	
Status disease at vaccination, *n* (%)			.001
Complete remission	289 (93)	58 (68)	
Partial remission	9 (3)	19 (22)	
Not in response	12 (4)	9 (10)	
Time from transplant to COVID-19 vaccine, months (range)	98 (4–646)	88 (3–763)	.3
< 6 months	6 (2)	6 (7)	
≥ 6 month to 1 year	12 (4)	5 (6)	
≥ 1 year	293 (94)	75 (87)	
Conditioning Regimen, *n* (%)			
Melphalan		57 (66)	
BEAM		29 (34)	
TBF	95 (24)		
TBI-based	27 (7)		
FluBuCy	33 (8)		
FluBu	94 (24)		
FluMel	29 (9)		
Others	32 (10)		
Allo-SCT, *n* (%)			
HLA identical sibling donor	127 (41)		
URD	102 (33)		
Haplo-identical family donor	76 (24)		
UCBT	6 (2)		

(Continues)

TABLE 1 (Continued)

Characteristics	Allo-SCT ($n = 311$)	ASCT ($n = 86$)	p value
Donor/recipient HLA mismatch, *n* (%)	92 (30)		
GvHD prophylaxis			
Post-Cy based	140 (45)		
Sirolimus based	116 (37)		
CNI based	229 (74)		
ATG-based conditioning regimen, *n* (%)	22 (8)		
Conditioning regimen intensity, *n* (%)			
MAC	133 (43)		
RIC	178 (57)		
IS drugs at vaccination, *n* (%)	104 (33)	45 (52)	.01
IS without corticosteroids, *n* (%)	86 (28)	18 (21)	.2
Corticosteroids at vaccination, *n* (%)	19 (6)	28 (33)	.001
< 0.5 mg/kg	15 (79)	3 (8)	
≥ 0.5 mg/kg	4 (21)	25 (92)	
Active GvHD at vaccination, *n* (%)	84 (27)	0	
Acute GvHD	2 (0.6)		
Chronic GvHD	82 (26)		
Lenalidomide maintenance, *n* (%)	0	16 (21)	
Ruxolitinib as GvHD therapy	11 (4)	—	
Blood count before vaccination ($\times 10^9$/ml)			ns
Absolute neutrophile counts, median (range)	2.96 (0.06–11.57)	2.7 (0.44–15.4)	
Absolute lymphocyte counts, median (range)	2.15 (0.28–19.4)	1.53 (0.65–4.1)	
SARS-CoV-2 serological status prior to vaccination, *n* (%)	198 (63)	31 (36)	<.001
Negative IgG	187 (94)	25 (81)	
Positive IgG	11 (6)	6 (19)	
Prior PCR positive COVID-19, *n* (%)	22 (7)	4 (5)	
Time from two dose to serologies, median days (range)	21 (15–59)	22 (15–52)	ns
Median time between vaccine doses, median days (range)	28 (18–105)	28 (17–98)	
SARS-CoV-2-reactive IgG at 3 weeks after full vaccination, *n* (%)	242 (78)	73 (85)	.2
COVID-19 after vaccination, *n* (%)	1	0	
Median follow-up after the two-vaccine dose, days (range)	26 (15–162)	39 (15–82)	.4

Abbreviations: ALL, acute lymphoblastic leukemia; Allo-HSCT, allogeneic stem cell transplantation; AML, acute myeloid leukemia; ATG, anti-thymocyte globulin; BEAM, BCNU, etoposide, cytarabine and melphalan; CLL, chronic lymphocytic leukemia; CNI, calcineurin inhibitor; FluBuCy, fludarabine, busulphan, and cyclophosphamide; FluMel, fludarabine and melphalan; GvHD, graft versus host disease.; HD, Hodgkin's disease; IS, Immunosuppressors; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; MM, multiple myeloma; MPN, chronic myeloproliferative neoplasm; NHL, non-Hodgkin's lymphoma; Post-Cy, posttransplant cyclophosphamide; RIC, reduced-intensity conditioning; TBF, thiotepa, fludarabine and busulphan; TBI, total body irradiation; UCBT, umbilical cord blood transplantation; URD, adult unrelated donor.

are summarized in Table 1. The median age was 59 years (range 18–80). Overall, the most common hematological disease was acute myeloid leukemia ($n = 112$, 36%) followed by multiple myeloma (MM; $n = 66$, 16.6%) and non-Hodgkin's lymphoma (NHL; ($n = 63$, 14.6%).

ASCT recipients were significantly older, most of them being transplanted for MM. Among the 311 allo-HSCT recipients, there were 41% from a human leukocyte antigen (HLA)-identical sibling donor, 33% from an adult unrelated donor (URD), 24% from a haploidentical family donor, and 2% from an umbilical cord blood donor. Prevaccination serological SARS-CoV-2-reactive IgG antibody result was available in 229 (57.6%) out of 397 cases at a median of 0 days (range 0–92 days) before vaccination and was positive in 17 cases (8%). In addition, SARS-CoV-2 serology status within 2 weeks before the first dose of vaccine was available in 205 patients, of which 189 (93%) were negative.

Overall, SARS-CoV-2-reactive IgG antibody tests were positive in 315 of 397 recipients (79%) at a median of 21 days (range, 15–59 days) after the full vaccination schedule. However, 26 recipients had prior PCR-proven COVID-19 and their prevaccine serology was positive in 17/19 available cases. After excluding the 26 patients with prior COVID-19 (their serological results were analyzed separately), there were 371 recipients evaluable for primary SARS-CoV-2-reactive IgG antibody detection, and 291/371 (78%) had detectable antibodies after full vaccination. Of note,

TABLE 2 Univariate analysis of predictive factors of SARS-CoV-2-reactive IgG antibody detection in patients without prior COVID-19

Characteristics	Allo-SCT ($n = 289$) OR (95% CI)	*p* value	ASCT ($n = 82$) OR (95% CI)	*p* value
Type of vaccine, *n* (%)				
Moderna mRNA-1273 vs. others	2.06 (1.1–4.2)	.04	0.27 (0.03–2.2)	.23
Pfizer-BionTech BNT162b2 vs. others	0.48 (0.2–1.01)	.055	1.8 (0.2–15.56)	.6
Age (years)			0.96 (0.89–1.03)	.25
17–30 years, *n* (%)	1		NT	
31–40 years, *n* (%)	0.6 (0.17–2.09)	.4	NT	
41–50 years, *n* (%)	0.6 (0.18–1.9)	.38	NT	
51–60 years, *n* (%)	1.01 (0.3–3.1)	.97	NT	
61–70 years, *n* (%)	0.46 (0.15–1.3)	.15	NT	
>71 years, *n* (%)	0.95 (0.22–4)	.9	NT	
Male sex	1.06 (0.6–1.8)	.83	1.2 (0.36–4.1)	.7
Baseline disease			NT	
AML	1			
MDS	0.87 (0.37–1.9)	.71		
NHL	1.48 (0.58–3.7)	.4		
MM	0.54 (0.12–2.4)	.42		
CLL	0.89 (0.56–2.1)	.9		
HD	0.81 (0.32–2)	.66		
MPN	1.4 (0.37–5.3)	.61		
ALL	1.2 (0.49–2.9)	.66		
Others	1.01 (0.4–2.6)	.9		
B cell NHL vs. others			0.15 (0.04–0.57)	.005
Status disease at vaccination				
Complete remission	1		1	
Partial remission	1.7 (0.2–15.1)	.59	0.85 (0.2–3.6)	.8
Not in response	0.87 (0.2–3.4)	.87	0.59 (0.1–3.4)	.56
Time from transplant to COVID-19 vaccine				
<6 months	0.05 (0.006–0.43)	.008	1 (0.11–9.2)	.9
≥6 month to 1 year	0.4 (0.14–1.7)	.2	0.33 (0.028–4.1)	.4
≥1 year	1		1	.9
<1 year	0.24 (0.094–0.65)	.005	0.72 (0.13–3.86)	.7
Conditioning Regimen			NT	
TBF vs. others	0.9 (0.54–1.8)	.97		
FluBu vs. others				
Allo-HSCT			NT	
HLA identical sibling donor	1			
URD	0.62 (0.32–1.2)	.15		
Haplo-identical family donor	0.65 (0.3–1.33)	.24		
UCBT	1.1 (0.12–10.1)	.9		
Donor/recipient HLA mismatch	0.84 (0.46–1.5)	.57	NT	
GvHD prophylaxis			NT	
Post-Cy based	1.2 (0.69–2.09)	.5		
Sirolimus based	1.1 (0.64–2.03)	.62		
CNI based	1			
ATG-based conditioning regimen	0.96 (0.3–2.7)	.94	NT	

(Continues)

TABLE 2 (Continued)

Characteristics	Allo-SCT ($n = 289$) OR (95% CI)	*p* value	ASCT ($n = 82$) OR (95% CI)	*p* value
Conditioning regimen intensity			NT	
MAC	1			
RIC	0.93 (0.54–1.5)	.8		
IS drugs at vaccination	0.4 (0.24–0.75)	.003	0.6 (0.18–2.04)	.42
IS and corticosteroids				
IS and corticosteroids	1		1	
IS without	1.7 (0.6–4.8)	.3	4.73 (0.5–43.7)	.17
None of them	2.8 (1.03–7.6)	.04	3.5 (0.8–15.9)	.095
Corticosteroids at vaccination	0.34 (0.12–0.9)	.03	0.35 (0.1–1.1)	.08
Active GvHD at vaccination	0.56 (0.3–1.03)	.06	NT	
Lenalidomide maintenance			1.9 (0.21–16.39)	.56
Ruxolitinib as GvHD therapy	0.22 (0.058–0.85)	.029	NT	
Blood count before vaccination ($\times 10^9$/ml)				
Lymphocyte count < 0.5 × 109/ml	0.1 (0.03–0.33)	<.0001		
Lymphocyte count < 1.0 × 109/ml	0.25 (0.12–0.4)	<.0001	0.5 (0.12–2.28)	.39

Abbreviations: ALL, acute lymphoblastic leukemia; Allo-HSCT, allogeneic stem cell transplantation; AML means acute myeloid leukemia; ATG, anti-thymocyte globulin; CLL, chronic lymphocytic leukemia; CNI, calcineurin inhibitor; FluBuCy, fludarabine, busulphan; GvHD, graft versus host disease; HD, Hodgkin's disease; IS, Immunosuppressors; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; MM, multiple myeloma; MPN, chronic myeloproliferative neoplasm; NHL, non-Hodgkin's lymphoma; NT, not tested; Post-Cy, posttransplant cyclophosphamide; RIC, reduced-intensity conditioning; TBF, thiotepa, fludarabine and busulphan; UCBT, umbilical cord blood transplantation; URD, adult unrelated donor.

seroconversion was documented in 145/189 patients (77%) with confirmed negative serostatus within 2 weeks before vaccination.

3.2 | Vaccination kinetics, AEs, and breakthrough SARS-CoV-2 infection

Most patients received the mRNA-1273 (or Moderna®) vaccine ($n = 328$, 82%) followed by mRNA-BNT162b2 (Pfizer-BionTech®) vaccine ($n = 59$, 15%). The vast majority of recipients ($n = 365$, 92%) received the first vaccine dose from week 14–19 of the year 2021 (Figure S1). The vaccines were well tolerated with no serious AEs. Self-reported AEs after the first and second dose of the vaccine are summarized in Figure S2. Mild AEs occurred in 35 out of 397 (9%) and were more commonly reported after the first dose. The most common reported AE was local pain in the puncture site.

Only one allo-HSCT recipient (0.2%) from a URD with prior negative serostatus and vaccinated with mRNA-1273 at 6 months after transplant developed asymptomatic SARS-CoV-2 infection 10 days after the second dose. At 3 weeks after the second dose, his serological SARS-CoV-2-reactive IgG antibodies were negative (280 BAU/ml).

3.3 | Antibody detection in allo-HSCT and ASCT recipients

We performed a logistic regression univariate analysis of variables that could influence antibody production in allo-HSCT and ASCT recipients. Table 2 shows variables that significantly influenced the detection of SARS-CoV-2-reactive IgG antibodies.

Multivariate analyses in allo-HSCT recipients revealed vaccination timing from transplant (< 1 year after stem cell infusion) was associated with lower probability of seropositivity (odds ratio [OR] 0.3, 95% confidence interval (CI) 0.15–0.9, $p = .04$), as well as lymphopenia (< 1×10^9/ml; OR 0.33, 95% CI, 0.16–0.69, $p = .003$) and active GvHD (OR 0.51, 95% CI, 0.27–0.98, $p = .045$) were related with a lower likelihood of having detectable SARS-CoV-2-reactive IgG antibodies. Variables associated with lower rates of detection in ASCT recipients in multivariate analysis were active treatment with corticosteroids (OR 0.20, 95% CI. 0.02–0.87) and NHL as the underlying disease (OR 0.09, 95% CI, 0.02–0.44, $p = .03$).

3.4 | Antibody response in recipients with prior COVID-19

Twenty-six patients (15 men and 11 women) had a prior history of PCR-proven COVID-19 before vaccination. Most of the recipients ($n = 22$) developed COVID-19 after allo-HSCT, whereas four after ASCT. All patients received the SARS-CoV-2 vaccine more than 1 year after stem cell infusion. Their overall seropositivity postvaccination was 92%, and only two allo-HSCT recipients (one from a haploidentical family donor and the other from a URD) did not develop detectable SARS-CoV-2-reactive IgG antibodies. In fact, both of them did not mount an antibody response after COVID-19 and remained seronegative after two doses of the Moderna® mRNA-1273 vaccine.

TABLE 3 Logistic regression and median test analyses of anti-S1 IgG serostatus and titers after full vaccination Schedule in allo-HSCT recipients according to conditions potentially associated with antibody production

Characteristics	Positive antibodies OR (95% CI)	*p* value	Median titers in BAU/ml, (IQRs) ($n = 142$)	*p* value
Age (years), median (range)				.005
17–30 years, *n* (%)	1		222 378.82 (115 508–280 000)	
31–40 years, *n* (%)	0.5 (0.08–3.4)	.5	33 005.66 (0–245 766)	
41–50 years, *n* (%)	0.42 (0.08–2.9)	.4	207 891.2 (140–280 000)	
51–60 years, *n* (%)	0.5 (0.09–2.7)	.4	53 948.22 (210–202 096)	
61–70 years, *n* (%)	0.63 (0.11–3.3)	.6	150 426.5 (5164–280 000)	
>71 years, *n* (%)	1.8 (0.14–23)	.6	51 384.26 (10 953–181 032)	
Sex				.7
Male	0.78 (0.34–1.78)	.5	113 633.69 (3117–280 000)	
Female	NT		128 832 (280–249 249)	
Type of donor				.039
HLA identical sibling donor	1		197 155.9 (22 027–280 000)	
URD	0.46 (0.17–1.2)	.1	74 662.72 (0–194 163)	
Haplo-identical family donor	0.5 (0.16–1.7)	.28	23 042.97 (0–241 004)	
UCBT	0.48 (0.04–5.1)	.55	197 103.1 (47 345–261 205)	
Donor/recipient HLA mismatch, *n* (%)	0.7 (0.3–1.9)	.58		.59
Yes			43 167 (0–235 483)	
No			126 461.63 (6915–280 000)	
GvHD prophylaxis				
Post-Cy based	1.2 (0.45–3.5)	.6	26 323 (0–244 459)	.4
Not post-Cy	NT		134 469 (6958–273 124)	
Sirolimus based	1.26 (0.49–3.2)	.6		
Yes			132 489.6 (6888.4–253 568)	.8
No			115 185.6 (280–250 028)	
CNI based	2 (0.18–23.5)	.5		
Yes			122 500.9 (1084–255 229)	.2
No			0 (0–18 407)	
ATG-based conditioning regimen, *n* (%)	0.68 (0.17–2.7)	.6		
ATG			197 103 (1707–280 000)	.7
No ATG			115 185.6 (1029–247 222.6)	
Conditioning regimen intensity, *n* (%)				
MAC	NT		167 508 (280–280 000)	.4
RIC	0.86 (0.3–1.9)	.7	92 946 (973.5–225 463)	
IS drugs at vaccination, *n* (%)				
No	2.0.55 (0.8–7.9)	.1	143 773 (70–249 943)	
Yes			53 948 (6888–253 344)	.08
Corticosteroids at vaccination, *n* (%)	0.7 (0.14–3.78)	.7		
Yes			23 922.6 (229.5–155 002)	.2
No			122 500.9 (1005.8–273 124)	
Active GvHD at vaccination, *n* (%)	0.8 (0.33–2)	.67		
Yes			83 402.18 (140–242 304.8)	.1
No			144 340 (2458.1–260 430)	
Lymphocyte count < 1×10^9/ml	0.6 (0.17–2.7)	.5		
Yes			8432 (150.8–186 221.3)	.36
No			142 842 (4470–277 708.1)	
Lymphocyte count < 0.5×10^9/ml	0.21 (0.04–1.1)	.07		
Yes			301.66 (0–10 093.95)	.037
No			142 842.3 (5858.16–280 000)	

Abbreviations: Allo-HSCT, allogeneic stem cell transplantation; ATG, anti-thymocyte globulin; CNI, calcineurin inhibitor; GvHD, graft versus host disease; HLA, human leukocyte antigen; IS, Immunosuppressors; MAC, myeloablative conditioning; NT, not tested; OR, odds ratio; post-Cy, posttransplant cyclophosphamide; RIC, reduced-intensity conditioning; UCBT, umbilical cord blood transplantation; URD, adult unrelated donor.

TABLE 4 Probabilities of SARS-CoV-2-reactive IgG antibody detection rates according to recipients and procedures' characteristics

	Allo-HSCT	ASCT	Lymphocyte count $<1 \times 10^9$/ml	Lymphocyte count $<0.5 \times 10^9$/ml	Active GvHD	Without GvHD	Corticosteroids	Without corticosteroids	Multiple myeloma	NHL	Vaccine <1 year after infusion	Vaccine ≥1 year after infusion
Allo-HSCT	77.8%											
ASCT		87%							91.8%[b]	60%[b]		
Lymphocyte count $< 1 \times 10^9$/ml	53.3%	83%			31%[a]	65.5%[a]	14%[a]	60.5%[a]	77.8%[b]	NC[b]	33.3%[a]	60%[a]
Lymphocyte count $\geq 1 \times 10^9$/ml	82.3%	87.1%			80%[a]	82.9%[a]	83%[a]	82.2%[a]	94.7%[b]	60%[b]	83.1%[a]	83.1%[a]
Lymphocyte count $< 0.5 \times 10^9$/ml	28%	NC			0%[a]	80%[a]	0%[a]	36%[a]	NC[b]	NC[b]	33.3%[a]	27.3%[a]
Lymphocyte count $\geq 0.5 \times 10^9$/ml	80%	86.6%			79%[a]	80.6%	68.8%[a]	81%[a]	91.5%[b]	60%[b]	53.3%[a]	82.3%[a]
Active GvHD	71%						64.3%[a]	72.9%[a]			50%[a]	72.5%[a]
Without GvHD	80%						40%[a]	81.1%[a]			50%[a]	82.7%[a]
corticosteroids	57.9%	76%							81%[b]	50%[b]	33.3%[a]	66.7%[a]
Without corticosteroids	79.1%	92%							100%[b]	70%[b]	53.3%[a]	80.6%[a]
Under IS	69.2%	83.3%	39%[a]	25%[a]	66.7%[a]	71.7%[a]	61%[a]	70.9%[a]	88.9%[b]	40%[b]	40%[a]	74.2%[a]
Without IS	82.1%	91%	76%[a]	NC[a]	78.8%[a]	82.8%[a]	NC	82.5%[a]	100%[b]	70%[b]	NC[a]	82.4%[a]
Lenalidomide									85%[b]			
Without lenalidomide									93.8%[b]			
Vaccine < 1 year after infusion	50%	83.3%							NC[b]	NC[b]		
Vaccine ≥ 1 year after infusion	80%	89.6%							93%[b]	66.6%[b]		

Abbreviations: Allo-HSCT refers to allogeneic hematopoietic stem cell transplant; ASCT, autologous stem cell transplantation; GvHD, graft versus host disease; IS, immunosuppressor drugs; NC, not calculable when the subgroup had less than five patients.

[a]Probabilities calculated only for allo-HSCT recipients.

[b]Probabilities calculated only for ASCT recipients.

3.5 | Anti-S1 IgG antibody titers in allo-HSCT recipients

To assess, in a homogeneous cohort, the magnitude of anti-S1 IgG titers at 3–6 weeks after full vaccination, we selected only the patients who were tested using a WHO standardized Abbott Architect SARS-CoV-2 IgG Quant II chemiluminescent microparticle immunoassay. There were 154 evaluable patients, including 142 allo-HSCT recipients and 12 ASCT. The median anti-S1 IgG titer was 109877.5 BAU/ml, (range 0–280 000; interquartile ranges 603.3–244757.57). We did not find statistically significant differences in the median anti-S1 IgG titers between allo-HSCT and ASCT (median allo-HSCT 115347.23 BAU/ml vs. median ASCT 3830.0 BAU/ml, $p = .36$).

To evaluate the potential independent impact of variables shown to influence antibody detection in the univariate analysis, we performed a subanalysis only in allo-HSCT recipients. The clinical characteristics of the 142 recipients included in this subanalysis are summarized in Table S2, and there were no significant differences with respect to the whole allo-HSCT cohort. The anti-S1 IgG detection rate was 80% (114/142 recipients). Univariate logistic regression analyses and median test results are shown in Table 3. In multivariate analysis, the only factors significantly associated with lower median anti-S1 IgG titers were the type of donor and a lymphocyte count $< 0.5 \times 10^9$/ml at vaccination (Figure S3A,B).

3.6 | Probability of antibody response according to predictive factors

We estimated the probability of having detectable SARS-CoV-2-reactive IgG antibodies according to the type of procedure and the presence of relevant conditions and/or several combinations of these conditions that may hamper antibody production (Table 4). In allo-HSCT recipients, the lowest rate of antibody detection occurred in recipients with active GvHD and lymphopenia $< 0.5 \times 10^9$/ml (0%), followed by any immunosuppressive treatment and lymphopenia $< 0.5 \times 10^9$/ml (25%), whereas the highest rate was observed in recipients without active GvHD and immunosuppressive drugs (82.8%). Finally, among ASCT recipients, those with MM showed a seropositivity rate of 91.2%, whereas in NHL, it was 60% and 100% in Hodgkin's disease. The lowest detection rate post-ASCT was observed in relapsed NHL patients under active treatment (40%) and in those under corticosteroid therapy (50%). In contrast, the highest probability of having detectable antibodies was observed in MM patients not receiving neither immunosuppressive nor corticosteroid treatment (100%, each).

4 | DISCUSSION

We report herein a real-life experience of COVID-19 vaccination and qualitative SARS-CoV-2-reactive IgG antibody monitoring in a large series of HSCT recipients from 14 hematology units in Spain. Vaccination was well tolerated (9% mild AEs) with an overall encouraging anti-S IgG detection rate of 79% (78% in allo-HSCT and 85% in ASCT recipients). We identified some potential predictive factors and estimated serological responses by these risk factors. Lymphopenia $< 1 \times 10^9$/ml was the main factor related to lower probabilities of detectable antibodies in allo-HSCT recipients. In addition, active GvHD at the time of vaccination predicted a lower probability of seropositivity, while vaccination after the first-year posttransplant provided higher probabilities in the allo-HSCT setting. In turn, seropositivity rates were lower in ASCT recipients under corticosteroid treatment and in those with B-cell NHL.

Although we used a qualitative assessment of SARS-CoV-2-reactive IgG detection, the first encouraging observation was the high seropositivity rate (79%) observed in these immunosuppressed patients, which is in contrast with the response rate reported in the solid organ transplant setting (30%–59%).[23–26] Our detection rates are in-line with recent experiences in oncohematological patients with mRNA-based vaccines (> 75% of serological responses),[15,16,20,21] and in particular with recent studies conducted in allo-HSCT recipients (> 70% seroconversion).[17,27–29] Although for the study purpose we use seropositivity instead of seroconversion, we also were able to evaluate seroconversion in 189 recipients with known seronegative SARS-CoV-2 serologies within 2 weeks before vaccination and found similar rates (77%). This fact supports that, even though different serological methodologies were applied and irrespective of pre-vaccination serostatus, SARS-CoV-2-reactive IgG detection rates were consistent and reliable through different studies conducted in different countries. While the optimal serological response assessment that implies definite viral protection (technique, standardization, and protective antibody titer threshold) remains to be determined, qualitative evaluation could be useful in identifying very poor responders in daily clinical practice.

Antibody response to any vaccine-preventable infectious disease in HSCT recipients is largely driven by the disease status, conditioning intensity, type of donor, stem cell source, current or past immunosuppressors, the presence of GvHD, lymphopenia, the interval between transplant and vaccination, age, and the type of vaccine.[30] In our series, and in particular, in allo-HSCT, the most relevant factor limiting the antibody detection was lymphopenia $< 1 \times 10^9$/ml. This lymphocyte count threshold has been already identified as a risk factor for poor SARS-CoV-2 vaccine response in allo-HSCT recipients.[17] Lymphopenia constitutes one of the most important surrogate markers of profound immunosuppression after transplant increasing the risk for poor outcomes from several different viral infections (including other community-acquired respiratory viruses, cytomegalovirus, and of course SARS-CoV-2) in HSCT.[1,11,31–35] Thus, strategies aimed at improving lymphoid reconstitution should be in the focus of research in order to enhance antibody production after vaccination and to limit the consequences of such viral infections. Another expected factor associated with lower SARS-CoV-2-reactive IgG antibody detection was the presence of active GvHD at the time of vaccination. GvHD is associated with profound immunosuppression largely due to the immunosuppressive drugs that impair T and B cell functions. In this scenario, mounting antibody responses with any vaccine is challenging.[30] However,

in our allo-HSCT series, recipients with active GvHD showed detectable antibodies in 80% of recipients with a lymphocyte count > 1×10^9/ml. This fact suggests that SARS-CoV-2 vaccination in recipients with active GvHD (most of them with chronic forms) should not be regarded as futile. In contrast, our study confirms that the timing from transplant to vaccination was relevant, as seen with other vaccines in allo-HSCT recipients.[10] Vaccination more than 1 year after transplantation led to higher rates of detectable SARS-CoV-2-reactive IgG antibodies. However, this fact should not be used to defer SARS-CoV-2 vaccination at a moment when the incidence of the infection in the community remains high since half of the patients vaccinated earlier had a serological response.

Regarding predictive factors of seropositivity in ASCT recipients, we identified the use of corticosteroids at the time of vaccination and NHL as underlying disease as conditions associated with lower detection rates. While corticosteroids are recognized as interfering with the production of SARS-CoV-2 antibodies[36] unexpectedly, we found that ASCT recipients with MM had a high probability of developing detectable SARS-CoV-2-reactive IgG antibodies (91.8%). This is consistent with a recent study in 159 MM patients in which the serological response rate in those vaccinated after ASCT ($n = 77$) was also high (89.2%).[21] In addition, all patients with Hodgkin's lymphoma had detectable SARS-CoV-2-reactive IgG antibodies ($n = 11$, 100%). Finally, in the ASCT cohort, the lowest seropositivity rate (60%) was found in patients with NHL. This group of patients received anti-CD20 monoclonal antibodies (moAb) treatment before ASCT and as a part of high-dose chemotherapy conditioning. Poor response to vaccination has been well described in patients treated with anti-CD20 moAb and lasting 6–12 months or more.[15,18,20]

Based on the current data, SARS-CoV-2-reactive IgG antibody detection monitoring could be helpful in most allo-HSCT recipients since the prevaccine probability of serological response to a community-acquired infection is lower than in the general population, except for those with prior COVID-19 history (detection rate 92%).

To assess the predictive factors of quantitative anti-S1 IgG antibody production, we performed a subanalysis in 142 allo-HSCT recipients. Again, we found lymphopenia (< 0.5×10^9/ml) as the main factor associated with lower antibody titers. However, we did not find any association with active GvHD, immunosuppressors, type of vaccine, corticosteroid therapy nor the timing of vaccination likely due to the small number of patients having these factors. Interestingly, however, we also found that type of donor was associated with the lower amount of antibody production. Recipients of allo-HSCT from HLA-identical sibling showed the highest median antibody titers followed by adult URD recipients, whereas recipients of haploidentical allo-HSCT had the lowest median antibody titers. These data may emphasize the critical role of HLA molecules in antigen presentation, T cell recognition, and antibody production.[37,38] Therefore, we can hypothesize that minor and/or major HLA mismatches between donor and recipient may well have an impact on response to vaccination.

Our study has several limitations. We focused on qualitative antibody testing to define seropositivity using different serological tests. Most of the recipients (93%) received vaccination after 1 year of transplant. We were not able to evaluate the effect of prior anti-CD20 therapy in the context of transplant due to the low number of patients receiving this treatment in our cohort. Our study was not designed to evaluate the risk of worsening/triggering GvHD after mRNA vaccines. We did not have prevaccination status data in 43% of the cases and thus we cannot exclude the presence of some seropositive patients due to asymptomatic SARS-CoV-2 infection with prior seropositivity before vaccination, although the seroconversion rate was similar in those with known seronegative SARS-CoV-2-reactive IgG test within 2 weeks prior to vaccination (77%). We also did not analyze neutralizing antibody titers nor T-cell responses after vaccination. Another limitation of our study is the lack of serological response comparison between HSCT recipients and healthy individuals. However, the large number of allo-HSCT recipients included, the multicenter approach and the concordance of our results with other preliminary reports should be considered as strengths.

In a cohort of HSCT recipients vaccinated more than 1 year after transplant (93%), we provided encouraging seropositive SARS-CoV-2-reactive IgG antibody rates after mRNA-based SARS-CoV-2 vaccines in these immunocompromised patients. The lymphocyte count and active GvHD should be taken into account in allo-HSCT recipients for decision-making or patient's counseling with regard to the best timing for vaccination. ASCT recipients who received prior anti-CD20 moAb therapy or under corticosteroids therapy require strategies to improve vaccine-induced serological responses.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

AUTHOR CONTRIBUTIONS

Authors who were responsible for the conception and the design of the study: José Luis Piñana, Angel Cedillo, and Anna Sureda.

Authors who performed the data analysis and generated the tables and figures: José Luis Piñana, David Navarro, and Rodrigo Martino.

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Authors who were responsible for writing the manuscript:

- José Luis Piñana, Rodrigo Martino, and David Navarro were responsible for writing and supervising the writing of the manuscript.
- All coauthors were responsible for reviewing the analysis interpretation, suggesting modifications to the text, critically reviewing the manuscript, and for final approval of the manuscript.

PATIENT CONSENT STATEMENT

All patients included in this registry gave their signed informed consent according to the declaration of Helsinki.

DATA AVAILABILITY STATEMENT

Data available upon request by email to the Spanish hematopoietic transplant and cell therapy group (GETH-TC).

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SUPPORTING INFORMATION

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