SARS-CoV-2 vaccine response and rate of breakthrough infection in patients with hematological disorders

José Luis Piñana1,2*, Lucia López-Corral3, Rodrigo Martino4, Lourdes Vazquez3, Ariadna Pérez1,2, Gabriel Martin-Martin3, Beatriz Gago5, Gabriela Sanz-Linares6, Andrés Sanchez-Salinas7, Lucía Villalon8, Venancio Conesa-García9, María T. Olave10, Magdalena Corona11, Sara Marcos-Corrales3, Mar Tormo1,2, José Ángel Hernández-Rivas12, Juan Montoro13, Alicia Rodríguez-Fernández14, Irene Risco-Gálvez15, Pablo Rodríguez-Belenguer16, Juan Carlos Hernandez-Boluda1,2,19, Irene García-Cadenas4,Montserrat Ruiz-Garcia17, Juan Luis Muñoz-Bellido18, Carlos Solano1,2,19, Ángel Cedillo20, Anna Sureda6 and David Navarro2,21 on behalf of the Infectious Complications Subcommittee of the Spanish Hematopoietic Stem Cell Transplantation and Cell Therapy Group (GETH-TC)

Abstract

Background: The clinical efficacy of SARS-CoV-2 vaccines according to antibody response in immunosuppressed patients such as hematological patients has not yet been established.

Patients and methods: A prospective multicenter registry-based cohort study conducted from December 2020 to December 2021 by the Spanish transplant and cell therapy group was used to analyze the relationship of antibody response at 3–6 weeks after full vaccination (2 doses) with breakthrough SARS-CoV-2 infection in 1394 patients with hematological disorders.

Results: At a median follow-up of 165 days after complete immunization, 37 out of 1394 (2.6%) developed breakthrough SARS-CoV-2 infection at median of 77 days (range 7–195) after full vaccination. The incidence rate was 6.39 per 100 persons-year. Most patients were asymptomatic (19/37, 51.4%), whereas only 19% developed pneumonia. The mortality rate was 8%. Lack of detectable antibodies at 3–6 weeks after full vaccination was the only variable associated with breakthrough infection in multivariate logistic regression analysis (Odds Ratio 2.35, 95% confidence interval 1.2–4.6, \( p = 0.012 \)). Median antibody titer were lower in cases than in non-cases (1.83 binding antibody units (BAU)/mL (range 0–4854.93) vs 730.81 BAU/mL (range 0–56,800), respectively (\( p = 0.007 \))). We identified 250 BAU/mL as a cutoff above which incidence and severity of the infection were significantly lower.

Conclusions: Our study highlights the benefit of developing an antibody response in these highly immunosuppressed patients. Level of antibody titers at 3 to 6 weeks after 2-dose vaccination links with protection against both breakthrough infection and severe disease for non-Omicron SARS-CoV-2 variants.

*Correspondence: jlpinana@gmail.com
1 Division of Clinical Hematology, Hematology Department, Hospital Clínico Universitario de Valencia, Avda Blasco Ibáñez, 17, 46010 Valencia, Spain
Full list of author information is available at the end of the article

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Keywords: SARS-CoV-2 vaccines, Breakthrough SARS-CoV-2 infection, Correlates of protection, Hematological malignancies, Allogeneic stem cell transplantation, Autologous stem cell transplantation, COVID-19, Vaccine, Immunocompromised patients, Moderna mRNA-1273, Pfizer-BioNTech BNT162b2

Introduction
The coronavirus infectious disease 2019 (COVID-19) pandemic caused by the new coronavirus (SARS-CoV-2) can have a dreadful impact in hematological patients, with mortality rates exceeding 25% [1–6]. SARS-CoV-2 vaccination is expected to reduce the severity of COVID-19 in these immunocompromised patients [7–11]. Although the antibody response after full SARS-CoV-2 vaccination in hematological patients is of a lower magnitude than in the general population [12–18], a clinical benefit is still expected, as is the case with influenza vaccination in allogeneic hematopoietic stem cell transplant (allo-HSCT) recipients [19]. Since no prospective randomized SARS-CoV-2 vaccine trials have been conducted in these patients, vaccine efficacy data are lacking in this scenario.

The current study analyzes the clinical benefit of full SARS-CoV-2 vaccination (2 doses) through an observational registry conducted by the Spanish Hematopoietic Stem Cell Transplantation and Cell Therapy Group (GETH-TC) aimed at monitoring the response to SARS-CoV-2 vaccine and the breakthrough SARS-CoV-2 infections over time in a large cohort of 1394 patients with hematological disorders.

Patients and methods
Study population
This is a prospective multicenter registry-based cohort study conducted by the Infectious Complications Sub-committee (GRUCINI) of the GETH-TC in collaboration with the Spanish Society of Hematology and Hemo therapy (SEHH). Details of this registry have been previously described elsewhere [20, 21]. In brief, the registry included consecutive adult patients with a prior history of hematological disorders who were fully vaccinated against COVID-19 between December 30, 2020, and June 30, 2021, in 21 participating Spanish centers. Patients were followed and monitored for development of SARS-CoV-2-reactive IgG antibodies (SCoV2-R-A) and the breakthrough SARS-CoV-2 infections over time in a large cohort of 1394 patients with hematological disorders.

Technical considerations and definitions
Antibody detection or seropositivity was defined when SARS-CoV-2-reactive IgG antibodies (SCoV2-R-A) were detected at any level above the lower limit of detection level for each test used. We assessed seropositivity using serological ELISA or chemiluminescence immunoassay following manufacturer instructions according to their availability at the microbiology services of each participating center. As recommended by the SEHH, in vaccinated individuals serological testing included the detection of IgG against both the nucleocapsid (N) and surface (S) proteins (anti-N and anti-S IgG, respectively) [7]. Of the 1394 patients included, 1244 (89%) received quantitative assessment, whereas the remainder was assessed through qualitative testing. Antibody levels were normalized according to the WHO standard, and results were reported as SCoV2-R-A binding antibody units per milliliter (BAU/mL). Additional file 1: Table S1 summarizes the technical characteristics of the serological tests used and normalization of antibody titers to BAU/mL according to WHO standards.

Pre-vaccination SARS-CoV-2 infection was defined as patients with prior history of PCR-proven COVID-19 and/or positive SARS-CoV-2 serostatus (IgG and/or IgM) before the first vaccine dose. Patients with respiratory symptoms underwent PCR screening for the development of SARS-CoV-2 according to the treating physician criteria. Breakthrough SARS-CoV-2 infection was defined as molecular (PCR test) or humoral (anti-N seroconversion between two
with quantitative antibody testing, the median SCoV2-R-A titer was 720.26 BAU/mL (range 0–58,600). We compared SCoV2-R-A titers at 3–6 weeks after full vaccination in patients with and without SARS-CoV-2 infection prior to vaccination (excluding 7 patients with breakthrough SARS-CoV-2 infection after the second vaccine dose and before the first serological testing) and found higher titers in those with (median 2550 BAU/mL, range 0–10,400) vs those without (median 493.6 BAU/mL, range 0–6338.6) (p < 0.0001) infection (Fig. 1).

Breakthrough SARS-CoV-2 infection

We identified 37 patients (2.6%) with breakthrough SARS-CoV-2 infection at median of 77 days (range 7–195) after the second vaccine dose. The overall incidence rate of breakthrough SARS-CoV-2 infection was 6.39 per 100 persons-year. The main clinical and SARS-CoV-2 breakthrough infection characteristics are detailed in Table 2. Most patients were diagnosed through molecular PCR testing (n = 22, 60%), whereas those remaining (n = 15, 40%) were diagnosed by seroconversion of anti-N between two consecutive serological tests. Seven patients (19%) developed SARS-CoV-2 infection between the second vaccine dose and SCoV2-R-A testing at 3–6 weeks, with an incidence rate of 6.14 per 100 persons-year. Twelve patients (32%) developed the infection between 3–6 weeks and 3 months after the complete vaccination with an estimated incidence rate of 6.9 per 100 persons-year. Finally, 18 patients had the infection between 3 and 7 months after the complete vaccination with an estimated incidence rate of 14.09 per 100 persons-year. Eighteen patients had COVID-19 (48.6%), whereas 19 (51.4%) were asymptomatic. SARS-CoV-2 was detected by PCR in 4 asymptomatic patients during screening performed before hospital admission for scheduled procedures/treatments. Pneumonia was documented in 7 cases (19%), whereas the SARS-CoV-2 infection-related hospital admission rate was 32% (n = 12). There were 3 COVID-19-related deaths (8%) at a median of 26 days (range 7–67) after SARS-CoV-2 detection.

Risk factors (including antibody level titers) for breakthrough SARS-CoV-2 infection

After excluding 7 patients with breakthrough SARS-CoV-2 infection before the first serological testing, we performed a univariate and multivariate regression model to assess predictors of breakthrough SARS-CoV-2 infection (Table 3). None of the 109 patients who developed COVID-19 before vaccination developed breakthrough infection (p = 0.1 in univariate analysis). The only variable that was found to have an impact on the risk of breakthrough SARS-CoV-2 infection in univariate and multivariate analyses was absence of SCoV2-R-A
detection at 3–6 weeks after the second vaccine dose [odds ratio (OR) 2.35 95% confidence interval (CI) 1.2–4.6, \( p = 0.012 \)]

Regarding the impact of the magnitude of SCoV2-R-A load, we restricted the analysis to 27 patients, since 7 cases became infected before the first antibody determination after vaccination and another 3 cases only had qualitative SCoV2-R-A testing. Overall, 1234 patients were evaluable for antibody levels normalized as BAU/mL. The median SCoV2-R-A levels at 3–6 weeks after the full vaccination were significantly lower in the 27 patients with breakthrough SARS-CoV-2 infection as compared to those without [1.83 BAU/mL (range

Table 1  Patient characteristics

| Characteristics                                      | \( n = 1394 \) |
|------------------------------------------------------|---------------|
| Prior COVID-19, \( n \) (%)                          | 109 (7.9)     |
| Diagnosed by PCR                                     | 95 (7)        |
| Positive serostatus prior to vaccination             | 37 (2.6)      |
| Negative serostatus prior to vaccination             | 13 (1)        |
| Detected by pre-vaccine serological test             | 14 (1.5)      |
| Median time from COVID-19 to vaccination, days (range)| 185 (33–460) |
| Serological status prior to vaccination, \( n \) (%)  | 50 (4)        |
| Positive                                              | 50 (4)        |
| Negative                                              | 422 (30)      |
| Not tested                                            | 922 (66)      |
| Median time from serology to vaccination, days (range)| 0 (0–386)    |
| Type of vaccine, \( n \) (%)                         |               |
| Moderna mRNA-1273                                    | 983 (70.5)    |
| Pfizer-BioNTech BNT162b2                              | 362 (26)      |
| Adenoviral vector-based                               | 49 (3.5)      |
| Age (years), median (range)                          | 63 (18–97)    |
| 18–40 years, \( n \) (%)                            | 143 (10)      |
| 41–60 years, \( n \) (%)                            | 496 (35.5)    |
| 61–70 years, \( n \) (%)                            | 373 (26.8)    |
| > 71 years, \( n \) (%)                             | 382 (27.4)    |
| Male, \( n \)                                        | 784 (56.3)    |
| ECOG 0–1 at vaccination                              | 1351 (97)     |
| Baseline disease, \( n \) (%)                        |               |
| AML                                                   | 179 (12.8)    |
| ALL                                                   | 46 (3.3)      |
| MDS                                                   | 158 (11.3)    |
| B-cell NHL                                            | 302 (21.6)    |
| T cell NHL                                            | 38 (2.7)      |
| Plasma cell disorders                                 | 236 (16.9)    |
| CLL                                                   | 158 (11.3)    |
| HD                                                    | 103 (7.4)     |
| cMPN                                                  | 139 (10)      |
| Aplastic anemia                                       | 16 (1)        |
| Non-malignant disorders                               | 18 (1.3)      |
| Type of cell therapy                                  |               |
| Allo-HSCT                                             | 369 (26.5)    |
| ASCT                                                  | 110 (8)       |
| CAR-T                                                 | 21 (1.5)      |
| Status disease at vaccination, \( n \) (%)           |               |
| Complete remission                                    | 824 (59.2)    |
| Partial remission                                     | 162 (11.6)    |
| Active disease                                        | 408 (29.2)    |
| Time last treatment to COVID-19 vaccine, months (range)|               |
| Untreated                                             | 172 (12.3)    |
| Active treatment                                      | 509 (36.5)    |
| \( \geq 6 \) month to 1 year                         | 92 (6.6)      |
| \( \geq 1 \) year                                     | 621 (44.5)    |
| Immunosuppressants drugs at vaccination, \( n \) (%) | 300 (21.5)    |
| Corticosteroids at vaccination, \( n \) (%)          | 255 (18.6)    |

Table 1  (continued)

| Characteristics                                      | \( n = 1394 \) |
|------------------------------------------------------|---------------|
| Daratumumab, \( n \) (%)                            | 46 (3.3)      |
| Venetoclax, \( n \) (%)                              | 14 (1)        |
| Anti-CD-20 moAb, \( n \) (%)                         | 241 (17.3)    |
| <6 months before 1st vaccine dose                     | 87 (6.2)      |
| 6 to 1 year before 1st vaccine dose                   | 25 (1.8)      |
| >1 year before 1st vaccine dose                       | 129 (9.3)     |
| BTK inhibitor therapy, \( n \) (%)                   | 63 (4.5)      |
| TKI therapy, \( n \) (%)                             | 40 (2.9)      |
| Lenalidomide maintenance, \( n \) (%)                | 120 (8.6)     |
| Ruxolitinib therapy, \( n \) (%)                     | 14 (1)        |
| Blood count before vaccination (\( \times 10^{9}/\text{mL} \)) |
| Absolute neutrophile counts, median (range)          | 3.1 (0–46.7)  |
| Absolute lymphocyte counts, median (range)           | 1.73          |
| Absolute lymphocyte counts < 1 \( \times 10^{5}/L \)  | 265 (18.6)    |
| Time from 2nd dose to first serologies, median days (range)| 21 (12–62) |
| Median time between vaccine doses, median days (range)| 28 (17–115)  |
| Patient with SCoV2-R-A titers at 3–6 weeks after full vaccination, \( n \) (%) | 1244 (89%)   |
| Median SCoV2-R-A titers at 3–6 weeks in BAU/mL, \( n \) (%) | 715 (0–56,800) |
| Third vaccine dose given, \( n \) (%)                | 550 (39.5)    |
| Time from 2nd dose to 3rd dose, days (range)          | 153 (39–269)  |
| Median follow-up after full vaccination, days (range) | 165 (12–269)  |
| COVID-19 after vaccination, \( n \) (%)              | 37 (2.7)      |
| Median time from vaccination to SARS-CoV-2 infection, days (range) | 77 (7–195) |

PCR, Polymerase chain reaction; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; B-cell NHL, B-cell non-Hodgkin lymphoma; T cell NHL, T cell non-Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; HD, Hodgkin disease; MPN, chronic myeloproliferative neoplasm; Allo-HSCT, allogeneic stem cell transplantation; ASCT, autologous stem cell transplantation; CAR-T, T cell chimeric antigen receptor; moAb, monoclonal antibody; BTK inhibitor, Bruton’s tyrosine kinase inhibitor; TKIs, tyrosine kinase inhibitors; and SCoV2-R-A, SARS-CoV-2-reactive IgG antibodies.
0–4854.93) vs 730.81 BAU/mL (range 0–56,800), respectively (p = 0.007) (Fig. 2). SCoV2-R-A levels were classified as “low” (<250 BAU/mL) in 501 patients (41%) and as “high” (>250 BAU/mL) in 542 (44%) or “very high” (>4900 BAU/mL) in 191 (15%) cases.

Although the median SCoV2-R-A levels were higher in asymptomatic breakthrough SARS-CoV-2 infection (n = 13) than in those with COVID-19 (n = 14), the difference was not statistically significant [792.57 BAU/mL (range 0–2550) vs 0 BAU/mL (range 0–485.93), p = 0.44]. Additionally, median SCoV2-R-A levels were lower, although not statistically significant, in those requiring hospital admission vs those who did not [0 BAU/mL (range 0–195.15) vs 309.57 BAU/mL (range 0–4854.93), respectively, p = 0.2]. However, breakthrough SARS-CoV-2 infection was more common in the group with “low” SCoV2-R-A levels, as was COVID-19, pneumonia, hospital admission and oxygen requirement (p ≤ 0.05 for all comparisons) (Table 4). Breakthrough SARS-CoV-2 infection severity did not show significant differences according to the timing after the second vaccine dose (after 2nd dose and first serological testing vs the first testing and 3rd months vs after the 3rd months).

**Discussion**

The current study highlights the influence of qualitative and quantitative humoral response monitoring early after full SARS-CoV-2 vaccination in predicting the risk of breakthrough SARS-CoV-2 infection in hematological patients. Patients lacking SCoV2-R-A at 3–6 weeks after vaccination had an increased risk of breakthrough SARS-CoV-2 infection. In addition, higher levels of SCoV2-R-A early after complete vaccination were linked to a lower risk of breakthrough SARS-CoV-2 infection and lower disease severity.

Hematological patients are historically characterized by a low humoral response rate with any vaccine-preventable disease [22, 23]. However, development of mRNA vaccines during the SARS-CoV-2 pandemic has overcome the poor serological response rates in this particular population (>70%) [14, 19, 20, 24, 25]. The median 720.26 BAU/mL found in our cohort was similar to the results reported in other large series of patients with diverse hematological conditions (median values < 1 × 10^3 BAU/mL) and significantly lower than those found in healthy individuals (> 1 × 10^3 BAU/mL) [26]. Although the clinical benefit of mounting a serological response is currently lacking in this scenario, to the best of our knowledge this is the first report providing evidence of its link with clinical efficacy. Notably, although prior SARS-CoV-2 infection was not significantly associated with
lower risk of breakthrough SARS-CoV-2 infection in our series, none of these patients were infected after vaccination. We previously reported a higher rate of detectable SCoV2-R-A in this patient subset [21], whereas in the current study we were able to demonstrate higher SCoV2-R-A titers compared to SARS-CoV-2-naïve patients. It is likely that the higher antibody titers along with natural immunity may confer strong protection in these patients. The design of our registry (prospective longitudinal with several SCoV2-R-A determinations over time) enabled us to capture occurring breakthrough SARS-COV-2 infections through PCR screening in symptomatic patients or in asymptomatic patients at different pre-specified time points.

Table 2 Characteristics of patients with breakthrough SARS-CoV-2 infection

| Characteristics                                      | SARS-CoV-2 infection (n = 37) |
|------------------------------------------------------|------------------------------|
| Prior COVID-19, n/n evaluable (%)                    | 0/109                        |
| Type of vaccine, n/n evaluable (%)                   | Moderna mRNA-1273 24/982 (2.4) |
|                                                     | Pfizer-BioNTech BNT162b2 11/362 (3) |
|                                                     | Adenoviral vector-based 2/50 (4) |
| Age (years), n/n evaluable (%)                       | 18–40 years 6/144 (4.2)      |
|                                                     | 41–60 years 17/495 (3.4)     |
|                                                     | 61–70 years 6/373 (1.6)      |
|                                                     | > 71 years 8/382 (2)        |
| Male, n (nEvaluable (%)                              | 25/784 (3.2)                |
| Baseline disease, n/n evaluable (%)                  | AML 5/180 (2.7)             |
|                                                     | ALL 1/46 (2.1)              |
|                                                     | MDS 5/158 (3.1)             |
|                                                     | B-cell NHL 5/301 (1.7)      |
|                                                     | T cell NHL 3/38 (8)         |
|                                                     | Plasma cell disorders 5/236 (2.1) |
|                                                     | CLL 4/158 (2.5)             |
|                                                     | HD 6/103 (5.8)              |
|                                                     | cMPP 2/139 (2.4)            |
|                                                     | Aplastic anemia 0/16        |
|                                                     | Non-malignant disorders 1/17 (5.5) |
| Cell therapy, n /n evaluable (%)                     | 18/501 (3.6)                |
| Type of cell therapy, n /n evaluable (%)            | Allo-HSCT 13/370 (3.5)      |
|                                                     | ASCT 5/110 (4.7)            |
|                                                     | CAR-T 0/21                  |
| Status disease at vaccination, n /n evaluable (%)    | Complete remission 21/825 (2.5) |
|                                                     | Partial remission 6/162 (3.7) |
|                                                     | Active disease 10/407 (2.4)  |
| Time last treatment to COVID-19 vaccine, n /n evaluable (%) | Untreated 7/172 (4)         |
|                                                     | Active treatment 10/509 (1.9) |
|                                                     | ≥ 6 month to 1 year 5/92 (5.4) |
|                                                     | ≥ 1 year 15/620 (2.4)       |
| Immunosuppressant drugs at vaccination, n /n evaluable (%) | 13/300 (4.3)               |
| Corticosteroids at vaccination, n /n evaluable (%)   | 8/255 (3.1)                |
| Daratumumab, n /n evaluable (%)                      | 1/46 (2.1)                 |
| Venetoclax, n /n evaluable (%)                       | 0/14                        |
| Anti-CD-20 moAb, n /n evaluable (%)                  | 4/241 (1.6)                |
| BTK inhibitor therapy, n /n evaluable (%)           | 3/63 (4.7)                 |
| TKI therapy, n /n evaluable (%)                      | 1/40 (2.5)                 |
| Lenalidomide, n /n evaluable (%)                     | 2/120 (1.7)                |
| Ruxolitinib therapy, n /n evaluable (%)             | 0/14                        |

Table 2 (continued)

| Characteristics                                                                                     | SARS-CoV-2 infection (n = 37) |
|-----------------------------------------------------------------------------------------------------|------------------------------|
| Absolute lymphocyte counts < 1 × 10^9/L, n /n evaluable (%)                                        | 9/260 (3.4)                  |
| Intervals from 2nd dose to SARS-CoV-2 infection, n /n patients at risk (%)                          | At 30 days after 2nd dose 14/1361 (1) |
|                                                     | At 60 days after 2nd dose 3/1309 (0.2)                  |
|                                                     | At 90 days after 2nd dose 8/1227 (0.6)                  |
|                                                     | At 180 days after 2nd dose 12/518 (2.3)                 |
| SCoV2-R-A detection at 3–6 weeks, n /n evaluable (%)                                              | 17/30 (57)                   |
| Median SCoV2-R-A titer at 3–6 weeks, BAU/mL (range) [27 evaluable patients]                      | 1.83 (0–4854.95)            |
| SARS-CoV-2 infection after the third vaccine dose, n (%)                                          | 2/541 (0.3)                 |
| SARS-CoV-2 diagnosis, n /n evaluable (%)                                                          | PCR 22/37 (60)              |
|                                                     | Seroconversion of anti-N antibodies 15/37 (40)          |
|                                                     | Symptomatic SARS-CoV-2 infection, n /n evaluable (%)    | 18/37 (48.6)                |
|                                                     | Pneumonia, n /n evaluable (%)                          | 7/37 (19)                   |
|                                                     | Hospital admission, n /n evaluable (%)                  | 12/37 (32)                  |
|                                                     | Oxygen requirement, n /n evaluable (%)                  | 10/37 (27)                  |
|                                                     | ICU admission, n /n evaluable (%)                       | 3/37 (8)                    |
|                                                     | Death, n /n evaluable (%)                              | 3/37 (8)                    |
|                                                     | Median time to death from 2nd vaccine dose, days (range)| 82 (59–100)                |

AML, Acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; B-cell NHL, B-cell non-Hodgkin lymphoma; T cell NHL, T cell non-Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; HD, Hodgkin disease; MPN, chronic myeloproliferative neoplasm; Allo-HSCT, allogeneic stem cell transplantation; ASCT, autologous stem cell transplantation; CAR-T, T cell chimeric antigen receptor; moAb, monoclonal antibody; BTK inhibitor, Bruton’s tyrosine kinase inhibitor; TKIs, tyrosine kinase inhibitors; SCoV2-R-A, SARS-CoV-2-reactive IgG antibodies; Anti-N, SARS-CoV-2 nucleocapsid antibodies; and ICU, intensive care unit
from March 2021 to early December 2021) spanned the period between the fifth and sixth COVID-19 wave when the Delta variant was dominant in Spain. Thus, it is likely that our findings do not apply to the Omicron SARS-CoV-2 variant. In that period, the incidence of COVID-19 was relatively low [28]. This fact may explain in part the somewhat low incidence rate of SARS-CoV-2 infection (overall 6.39 per 100 persons-year) in the current study. Although hematological malignancies showed a higher risk of breakthrough infection compared to solid tumors [29], the rate observed in our cohort (2.6%) was similar to other series with comparable median follow-ups which included hematological patients (2.3%) [26] or healthcare workers (2.3%) [30]. However, we observed that the risk of breakthrough infection increased with longer follow-up. This fact could suggest either that a decrease in antibody titers over time may reduce protection (which formed the rationale behind boosters), or that the risk of being infected increases with longer exposure time in an ongoing pandemic.

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 yet been established. However, both binding and neutralizing antibodies are thought to be potential correlates of protection against COVID-19 and are correlated with each other [31, 32]. In fact, recent data in the general population suggest that higher levels of binding and neutralizing antibodies after the second dose correlate with a reduced risk of symptomatic infection [33, 34]. In line with these observations, our findings support that SCoV2-R-A titration early after vaccination could be an accurate strategy to predict breakthrough infection risk and could be useful in counseling additional vaccine doses or anti-SARS-CoV-2 monoclonal antibodies in this immunosuppressed population. This assumption is supported by the fact that patients without detectable antibodies had higher risk of breakthrough infection, patients with breakthrough infection had lower SCoV2-R-A titers and those with higher antibody titers showed lower disease severity.

A vaccine efficacy of 80% against symptomatic infection in the general population was achieved with 264 BAU/ml [33]. In the COVE trial, this threshold shows >90% vaccine efficacy [34]. Based on these data, we empirically selected the cutoff of 250 BAU/mL to segregate our cohort into poor and good responders. The cutoff of 250 BAU/mL in our series predicted risk of breakthrough infection and disease severity. No patients with SCoV2-R-A >250 BAU/mL were admitted to hospital due to SARS-CoV-2 in our cohort. Nevertheless, the kinetics wane of SCoV2-R-A waning after vaccination in this scenario remains to be determined in order to establish the best time points for serological monitoring and the optimal moment to administer further vaccine doses.

Finally, we observed an important reduction in COVID-19 severity, exemplified by reduced overall pneumonia (19%), symptomatic SARS-CoV-2 infection (48.6%) and mortality (8%) rates. Rates of these outcomes in hematological patients with COVID-19 during the first and second COVID-19 waves were as high as >70%, >90% and >25%, respectively [1]. Our findings are in line with real world data, where both mRNA vaccines were shown to reduce symptomatic SARS-CoV-2 infection, COVID-19-related symptoms, hospital admissions and mortality in adults [35–38]. Although the severity of COVID-19 seems lower after vaccination, severely immunosuppressed patients still develop life-threatening disease. In these vulnerable patients, preventive transmission measures (hand washing, social distancing, wearing mask, etc.) are still highly recommended. However, the largest reduction in the incidence of respiratory virus infections in immunocompromised patients has been observed when preventive transmission measures have been instituted globally [39] as compared to when such measures are applied only to immunosuppressed patients and their caregivers; in fact, in these latter scenarios the time of onset and incidence of different respiratory virus infections (including SARS-CoV-2) in HSCT recipients strongly mirror those in the patients’ communities [1, 19].

The limitations of this study comprise the use of different serological tests, absence of neutralizing antibody testing, absence of cellular immune response analyses and the lack of molecular data regarding the SARS-CoV-2 variants in patients with breakthrough infections. However, most SARS-CoV-2 infections reported in our cohort occurred when the Delta variant was dominant in Spain. The performance of antibody titration with the omicron variant remains to be evaluated.

Conclusion
We provide evidence that serological monitoring after SARS-CoV-2 vaccination could be useful in identifying hematological patients at high risk of breakthrough SARS-CoV-2 infection. SCoV2-R-A levels link with protection in this vulnerable population being 250 BAU/
Table 3  Logistic regression univariate and multivariate analyses of factors predicting SARS-CoV-2 breakthrough infection after full vaccination

| Characteristics                                      | SARS-CoV-2 infection | p value | SARS-CoV-2 infection | p value |
|------------------------------------------------------|----------------------|---------|----------------------|---------|
|                                                      | Univariate OR (95% CI) |         | Multivariate OR (95% CI) |         |
| Prior COVID-19                                       | 0.2 (0.02–1.2)       | 0.1     | ns                   |         |
| Type of vaccine                                       |                      |         |                      |         |
| Moderna mRNA-1273                                    | 1                    |         |                      |         |
| Pfizer-BionTech BNT162b2                              | 0.6 (0.14–2.6)       | 0.5     |                      |         |
| Adenoviral vector-based                               | 0.75 (0.16–3.5)      | 0.7     |                      |         |
| Age (years)                                          |                      |         |                      |         |
| 18–40 years                                          | 1                    |         |                      |         |
| 41–60 years                                          | 0.8 (0.32–2.1)       | 0.67    |                      |         |
| 61–70 years                                          | 0.37 (0.12–1.18)     | 0.09    | ns                   |         |
| > 71 years                                           | 0.49 (0.16–1.44)     | 0.19    |                      |         |
| Male sex                                             | 1.6 (0.8–3.2)        | 0.166   |                      |         |
| Baseline disease                                      |                      |         |                      |         |
| ALL                                                  | 1                    |         |                      |         |
| AML                                                  | 1.3 (0.14–11.2)      | 0.8     |                      |         |
| MDS                                                  | 1.47 (0.16–33)       | 0.7     |                      |         |
| B-cell NHL                                           | 0.76 (0.08–6.6)      | 0.8     |                      |         |
| T cell NHL                                           | 3.8 (0.38–38.4)      | 0.25    |                      |         |
| Plasma cell disorders                                | 0.97 (0.11–8.5)      | 0.9     |                      |         |
| CLL                                                  | 1.16 (0.12–10.7)     | 0.9     |                      |         |
| HD                                                   | 2.78 (0.32–23.8)     | 0.35    |                      |         |
| cMPN                                                 | 0.65 (0.05–7.4)      | 0.7     |                      |         |
| Aplastic anemia                                      | 0.00                 | 0.99    |                      |         |
| Non-malignant disorders                              | 2.6 (0.15–44.7)      | 0.5     |                      |         |
| Status disease at vaccination                        |                      |         |                      |         |
| Complete remission                                   | 1                    |         |                      |         |
| Partial remission                                    | 1.47 (0.58–3.7)      | 0.4     |                      |         |
| Active disease                                       | 0.92 (0.45–2.06)     | 0.9     |                      |         |
| Time from last treatment to COVID-19 vaccine         |                      |         |                      |         |
| Untreated                                            | 1                    |         |                      |         |
| Under treatment                                      | 0.47 (0.17–1.26)     | 0.13    |                      |         |
| > 6 months to 1 year                                 | 1.35 (0.41–4.39)     | 0.6     |                      |         |
| ≥ 1 year                                             | 0.58 (0.23–1.45)     | 0.24    |                      |         |
| Cell therapy                                         |                      |         |                      |         |
| Yes                                                  | 0.58 (0.3–1.1)       | 0.1     | ns                   |         |
| No                                                   | 1                    |         |                      |         |
| Allo-HSCT                                             | 1.6 (0.82–3.4)       | 0.15    |                      |         |
| ASCT                                                 | 2.19 (0.8–5.98)      | 0.12    |                      |         |
| CAR-T                                                | 0.00                 | 0.99    |                      |         |
| Corticosteroids at vaccination                       | 1.2 (0.56–2.7)       | 0.59    |                      |         |
| Daratumumab                                          | 0.8 (0.1–6)          | 0.83    |                      |         |
| Venetoclax                                            | 0.00                 | 0.99    |                      |         |
| Anti-CD-20 moAb                                      | 0.57 (0.2–1.6)       | 0.29    |                      |         |
| Bruton’s TKI therapy                                 | 1.9 (0.57–6.4)       | 0.29    |                      |         |
| TKI therapy                                          | 0.95 (0.12–7)        | 0.9     |                      |         |
| Lenalidomide                                         | 0.6 (0.14–2.5)       | 0.48    |                      |         |
| Ruxolitinib                                          | 0.00                 | 0.99    |                      |         |
| SCoV2-R-A negative at 3–6 weeks after 2 doses       | 2.5 (1.3–4.9)        | 0.007   |                      |         |
| Lymphocyte count < 0.5 × 10^9/L                      | 0.75 (0.09–5.4)      | 0.75    |                      |         |
| Lymphocyte count < 1.0 × 10^9/L                      | 1.5 (0.7–3.3)        | 0.27    |                      |         |
mL a potentially discriminative cutoff for non-Omicron SARS-CoV-2 variants. Finally, severity of SARS-CoV-2 infection in hematological patients has experienced an encouraging improvement in the post-vaccine period.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s13045-022-01275-7.

Table 3 (continued)

| Variable                          | < 250 BAU/mL (n = 501) | 250 to 4900 BAU/mL (n = 542) | > 4900 BAU/mL (n = 191) | p value |
|-----------------------------------|------------------------|------------------------------|-------------------------|---------|
| SARS-CoV-2 infection              | 17 (3.4%)              | 10 (1.8%)                    | 0                       | 0.018   |
| Symptomatic SARS-CoV-2            | 10 (2%)                | 3 (0.5%)                     | 0                       | 0.035   |
| Pneumonia                         | 4 (0.7%)               | 0                             | 0                       | 0.05    |
| Hospital admission                | 8 (1.5%)               | 0                             | 0                       | 0.012   |
| Oxygen requirement                | 7 (1.3%)               | 0                             | 0                       | 0.006   |
| ICU admission                     | 2 (0.35%)              | 0                             | 0                       | 0.2     |
| Death                             | 2 (0.35%)              | 0                             | 0                       | 0.2     |

Fig. 2  Median anti-SARS-CoV-2 IgG-reactive antibody titers measured in binding antibody units/mL (BAU/mL) at 3–6 weeks after the 2nd dose according to SARS-CoV-2 breakthrough infection. Patients who did not developed SARS-CoV-2 infection (n = 1207) had a median of 730.81 BAU/mL (range 0–58,600) vs 1.83 BAU/mL (range 0–4854.93) in those who did develop breakthrough infection (n = 27) (p = 0.007)

Table 4  SARS-CoV-2 infection severity according to anti-SARS-CoV-2 IgG-reactive antibody cutoffs in the 27 evaluable patients

Acknowledgements
REDCap is developed and supported by the Vanderbilt Institute for Clinical and Translational Research. We thank the Spanish Society of Hematology (SEHH) for its support on the study diffusion. We also offer our sincere thanks to the invaluable microbiology services for their commitment in SARS-CoV-2-reactive IgG antibody monitoring in these highly immunosuppressed patients from all participating centers, in particular to Santiago Muñoz Criado from Microbiological Division of Hospital Clínico Universitario of Salamanca and to Tamar Talaván from microbiological Division of Hospital Infanta Leonor of Madrid. Special thanks to all hematology units from participating centers for their commitment in the current study. Finally, we also want to thank patients, nurses and study coordinators for their foremost contributions in this study.

Author contributions
JLP, RM, DN and AC were responsible for the conception and the design of the study. JLP, RM, PR-B and DN performed the data analysis and generated the
tables and figures. JLP, LL-C, RM, LV, AP, GM-M, AF-M, BG, GS-L, AS-S, LV, VC-G, MTO, JL-I, SM-C, MT, MG-B, JÁH-R, JM, IE, CA, JCH-B, MR-G, JLM-B, CS, AS and DN were responsible for patient recruitment. JLP, RM and DN were responsible for writing and supervising the manuscript. All co-authors were responsible for reviewing the analysis interpretation, suggesting modifications to the text, critically reviewing the manuscript and for final approval of the manuscript. All authors read and approved the final manuscript.

Funding
None.

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

Declarations

Ethics approval and consent to participate
The local research ethics committee of the Hospital Clínico Universitario of Valencia approved the registry and study protocol (reference code 35.21). All patients included in this registry gave their signed informed consent in accordance with the declaration of Helsinki.

Competing interests
The authors declare that they have no competing interests.

Author details
1 Division of Clinical Hematology, Hematology Department, Hospital Clínico Universitario de Valencia, Avda Blasco Ibáñez, 17, 46010 Valencia, Spain. 2 Fundación INCLIVA, Instituto de Investigación Sanitaria Hospital Clínico Universitario de Valencia, Valencia, Spain. 3 Hematology Division, Hospital Universitario de Salamanca, Salamanca, Spain. 4 Hematology Division, Hospital Universitario Infanta Leonor, Madrid, Spain. 5 Hematology Division, Hospital Regional Universitario Carlos Haya, Málaga, Spain. 6 Hematology Division, Institut Català Oncologia-Hospital Duran i Reynals, IDIBELL, Universitat de Barcelona, Barcelona, Spain. 7 Hematology Division, Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain. 8 Hematology Division, Hospital Universitario Fundación Alcorcón, Madrid, Spain. 9 Hematology Division, Hospital General Universitario de Elche, Elche, Spain. 10 Hematology Division, Hospital Clínico Universitario Lozano Blesa, IIS Aragon, Saragossa, Spain. 11 Hematology Division, Hospital Ramón y Cajal, Madrid, Spain. 12 Hematology Division, Hospital Universitario Virgen Macarena, Seville, Spain. 13 Hematology Division, Hospital Universitario Infanta Leonor, Madrid, Spain. 14 Hematology Division, Hospital Universitario y politécnico La Fe, Valencia, Spain. 15 Hematology Division, Hospital Universitario Virgen Macarena, Seville, Spain. 16 Hematology Division, Hospital Arnau de Vilanova, Valencia, Spain. 17 Research Program on Biomedical Informatics (GIRD), Department of Experimental and Health Sciences, Hospital del Mar Medical Research Institute (IMIM), Universitat Pompeu Fabra, Barcelona, Spain. 18 Hospital General Universitari d’Elx, Elche, Spain. 19 Hospital Universitario de Salamanca, Salamanca, Spain. 20 Department of Medicine, School of Medicine, University of Valencia, Valencia, Spain. 21 Hematopoietic Stem Cell Transplantation and Cell Therapy Group (GETH) Office, Madrid, Spain. 22 Hospital Clínico Universitario de Valencia, Valencia, Spain.

Received: 4 March 2022 Accepted: 25 April 2022 Published online: 07 May 2022

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