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Cell-mediated and Neutralizing Antibody Responses to the SARS-CoV-2 Omicron BA.4/BA.5–adapted Bivalent Vaccine Booster in Kidney and Liver Transplant Recipients

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Background. The immunogenicity elicited by the Omicron BA.4/BA.5–adapted bivalent booster vaccine after solid organ transplantation (SOT) has not been characterized. **Methods.** We assessed cell-mediated and neutralizing IgG antibody responses against the BA.4/BA.5 spike receptor-binding domain at baseline and 2 wk after the administration of an mRNA-based bivalent (ancestral strain and BA.4/BA.5 subvariants) vaccine among 30 SOT recipients who had received ≥3 monovalent vaccine doses. Previous coronavirus disease 2019 history was present in 46.7% of them. We also recruited a control group of 19 nontransplant healthy individuals. Cell-mediated immunity was measured by fluorescent ELISpot assay for interferon (IFN)-γ secretion, whereas the neutralizing IgG antibody response against the BA.4/BA.5 spike receptor-binding domain was quantified with a competitive ELISA. **Results.** The median number of BA.4/BA.5 spike–specific IFN-γ–producing spot-forming units (SFUs) increased from baseline to 2 wk postbooster (83.8 versus 133.0 SFUs/10^6 peripheral blood mononuclear cells; $P=0.0017$). Seropositivity rate also increased (46.7%–83.3%; $P=0.001$), as well as serum neutralizing activity (4.2%–78.3%; $P<0.0001$). Patients with no prior coronavirus disease 2019 history experienced higher improvements in cell-mediated and neutralizing responses after booster vaccination. There was no correlation between BA.4/BA.5 spike–specific IFN-γ–producing SFUs and neutralizing activity. Nontransplant controls showed more robust postbooster cell-mediated immunity than SOT recipients (591.1 versus 133.0 IFN-γ–producing SFUs/10^6 peripheral blood mononuclear cells; $P<0.0001$), although no differences were observed for antibody responses in terms of postbooster seropositivity rates or neutralizing activity. **Conclusions.** Booster with the BA.4/BA.5–adapted bivalent vaccine generated strong subvariant-specific responses among SOT recipients. Booster-induced cell-mediated immunity, however, remained lower than in immunocompetent individuals.

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The evolution of the coronavirus disease 2019 (COVID-19) pandemic has been driven by 2 major factors: the widespread vaccination uptake and the appearance of new variants of concern (VoCs).[1,2] The interplay between natural and vaccine-derived "hybrid immunity" has contributed to modifying the clinical characteristics and severity of COVID-19 after solid organ transplantation (SOT).[3-8] This progress has occurred despite the lower immunogenicity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines in SOT recipients in comparison with the nonimmunocompromised population.[9,10]

The emergence in November 2021 of the Omicron VoC (Pango lineage B.1.1.529) represented a turning point in the pandemic.[11] With >15 mutations within the spike receptor-binding domain (RBD), this variant exhibits increased transmissibility and capacity for immune evasion.[2,12] A feature of the Omicron "complex" is its high genetic diversity, with the BA.4 and BA.5 lineages only differing at genomic positions outside of the spike region.[2,13] Because of the rapidly emerging evidence that the Omicron variant compromises the ability of mRNA-based vaccines to induce protective responses,[14-16] regulatory agencies issued an emergency use authorization for adapted bivalent vaccines targeting the BA.4/BA.5 spike in addition to the ancestral wild-type (D614G) spike protein. Recent studies have shown that the BA.4/BA.5–adapted bivalent vaccines, given as a booster after 3 or 4 doses of the original vaccine, elicit higher neutralizing responses than the monovalent booster.[17,18]

The BA.4/BA.5-adapted bivalent booster has been recommended by the European and Spanish regulatory agencies for immunocompromised patients.[19,20] Immunogenicity and safety data for the SOT population, however, are essentially lacking. We have reported that the monovalent mRNA-1273 vaccine frequently elicits discordant cell-mediated and antibody responses.[21] Whether these findings are to be expected with the bivalent booster in the ongoing Omicron era remains unknown. Therefore, we assessed the development of SARS-CoV-2 Omicron BA.4/BA.5 spike–specific cell-mediated immunity—with a fluorescent ELISpot assay—and neutralizing IgG antibody response against BA.4/BA.5 spike RBD—by means of a competitive ELISA—in a cohort of SOT recipients who received the bivalent booster vaccine.

MATERIALS AND METHODS

Study Population and Setting

In April 2021, we assembled a cohort of SOT recipients who received the full series of the mRNA-1273 vaccine (Spikevax, Moderna Biotech Madrid, Spain) at our center (ie, two 100 μg doses given 28 d apart). In that study, we analyzed the development of SARS-CoV-2–specific cell-mediated immunity, IgG seroconversion, and the serum-neutralizing activity against the spike protein.[21] In September 2022, we contacted these recipients again and invited them to participate in a new assessment after the receipt of the Omicron BA.4/BA.5–adapted bivalent booster. No exclusion criteria were applied, and all the patients who consented to participate and effectively received the booster vaccine were included in the present study, regardless of the quality of the immune response to the initial mRNA-1273 vaccine or their previous history of COVID-19.

The booster vaccine was given at our center between October 18 and November 25, 2022, as a single intramuscular 0.3-mL dose of tozinameran (15 μg of mRNA encoding the spike protein of the ancestral wild-type Wuhan strain) and famtozinameran (15 μg of mRNA encoding the spike protein of BA.4/BA.5 subvariants) encapsulated in lipid nanoparticles (Comirnaty Original and Omicron BA.4/BA.5, Pfizer-BioNTech, Puurs, Belgium). As per the recommendations of the Spanish authorities,[19,20] all participants had received at least 3 doses of a monovalent mRNA-based vaccine between April 2021 and August 2022, with a minimum 5-mo interval between the last dose and the BA.4/BA.5-adapted booster.

For the comparison of cell-mediated and humoral responses, we recruited a control group of nontransplant healthy individuals among healthcare personnel at the Unit of Infectious Diseases who were also given the BA.4/BA.5–adapted booster between October 18 and November 24, 2022.

We assessed Omicron BA.4/BA.5–specific cell-mediated and antibody immunity at baseline (prebooster) and 2 wk after the dose. Previous studies have shown that the cytokine milieu modulates the antibody response to influenza[22] and SARS-CoV-2 vaccination.[23] Therefore, we measured plasma levels of Th1-related (interferon [IFN]-γ, interleukin [IL]-1β, IL-2, IL-12p70), Th2-related (IL-4, IL-5, IL-10, IL-13), and proinflammatory and immunomodulatory cytokines (tumor necrosis factor-α, IL-6, IL-18, granulocyte–macrophage colony-stimulating factor [GM-CSF]) at baseline and at 2 wk after the booster.

The study was conducted in accordance with the ethical standards as laid down in the Declarations of Helsinki and Istanbul. The study protocol was approved by the institutional Research Ethics Committee, and all participants provided written informed consent.

SARS-CoV-2 Omicron BA.4/BA.5 Spike–specific Cell-mediated Immunity

We used a fluorescent ELISpot assay (FluoroSpot) for IFN-γ secretion with overlapping peptides mapped within the spike protein of the BA.4/BA.5 subvariant, as described elsewhere.[21,24] Samples were also stimulated with the SARS-CoV-2 nucleoprotein (NP). Results were expressed as IFN-γ–producing spot-forming units (SFUs) per 10^6 PBMCs. A detailed description is provided as Supplemental Digital Content (**SDC**, http://links.lww.com/TXD/A569).

Neutralizing IgG Antibodies Against the BA.4/BA.5 Spike RBD

The assessment of neutralizing IgG antibody titers against the RBD of the Omicron BA.4/BA.5 subvariant was performed with a competitive ELISA kit (anti–SARS-CoV-2 [BA.4 and BA.5] Neutralizing Antibody Titer Serologic Assay Kit [Spike RBD], ACROBiosystems, Newark, DE), following the manufacturer's instructions. This assay uses a standard sandwich ELISA format, with a microplate precoated with human angiotensin-converting enzyme 2 protein.[25] A detailed description is provided as Supplemental Digital Content (**SDC**, http://links.lww.com/TXD/A569).

To determine the presence of preexisting immunity against VoCs other than Omicron BA.4/BA.5, we investigated in baseline (prebooster) samples neutralizing IgG antibodies against the spike RBD of the ancestral wild-type strain

and Alpha (B.1.1.7), Beta (B.135), Gamma (P.1), and Delta (B.617.2) variants. We used a Luminex immunoassay (Invitrogen ProcartaPlex Human SARS-CoV-2 Variants Neutralizing Antibody Panel, Thermo Fisher Scientific, Waltham, MA), as detailed in Supplemental Methods (**SDC,** http://links.lww.com/TXD/A569).

Cytokine Quantification

Plasma cytokine levels (IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12p70, IL-13, IL-18, tumor necrosis factor-α, GM-CSF) were measured by means of a custom 12-plex Luminex immunoassay (Invitrogen ProcartaPlex Human Cytokine Panel, Thermo Fisher Scientific) according to manufacturer's instructions.

Statistical Analysis

Quantitative data are shown as the mean ± SD or the median with interquartile range (IQR). Qualitative data are expressed as absolute and relative frequencies. Categorical variables were compared with the χ^2 test. The Student *t* test or the Mann-Whitney *U* test was applied for continuous variables, whereas comparison between paired samples was performed with the Wilcoxon signed-rank test. Correlations were analyzed using Pearson's or Spearman's rho correlation coefficients, depending on the normality of the distributions. Statistical analysis was performed using SPSS version 20.0 (IBM Corp., Armonk, NY).

RESULTS

Study Population

Overall, we included 30 SOT recipients (**Table S1, SDC,** http://links.lww.com/TXD/A569). Almost half of them (46.7%; 14 of 30) had been diagnosed with COVID-19 before the BA.4/BA.5–adapted booster. Only 1 participant required hospital admission. The median interval from transplantation to the booster dose was 45.3 mo (IQR, 34.4–68.7). All the patients had previously received a third monovalent vaccine dose, and half of them (50.0% [15 of 30]) had a fourth dose.

Cell-mediated Response to the BA.4/BA.5-adapted Booster Vaccine

The analysis of BA.4/BA.5 spike–specific cell-mediated responses elicited by the booster vaccine was based on 27 patients because postbooster assessment was not possible in 3 cases due to insufficient PBMCs. The median number of BA.4/BA.5 spike–specific IFN-γ–producing SFUs significantly increased from baseline to 2 wk after the booster vaccination (83.8 [IQR, 35.9–160.4] versus 133.0 [IQR, 65.2–270.0] SFUs/10^6 PBMCs; *P* value for repeated measures = 0.0017; **Figure 1A**). This enhancement was higher among *naïve* patients (71.4 [IQR, 37.2–103.5] versus 125.0 [IQR, 57.8–283.3] SFUs/10^6 PBMCs; *P* value for repeated measures = 0.007) compared with those with a previous laboratory-confirmed diagnosis of COVID-19 (132.5 [IQR, 35.9–202.8] versus 154.9 [IQR, 66.7–266.4] SFUs/10^6 PBMCs; *P* value for repeated measures = 0.034). Nevertheless, there were no significant differences in postbooster responses between both subgroups (*P* = 0.719; **Figure S1, SDC,** http://links.lww.com/TXD/A569). Caucasian recipients (123.3 [IQR, 57.8–233.9] versus 364.8 [IQR, 179.7–585.5] SFUs/10^6 PBMCs; *P* = 0.005) and those with previous SOT (86.7 [IQR, 65.6–132.9] versus 140.2 [IQR, 57.8–283.3] SFUs/10^6 PBMCs; *P* = 0.015) had lower postbooster responses, although it should be noted that these features were present in only 4 and 5 participants, respectively (**Tables S2 and S3, SDC,** http://links.lww.com/TXD/A569).

We also compared SARS-CoV-2 NP-specific IFN-γ–producing responses—indicative of naturally acquired

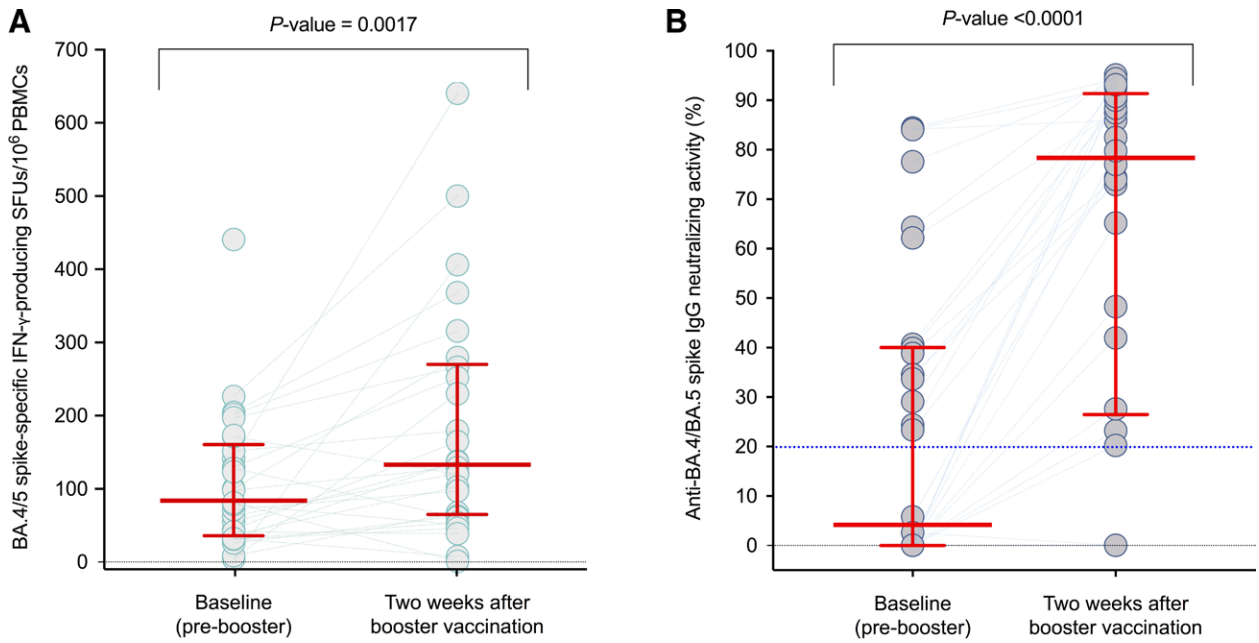

FIGURE 1. SARS-CoV-2 Omicron BA.4/BA.5–specific immune responses at baseline and at 2 wk after the booster vaccination and individual trajectories between both time points. A, Cell-mediated immunity in terms of number of BA.4/BA.5 spike–specific IFN-γ–producing SFUs (n = 27 [immunity was not measured in 3 patients because of insufficient PBMCs in the postbooster sample]). B, Antibody-neutralizing activity semiquantitatively estimated according to the percent inhibition of the sample with reference to the negative control (n = 30). The cutoff value for assay positivity (percent inhibition ≥20%) is denoted by the blue dotted line. Red bars and whiskers represent median values and interquartile ranges, respectively. IFN-γ, interferon-gamma; PBMC, peripheral blood mononuclear cell; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SFU, spot-forming unit.

immunity—according to the patient's history of COVID-19. As expected, recipients with no laboratory-confirmed diagnosis of SARS-CoV-2 infection in the past showed significantly lower NP-specific SFUs/10^6 PBMCs at baseline and at 2 wk after the booster vaccination compared with those with previous COVID-19 infection (**Figure S2, SDC,** http://links.lww.com/TXD/A569).

Neutralizing Antibody Response to the BA.4/BA.5-adapted Booster Vaccination

Next, we assessed the titers of anti-BA.4/BA.5 spike IgG antibodies at baseline and 2 wk after vaccination. Seropositivity rate (defined by the cutoff value of 20% signal inhibition) increased from 46.7% (14 of 30) to 83.3% (25 of 30), respectively (*P* value for repeated measures = 0.001). The neutralizing activity of the samples against the BA.4/BA.5 spike RBD (estimated as percent inhibition) varied from 4.2% (IQR, 0.01–40.0) to 78.3% (IQR, 26.5–91.4) after the booster (*P* value for repeated measures <0.0001; **Figure 1B**). We found higher increases in the serum neutralizing activity in *naïve* recipients (1.3% [IQR, 0.0–38.9] versus 81.1% [IQR, 5.8–93.3]; *P* value for repeated measures <0.001) than in those with previous COVID-19 (14.5% [IQR, 0.0–45.4] versus 75.6% [IQR, 59.4–88.9]; *P* value for repeated measures <0.001), although the magnitude of the postbooster response was similar between both subgroups (*P* = 0.853; **Figure S3, SDC,** http://links.lww.com/TXD/A569).

The rates of IgG seropositivity against the wild-type SARS-CoV-2 and other VoCs in samples obtained before the booster vaccination were high (ranging from 83.3% [25 of 30] for Gamma to 90.0% [27 of 30] for the ancestral wild-type strain and Delta). Recipients who were already seropositive to the ancestral virus or different VoCs were more likely to achieve an antibody response after the booster dose compared with seronegative participants, although the association was only significant for the Gamma variant (92.0% [23 of 25] versus 40.0% [2 of 5]; *P* = 0.022). Additionally, there was a correlation between prebooster antibody-neutralizing activity against the ancestral strain and other VoCs and the booster-elicited neutralizing activity against BA.4/BA.5 (**Table S4, SDC,** http://links.lww.com/TXD/A569).

Correlation Between Cell-mediated and Antibody Immunity

No correlation was observed between the number of BA.4/BA.5 spike–specific IFN-γ–producing SFUs and the serum neutralizing activity—estimated as the percent inhibition of the sample in the competitive ELISA—at 2 wk after booster (Spearman's rho correlation = 0.006; *P* = 0.978).

Comparison Between SOT Recipients and the Nontransplant Control Group

The nontransplant control group was composed of 19 nontransplant healthy individuals (**Table S5, SDC,** http://links.lww.com/TXD/A569). Postbooster cell-mediated response could not be assessed in one of them because of insufficient PBMCs in the stored sample. No significant differences in the baseline number of BA.4/BA.5 spike–specific IFN-γ–producing SFUs were observed between the nontransplant control group and SOT recipients (44.2 [IQR, 17.4–324.3] versus 83.8 [IQR, 35.9–160.4] SFUs/10^6 PBMCs; *P* = 0.333). Nontransplant controls, however, achieved more robust responses after boosting (median: 591.1 [IQR, 302.6–1113.9] versus 133.0 [IQR, 65.2–270.0] SFUs/10^6 PBMCs, respectively; *P* < 0.0001) (**Figure 2**).

Three healthy individuals lacked postbooster serum samples for the assessment of neutralizing antibody responses. Nontransplant controls showed higher IgG seropositivity rates than SOT recipients at baseline (75.0% [12 of 16] versus 46.7% [14 of 30]; P = 0.065) and at 2 wk after the BA.4/BA.5-adapted booster (100.0% [16 of 16] versus 83.3% [25 of 30], respectively; *P* = 0.147), although the differences were not statistically significant (**Figure 3A**). The neutralizing activity of prevaccination samples was significantly higher in nontransplant controls than SOT recipients (62.8% [IQR, 12.9–77.3] versus 4.2% [IQR, 0.0–40.0]; *P* = 0.022), although the difference between both groups was no longer present after booster vaccination (87.3% [IQR, 74.6–90.2] versus 78.3% [IQR, 26.5–91.4]; *P* = 0.278; **Figure 3B**).

Cytokine Profile and Response to Booster Vaccination

Baseline plasma levels of several cytokines (IL-2, IL-5, IL-12p70, and GM-CSF) were below the lowest limit of quantification of the immunoassay. Vaccination was associated with a significant increase in the levels of IL-2 (*P* value for repeated measures = 0.018). We found a clinically relevant and statistically significant positive correlation between the number of BA.4/BA.5 spike–specific IFN-γ–producing SFUs and IL-2 levels at 2 wk after booster (Spearman's rho correlation = 0.597; *P* = 0.001; **Figure S4, SDC,** http://links.lww.com/TXD/A569). No correlation was found between cytokine levels and the magnitude of the antibody-mediated response (data not shown).

Safety of the BA.4/BA.5-adapted Booster Vaccination

Sixteen recipients (53.3%) reported at least 1 adverse event after the administration of the booster vaccine, including pain at the injection site (33.3%; 10/30), fatigue (13.3%; 4 of 30), chills (13.3%; 4 of 30), myalgias (6.7%; 2 of 30), and headache (3.3%; 1 of 30). None of the adverse events were categorized as severe, and there were no episodes of graft rejection.

DISCUSSION

The antigenic novelty of the SARS-CoV-2 Omicron variant largely exceeds those of previous VoCs and may be comparable with the antigenic "shift" observed in influenza viruses.[2] The emergency use authorization granted to the bivalent booster relied on the concept of "immunobridging," which implies that the effectiveness of the candidate vaccine is inferred from the results of a clinical efficacy trial conducted under a given set of conditions to another.[26] Therefore, real-world evidence on the effectiveness of the bivalent booster is limited for the overall population[27,28] and remains virtually lacking for SOT recipients.

In this preliminary research, we have assessed the cell-mediated and antibody responses to the SARS-CoV-2 Omicron BA.4/BA.5-adapted bivalent vaccine booster in a cohort of SOT recipients with a high prevalence of previous COVID-19 that had received at least 3 doses of the monovalent vaccine. Most of them had detectable BA.4/BA.5 spike–specific cell-mediated immunity at the prebooster evaluation, with

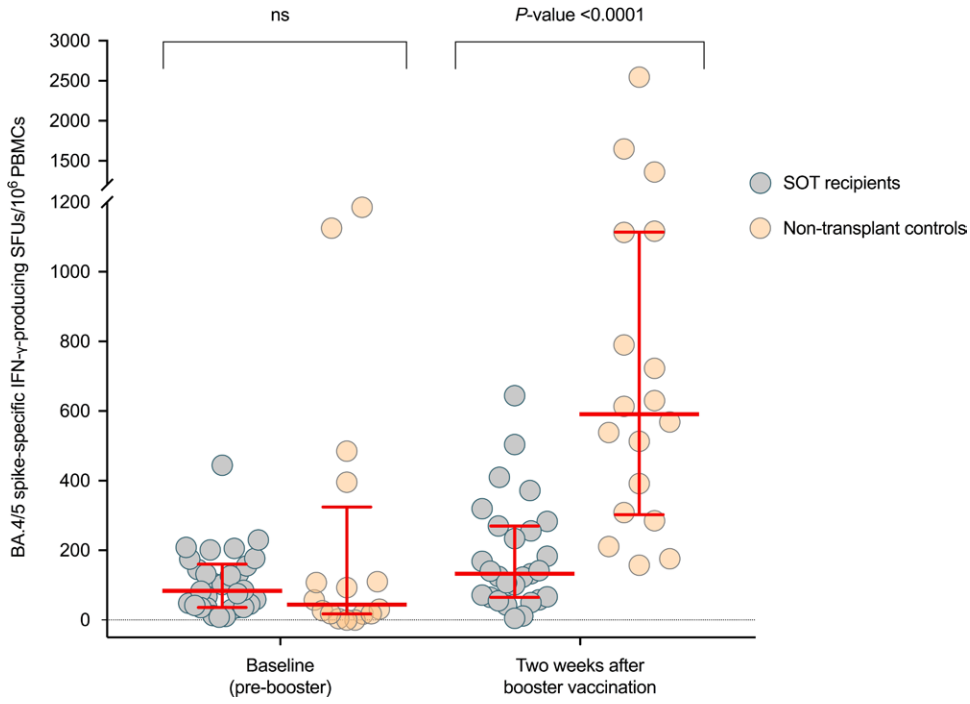

FIGURE 2. Comparison of the magnitude of cell-mediated immune responses elicited by the BA.4/BA.5–adapted booster vaccine between SOT recipients (n = 27) and the nontransplant control group (n = 18). Red bars and whiskers represent median values and interquartile ranges, respectively. Cell-mediated immunity was not measured in 1 nontransplant healthy individual because of insufficient PBMCs in the postbooster sample. IFN-γ, interferon-gamma; ns, nonsignificant; PBMC, peripheral blood mononuclear cell; SFU, spot-forming unit; SOT, solid organ transplantation.

no significant differences with nontransplant individuals. The booster dose elicited a significant increase in the number of BA.4/BA.5 spike–specific IFN-γ–producing SFUs. This effect, however, was less robust for SOT recipients than for the control group. Regarding the humoral response, neutralizing IgG antibodies against the BA.4/BA.5 spike RBD were present in almost half of the recipients at baseline. The seroresponse rate and the semiquantitatively estimated neutralizing activity significantly increased with the booster, resulting in similar postbooster immunity in the SOT and nontransplant groups.

We consider that these findings are informative in view of the well-established capacity for immune evasion shown by the newer Omicron subvariants in patients with vaccine-derived immunity against the ancestral SARS-CoV-2 strain. Additionally, conflicting results on the immunogenicity of the booster dose in immunocompetent individuals have been reported. Wang et al found no significant differences in the peak BA.4/BA.5 spike–specific neutralizing antibody response as compared with boosting with the monovalent vaccines.[29] In contrast, a number of studies have shown that a fourth dose of the bivalent vaccine induces higher neutralizing responses against BA.2- and BA.5-derived sublineages (including the BQ.1.1 and XBB.1 subvariants).[17,18] In a phase III trial, the BA.1-adapted BNT162b2 vaccine induced higher neutralizing activity than the original vaccine based on the ancestral strain, although cross-neutralization responses against BA.4/BA.5 subvariants did not substantially increase.[30] We are not aware of previous studies that have assessed the immunogenicity elicited by the BA.4/BA.5-adapted bivalent booster dose in the SOT setting. Reported research has been focused on the effect of repeated boosting with monovalent mRNA- or viral vector–based vaccine doses.[31-34] Al Jurdi et al[35] found a significant increase in IgG levels against the RBD of BA.2.12.1 and BA.4/BA.5 subvariants (but not for B.1.1.529 or the ancestral strain) after a fourth monovalent vaccine dose among KT recipients. Additionally, both the neutralizing activity and the proportion of patients with neutralizing responses >30% against BA.4/BA.5 also increased with the booster.[35] A recent meta-analysis confirmed that the seropositivity rate significantly increases upon booster uptake, although the figure remains below that of nontransplant controls.[10]

We explored the clinical determinants of the magnitude of postbooster cell-mediated responses. Previous SOT and Caucasian ethnicity were associated with lower numbers of IFN-γ–producing SFUs. Although having a history of prior transplantation may mirror a higher comorbidity burden, the differential impact of ethnicity was somewhat unexpected. A population-based study from the United Kingdom also identified White ethnicity being negatively associated with postvaccination antibody titers.[36] It has been proposed that immune recognition of SARS-CoV-2 epitopes would vary across different ethnic groups.[37] Surprisingly, there was no correlation between the number of SFUs and the trough levels of immunosuppressive drugs, which may be explained by the narrow concentration ranges of tacrolimus or everolimus observed in this cohort of stable SOT recipients. Notably, all these associations must be interpreted cautiously because of the low number of patients and the absence of multivariate adjustment.

As expected in a cohort with at least 3 monovalent vaccine doses and a frequent history of previous COVID-19, most of the SOT recipients were IgG seropositive for the ancestral SARS-CoV-2 strain and different VoCs already at baseline. Interestingly, the bivalent booster induced higher neutralizing antibody responses among seropositive recipients. Whereas a similar association has been shown for successive monovalent

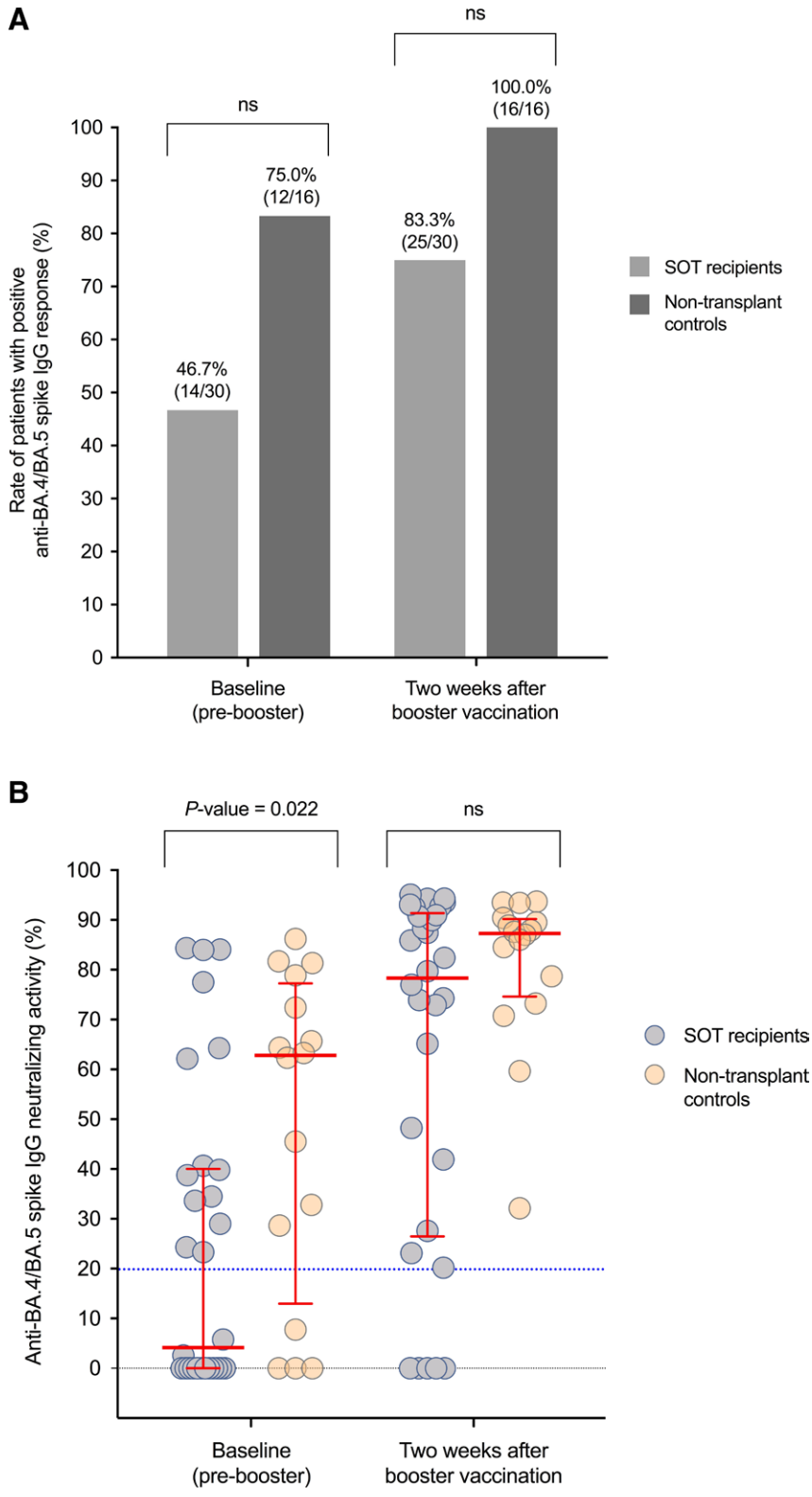

FIGURE 3. Comparison of antibody-mediated response elicited by the BA.4/BA.5-adapted booster vaccination between SOT recipients (n = 30) and the nontransplant control group (n = 16). A, IgG seropositivity rates at baseline and 2 wk after vaccination. B, Antibody-neutralizing activity at both points. Red bars and whiskers represent median values and interquartile ranges, respectively. The cutoff value for positivity in the competitive ELISA (percent inhibition ≥20%) is denoted by the blue dotted line. Three nontransplant healthy individuals lacked postbooster samples. ns, nonsignificant; SOT, solid organ transplantation.

vaccine doses,[38] our study supports the notion that "hybrid immunity" from previous infection plus vaccination provides stronger bivalent booster-elicited cross-reactive neutralization of the BA.4/BA.5 subvariant. It is likely that this circumstance may have contributed to dissolving the frequent discordance between cell-mediated and antibody responses that we

observed upon primary vaccination with the mRNA-1273 platform in our previous research.[21]

There are some limitations in our study, the most evident of which are the small sample size and the lack of a control group composed of SOT recipients receiving a monovalent booster. The first circumstance would be explained by the lower-than-expected recruitment rate because of the decreased risk perception and vaccine uptake in the current Omicron era. In contrast, the inclusion of a control group with the monovalent booster was not feasible because only the bivalent vaccine has been available in Spain since September 2022.[20] We investigated the antibody-neutralizing activity by means of a competitive ELISA instead of performing a plaque reduction neutralization test, which is the gold standard for the detection of SARS-CoV-2–specific neutralizing antibodies.[25] The fact that neutralizing activity was not expressed as binding antibody units/mL units makes it difficult to compare our results with previous studies. Additionally, cell-mediated responses or neutralizing IgG titers against the ancestral strain and other VoCs were not analyzed because of logistical considerations. It should be noted that there are no established cutoff values for the FluoroSpot assay that may act as a valid surrogate for protective immunity. The nontransplant control group was recruited among healthcare workers, which implies that there were baseline imbalances in age and comorbidities that may have influenced the comparison of immunogenicity results. Finally, no attempts have been made to estimate vaccine effectiveness.

Although limited by its size, our research provides a preliminary characterization of BA.4/BA.5 spike–specific cell-mediated and neutralizing IgG antibody responses after the administration of the BA.4/BA.5-adapted bivalent booster dose in SOT recipients. These findings would suggest that the cumulative effect of repeated monovalent vaccine doses and naturally acquired immunity in the Omicron era has contributed to reducing the initial gap in vaccine immunogenicity between the SOT population and immunocompetent individuals. Quantitative differences in the amount of the vaccine booster-elicited cell-mediated response, however, can still be detected.

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