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Antibody and T-cellular response to COVID-19 booster vaccine in SARS-CoV-1 survivors

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ABSTRACT

The severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) survivors are more likely to produce a potent immune response to SARS-CoV-2 after booster vaccination. We assessed humoral and T cell responses against SARS-CoV-2 in previously vaccinated SARS-CoV-1 survivors and naïve healthy individuals (NHIs) after a booster Ad5-nCoV dose. Boosted SARS-CoV-1 survivors had a high neutralization of SARS-CoV-2 Wuhan-Hu-1 (WA1), Beta, and Delta but is limited to Omicron subvariants (BA.1, BA.2, BA.2.12.1, and BA.4/BA.5). Most boosted SARS-CoV-1 survivors had robust SARS-CoV-2-specific $CD4^+$ and $CD8^+$ T cell responses. While booster vaccination in NHIs elicited less or ineffective neutralization of WA1, Beta, and Delta, and none of them induced neutralizing antibodies against Omicron subvariants. However, they developed comparable SARS-CoV-2-specific T cell responses compared to boosted SARS-CoV-1 survivors. These findings suggest that boosted Ad5-nCoV would not elicit effective neutralizing antibodies against Omicron subvariants in SARS-CoV-1 survivors and NHIs but induced comparable robust T cell responses. Achieving a high antibody titer in SARS-CoV-1 survivors and NHIs is desirable to generate broad neutralization.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants of concern (VOCs), Alpha, Beta, Gamma, Delta, and Omicron, have subsequently emerged [1]. Since the introduction of highly mutated and transmissible SARS-CoV-2 Omicron (B.1.1.529 or BA.1) into humans in November 2021 [1], the Omicron variant has quickly become globally dominant, and several Omicron subvariants with significant variations in their S proteins, including BA.1, BA.1.1, BA.2, and BA.3, have been reported [1]. Recent studies have shown that vaccine-induced neutralizing antibodies are extensively reduced to BA.1, BA.2, and BA.3 subvariants [2–9]. Moreover, the recently identified BA.2.12.1 and BA.4/BA.5 showed a higher transmission advantage over BA.1 and BA.2 [10], which poses a more critical challenge to the efficacy of current coronavirus disease 2019 (COVID-19) vaccines.

Several studies have shown a waning of the neutralizing response after vaccination or infection [11–13]. However, antibody responses can be enhanced upon booster vaccination, improving Omicron neutralization [4,14–16]. Previous studies have provided increasing evidence of cross-reactive T cells in naïve healthy individuals, SARS-CoV-1 survivors, and individuals infected with the human common cold coronavirus SARS-CoV-2 [17–22]. These data indicate that a COVID-19 vaccine may boost such preexisting cross-reactive memory T cells in some individuals with significant cross-reactive immunity and contribute to vaccine-induced protective immunity. Interestingly, a previous study showed a pansarbecovirus neutralizing antibody in SARS-CoV-1 survivors immunized with BNT162b2 capable of early VOC and sarbecoviruses identified in bats and pangolins [23], suggesting that boosting vaccination in SARS-CoV-1 survivors may elicit potent neutralizing antibodies and T-cell responses against SARS-CoV-2.

However, whether a booster COVID-19 vaccine will boost antibody and T-cell responses against SARS-CoV-2 in previously vaccinated SARS-

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CoV-1 survivors is unknown. To test this hypothesis, we assessed SARS-CoV-2-specific antibody and T-cell responses in SARS-CoV-1 survivors after receiving a second (booster) dose of the Ad5-nCoV vaccine and compared it with a second Ad5-nCoV booster in naïve healthy individuals.

2. Materials and methods

2.1. Human subjects and samples

In December 2021, 11 SARS-CoV-1 survivors previously immunized with the viral-vectored vaccine Ad5-nCoV at the end of January and beginning of February 2021 were enrolled to assess the immune response after boost vaccination, and blood samples were collected for analysis. Eleven survivors received a boost vaccination in November 2021. Meanwhile, nine naïve healthy individuals who received a boost vaccination of a single dose of Ad5-nCoV were enrolled. In addition, serum and peripheral blood mononuclear cell (PBMC) samples from seven unvaccinated and uninfected healthy individuals whose samples were collected in July 2021 were used as healthy controls (HCs). This study was conducted following the Declaration of Helsinki and approved by the Institutional Review Board of the Beijing Institute of Microbiology and Epidemiology (IRB number: AF/SC-08/02.124). All participants provided written consent.

2.2. Serum and PBMC isolation

Sera were separated by centrifugation at 2000 rpm for 10 min, aliquoted into three cryovials, and preserved at −80 °C until testing. PBMCs were isolated by density gradient centrifugation with Lymphoprep in SepMate tubes (Stemcell Technologies) according to the manufacturer's instructions. Briefly, the blood was placed on top of Lymphoprep in SepMate tubes and centrifuged at 1200 ×*g* for 10 min. PBMCs from the top layer were harvested and washed twice with fetal bovine serum (PBS) at 400 ×*g* for 10 min. Isolated PBMCs were frozen in cell recovery media containing 10% DMSO (GIBCO) supplemented with 90% heat-inactivated fetal bovine serum and stored in liquid nitrogen before assay analyses.

2.3. Pseudovirus neutralization test

Pseudovirus particles were generated by co-transfecting HEK 293 T cells (ATCC, CRL-3216) with human immunodeficiency virus backbones expressing firefly luciferase (pNL4–3-R-*E*-luciferase) and pcDNA3.1 vector encoding WA1 plasmid or mutated S proteins (Beta, Delta, and Omicron subvariants) as previously described [24]. The supernatants were harvested at both 24 h and 48 h post-transfection and clarified by centrifugation at 4000 rpm for 10 min before aliquoting and then stored at −80 °C until use. The SARS-CoV-2 pseudovirus neutralization test was performed as previously described [25]. In brief, 50 μl of 650–1300 $TCID_{50}$/ml pseudovirus of SARS-CoV-2 spike was incubated with duplicate 3-fold 8-point serial dilutions (starting 1:30) of heat-inactivated serum at 37 °C for 1 h, and 2×10^4 ACE2-transfected HeLa cells were then added to each well. After 48 h of incubation, the supernatant was removed, and Bio-Lite Luciferase Assay Substrate (DD1201, Vazyme, Nanjing, China) was added to each well, followed by incubation in darkness at room temperature for 3 min. The relative light unit (RLU) was then recorded on a GloMax 96 Microplate Luminometer (Promega), and 50% pseudovirus inhibitory dilution ($pVNT_{50}$) was evaluated with a four-parameter non-linear regression inhibitor curve in GraphPad Prism 8.4.1 (GraphPad Software). Samples with $pVNT_{50}$ values <30 (the limit of detection) were considered negative for neutralizing antibodies and were assigned to 10 for geometric mean titer calculation.

2.4. Activation-induced cell marker (AIM) T-cell assay

Cryopreserved PBMCs were thawed and resuspended in RPMI 1640 medium supplemented with 10% FBS and 1% penicillin/streptomycin (Cat. C15140–122, Gibco) and cultured at 1×10^6 cells per well in 96-well U-bottom plates (Cat. 3799, Corning) with the simulation of the S glycoprotein peptide pool (1 μg/ml per peptide from JPT, Berlin, Germany) corresponding to the pool of 315 overlapping peptides (15mers) spanning the complete amino acid sequence of the S glycoprotein for 24 h at 37 °C. Stimulation with an equal volume of DMSO was included as the negative control. After incubation, the cells were washed with PBS containing 2% FBS and stained with a LIVE/DEAD fixable dead cell stain kit (Cat. 565,388, BD Bioscience, San Jose, CA, USA), and antibodies against surface markers for 30 min at 4 °C and subjected to flow cytometry. Data were acquired using BD LSR FortessaTM X-20 Flow Cytometry and analyzed by FlowJo V10 software (Tree Star). The antibodies used in the AIM assay are listed in Table S1, and the gating strategy is shown in the supplementary Fig. S1.

2.5. Intracellular cytokine staining assay (ICS)

Approximately 1×10^6 PBMCs per well were cultured in 96-well U-bottom plates in RPMI-1640 (Gibco) supplemented with 10% FBS serum and 1% penicillin–streptomycin (Gibco) with an S glycoprotein peptide pool (1 μg/ml per peptide) for 19 h. Following 19 h of incubation at 37 °C with 5% CO_2, 1 μl/ml brefeldin A (Cat. 00–4506-51, eBioscience, San Diego, CA, USA) and monensin (Cat. 420,701, Biolegend, San Diego, CA) were added 5 h into the culture. The cells were then washed and stained with surface markers for 30 min on ice. Following surface staining, the cells were washed twice with FACS buffer. Cells were then fixed/permeabilized at 4 °C for 20 min in the dark using a Fixation/Permeabilization solution (Cat. 554,715, BD Biosciences, San Jose, CA, USA). Following fixation/permeabilization, cells were washed twice with 1× Perm/Wash Buffer, resuspended in 100 ml permeabilization buffer, and stained with intracellular/intranuclear antibodies for 30 min at 4 °C in the dark. Samples were washed twice with 1× Perm/Wash Buffer following staining. After the final wash, the cells were resuspended in 200 ml FACS buffer. Data were acquired using BD LSR FortessaTM X-20 Flow Cytometry and analyzed by FlowJo V10 software (Tree Star). Stimulation with an equimolar amount of DMSO was performed as the negative control, and PMA (50 ng/ml)/ionomycin (1 μg/ml) stimulation with the addition of BFA and monensin for 5 h was performed as the positive control. The antibodies used in the ICS assay are listed in Table S1, and the gating strategy is shown in the supplementary Fig. S1.

2.6. Virus-specific T-cell analysis

Antigen-specific activated $CD4^+$ cells were defined as activation of $OX40^+$ and $CD137^+$ cells, while the expression of $CD69^+$ and $CD137^+$ identified activated $CD8^+$ cells, as previously described [26]. Antigen-specific functional $CD4^+$ and $CD8^+$ T cells were defined as the expression of IFN-γ and TNF-α. Antigen-specific T cells were measured as background (DMSO) subtracted data. Following background subtraction of background DMSO cultures, negative values were set to zero. The threshold for positivity for antigen-specific $CD4^+$ T-cell responses (0 for AIM^+ and IFN-γ^+, 0.03% for TNF-α^+, and 0 for IFN-γ^+ TNF-α^+) and antigen-specific $CD8^+$ T-cell responses (0 for AIM^+, IFN-γ^+ and TNF-α^+, and 0.074 for IFN-γ^+ TNF-α^+) was calculated using the median 75th percentile of values obtained in all negative controls.

2.7. Statistical analysis

The Kruskal–Wallis test and Friedman test with the false discovery rate method were used for multiple group comparisons. All statistical analyses were performed using GraphPad Prism (version 8.4.2, La Jolla,

California, USA), and all statistical tests were 2-sided with a significance level of 0.05.

3. Results

3.1. Characteristics of the study subjects

We enrolled eleven SARS-CoV-1 survivors who received a homologous booster vaccination of Ad5-nCoV. Nine naïve healthy individuals (NHIs) who received a homologous boost vaccination of Ad5-nCoV were also enrolled. Blood samples from the two survivors with one Ad5-nCoV dose were collected after one dose vaccination with a median day of 305.0 (interquartile range [IQR] 305.0–305.0). Blood samples from 11 boosted survivors were collected 3–4 weeks after boost vaccination with a median day of 31 (IQR 21–31) and 31 (IQR 28–31) for boosted NHIs. Seven samples of serum and peripheral blood mononuclear cells (PBMCs) from biobanked normal healthy donors (unvaccinated and uninfected individuals), collected in July 2021, were included as healthy controls (HCs). All enrolled SARS-CoV-1 survivors were female, with a median age of 38 (IQR **34–47**), and their age and sex did not significantly differ from those of the NHIs and HCs (Table **1**).

3.2. Ad5-nCoV booster enhanced neutralizing antibodies against Beta and Delta but not Omicron subvariants in SARS-CoV-1 survivors

We first measured the serum neutralizing antibodies using a pseudovirus neutralization test. Of the eleven boosted SARS-CoV-1 survivors with boost vaccination, 8 (73%), 9 (82%), and 7 (64%) neutralized SARS-CoV-2 Wuhan-Hu-1 (WA1), Beta, and Delta, respectively, whereas only one to three (9% to 27.3%) of them had detection of neutralizing antibodies to Omicron subvariants (BA.1, BA.2, BA.2.12.1, and BA.4/BA.5) (Fig. 1A). In addition, the geometric mean titer (GMT) against WA1 (150, 95% confidence interval [CI] 46.2–489.7), Beta (106, 95% CI 38.9–288.6), and Delta (102, 95% CI 28.1–373.1) were comparable, and the GMT against WA1, Beta and Delta were significantly higher than the GMT against Omicron (18, 95% CI 9.0–36.5) (Fig. 1A). In contrast, with the Ad5-nCoV boosted NHIs, only 2 (22%) of 9 boosted NHIs had detectable neutralizing antibodies against WA1, Beta, and Delta with a GMT of 23 (95% CI 6.4–84.8), 19 (95% CI 6.9–51.9) and 26 (95% CI, 6.1–109.7), respectively, and none of them had detection of neutralizing antibodies to Omicron subvariants (Fig. 1B). There was no detectable serum neutralizing activity against WA1 and variants in HCs (Fig. 1C). Further comparisons of the GMT to each tested virus between boosted SARS-CoV-1 survivors and NHIs showed that antibody levels against WA1, Beta, and Delta in serum from the boosted SARS-CoV-1 survivors were significantly higher than the boosted NHIs (Fig. 1D). These findings revealed that boosted SARS-CoV-1 survivors elicited potent neutralizing antibodies against WA1, Beta, and Delta but limited neutralizing antibodies against Omicron subvariants.

Table 1
Characteristics of the study participants.

Characteristics	Ad5-nCoV boosted		Healthy controls
	SARS-CoV-1 survivors	Naïve healthy individuals	
No. of participants	11	9	7
Age (median, range)	40.0 (37.0–45.0)	38.0 (34.0–46.5)	39.0 (35.0–45.0)
Sex (%)			
Female	11 (100)	9 (100)	7 (100)
Time interval to blood sampling (Median days, IQR)			
One-dose to blood sampling (days)	305.0 (305.0–305.0)	305.0 (305.0–305.0)	NA
Booster dose to blood sampling (days)	31.0 (21.0–31.0)	31.0 (28.0–31.0)	NA

IQR, interquartile range; NA, not available.

3.3. SARS-CoV-2-specific memory $CD4^+$ and $CD8^+$ T cells in boosted SARS-CoV-1 survivors

We next assessed SARS-CoV-2-spike (*S*)-specific $CD4^+$ and $CD8^+$ T cells in boosted SARS-CoV-1 survivors and NHIs using an activation-induced marker (AIM) assay. We examined two populations of SARS-CoV-2-S-specific AIM^+ T cells: AIM^+CD4^+ ($CD137^+OX40^+$) T cells and AIM^+CD8^+ ($CD137^+CD69^+$) T cells (Fig. 2A and C). We observed an increase in AIM^+CD4^+ T-cell responses in both groups of participants (Fig. 2B). S-specific AIM^+CD4^+ T-cell responses were detected in 72.7% (8/11) of boosted SARS-CoV-1 survivors and 88.9% (8/9) of boosted NHIs, and the median frequencies (0.04%, IQR 0.00%–0.05% for boosted SARS-CoV-1 survivors and 0.092%, IQR, 0.042%–0.118% for NHIs) were significantly higher than those in HCs (Fig. 2B). We observed similar patterns with S-specific AIM^+CD8^+ T-cell responses, which significantly increased after boost vaccination in boosted SARS-CoV-1 survivors and NHIs groups compared to HCs, and 81.8% (9/11) and 77.8% (7/9) of boosted SARS-CoV-1 survivors and NHIs participants had detectable AIM^+CD8^+ T cells, with median frequencies of 0.094% (IQR, 0.02%–0.18%) and 0.07% (IQR, 0.015%–0.155%), respectively (Fig. 2D). In contrast, HCs had negligible S-specific $CD8^+$ and $CD4^+$ T-cell responses. Collectively, memory T-cell response was induced after booster vaccination, and the magnitude of the $CD4^+$ and $CD8^+$ T-cell memory response tended to be equal in the booster SARS-CoV-1 survivors compared to those with boosted NHIs.

3.4. The functionality of memory T cells to SARS-CoV-2 in boosted SARS-CoV-1 survivors

We next measured the functionality of the SARS-CoV-2-S-specific interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) cytokines secreting $CD4^+$ and $CD8^+$ T-cell responses by an intracellular cytokine staining (ICS) assay. We defined the frequencies of $cytokine^+$ $CD4^+$ and $CD8^+$ T cells as the percentage of cells positive for one cytokine (Fig. 3A and C). We found that 90.9% (10/11) of boosted SARS-CoV-1 survivors had detectable IFN-γ^+ $CD4^+$ T cells and 55.6% (5/9) had boosted NHIs, and the median S-specific IFN-γ^+ $CD4^+$ T-cell responses in boosted survivors (0.026%, IQR 0.011%–0.067%) were significantly higher than those in boosted NHIs (0.002%, IQR 0.00%–0.022%) and HCs (0) (Fig. 3B). SARS-CoV-2-S-specific IFN-γ^+ $CD8^+$ T cells were detected in 100% (11/11) of boosted SARS-CoV-1 survivors and 77.8% (7/9) of boosted NHIs (Fig. 3B). The boosted SARS-CoV-1 survivors also had higher median frequencies of S-specific IFN-γ^+ $CD8^+$ T cells of 0.136% (IQR 0.052%–0.593%) compared to HCs (Fig. 3D). In contrast, we observed that less boosted SARS-CoV-1 survivors and boosted NHIs had detectable S-specific TNF-α^+ $CD4^+$ or $CD8^+$ T-cell responses (Fig. 3B and D), the median S-specific TNF-α^+ $CD4^+$ T-cell responses were not significantly different among the three groups, except boosted survivors had a higher median frequency of TNF-α^+ $CD8^+$ T cells than HCs (Fig. 3D). Further analysis of TNF-α co-expression with IFN-γ^+ $CD4^+$ and $CD8^+$ T cells showed that most boosted SARS-CoV-1 survivors and boosted NHIs had detectable TNF-α co-expression with IFN-γ^+ $CD4^+$, but nearly all of them had no detection of SARS-CoV-2-S-specific TNF-α co-expression with IFN-γ^+ $CD8^+$ T cells (Fig. 3E and F). The median frequencies of TNF-α co-expression with IFN-γ^+ $CD4^+$ or $CD8^+$ T-cell responses were not significantly different among the three groups (Fig. 3E and F). In contrast, we observed that a few HCs had few cytokine-producing T-cell responses overall, although HCs were all sampled before any chance of exposure to the antigen of SARS-CoV-2, suggesting a possible pre-existing cross-reactive T cell memory in HCs [18,19,27]. Together, these data show that SARS-CoV-2-S-specific $CD4^+$ and $CD8^+$ T cells were detectable in most boosted SARS-CoV-1 survivors.

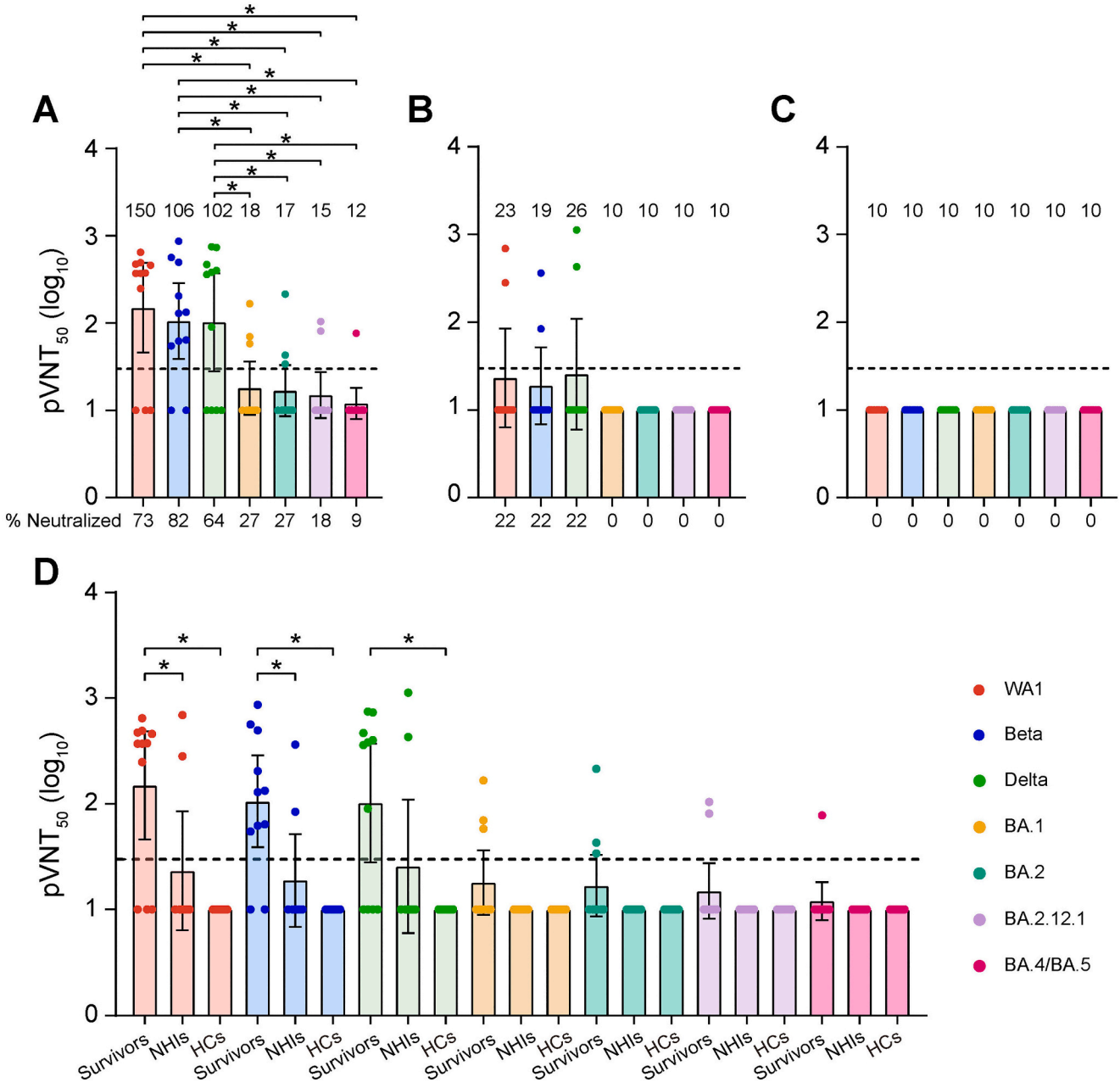

Fig. 1. The greater neutralizing antibodies to vaccination in boosted SARS-CoV-1 survivors compared with boosted NHIs. (A-C) Serum 50% pseudovirus neutralization titer ($pVNT_{50}$) against SARS-CoV-2 Wuhan-Hu-1 (WA1), Beta, Delta, BA.1, BA.2, BA.2.12.1, and BA.4/BA.5 in Ad5-nCoV-boosted SARS-CoV-1 survivors (A, $n = 11$), Ad5-nCoV-boosted naïve healthy individuals (NHIs, $n = 9$) (B), and healthy controls (HCs, $n = 7$) (C). (D) The comparison of geometric mean titer between three groups of boosted survivors, boosted NHIs, and HCs by respective pseudovirus. The heights of the bars and the numbers over the bars indicate the geometric mean titers, and the I bars indicate 95% confidence intervals. The numbers in parentheses indicate the fold-change in neutralization efficacy or resistance of respective variants relative to $pVNT_{50}$ of WA1. Each data point represents an individual sample (dots) and indicates the $pVNT_{50}$ obtained with each sample against the indicated pseudovirus. The dotted line shows the lower limit of detection (titer = 30) of the assay. Data were analyzed by using the two-tailed Friedman test (A-C) and two-tailed Kruskal–Wallis test (D) with the false discovery rate method for multiple comparisons, and only p values of <0.05 (indicating significance) are shown and are represented as $^*p < 0.05$.

4. Discussion

In the current stage of the COVID-19 pandemic, massive vaccination with COVID-19 vaccines is one of the main strategies to protect against COVID-19 infection or severe diseases. As of May 2022, 11 COVID-19 vaccines, including inactivated, viral vector-based, and mRNA-based vaccines against SARS-CoV-2 with different efficacy rates, have been approved by the World Health Organization (https://covid19.trackvaccines.org/agency/who/) and implemented worldwide. However, due to the waning of antibody responses after vaccination [28] and the continuous emergence of VOC [29], the current COVID-19 vaccines have been proven to be less or even ineffective against VOC [30,31], especially for the recently emerged Omicron subvariant [32,33].

In facing such challenges, repeated antigen exposure of SARS-CoV-2, such as homologous or heterologous booster vaccination, has been proven effective in enhancing immunity against SARS-CoV-2 VOC. More importantly, Tan et al. found that SARS-CoV-1 survivors immunized with BNT162b2 elicited a pansarbecovirus neutralizing antibody that

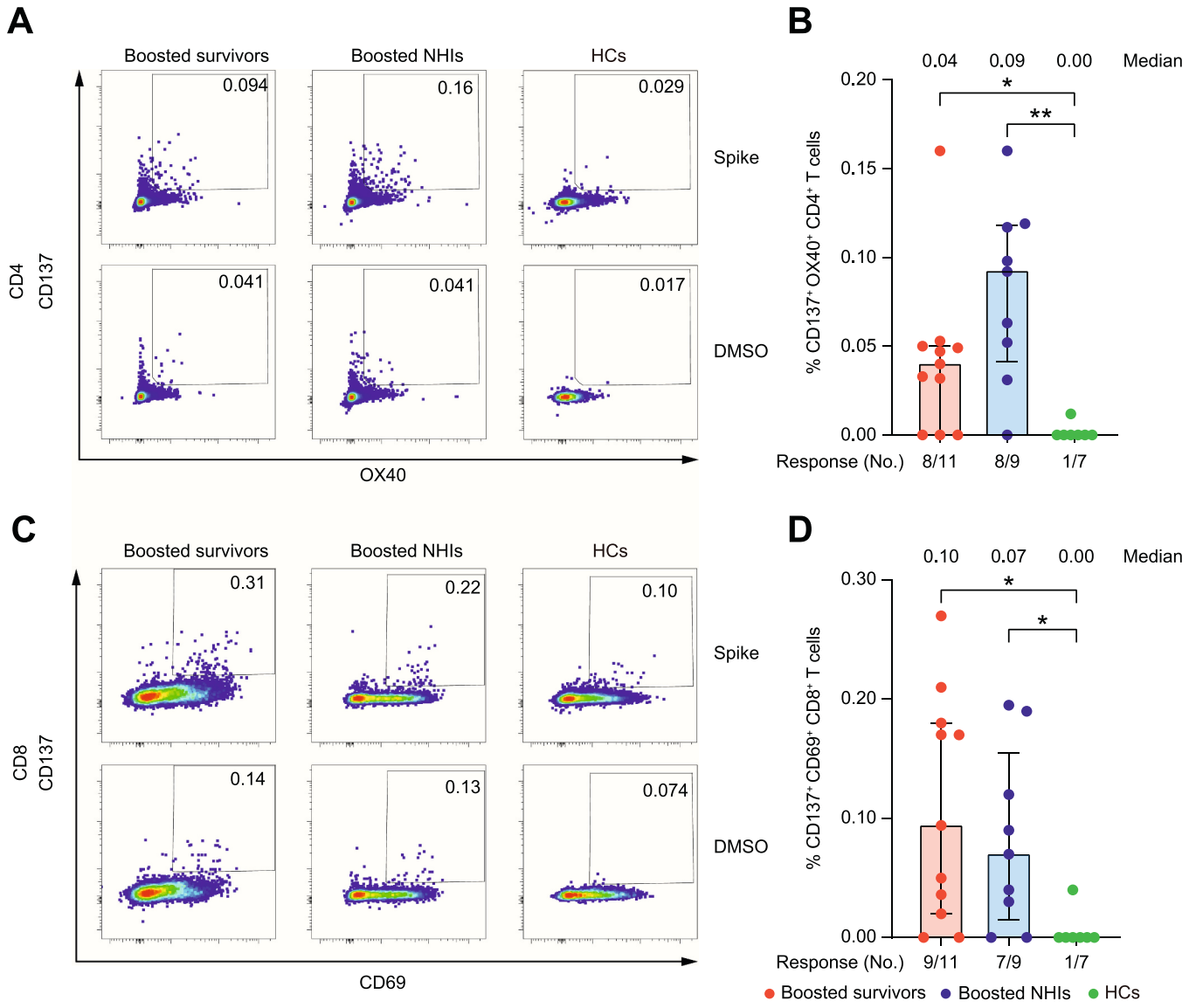

Fig. 2. SARS-CoV-2-specific $CD4^+$ and $CD8^+$ T-cell responses in boosted SARS-CoV-1 survivors and NHIs. (A, C) Representative flow cytometric plots of SARS-CoV-2-spike-specific $CD4^+$ T cells (A) and $CD8^+$ T cells (C) expressing OX40 and CD69 by activation-induced markers T-cell assay. (B, D) Comparison of SARS-CoV-2-specific $CD4^+$ (B) and $CD8^+$ T cells (D) expressing OX40 and CD69 in boosted SARS-CoV-1 survivors (n = 11), boosted naïve healthy individuals (NHIs, n = 9) and healthy controls (HCs). Box plots show all data points and indicate the median and interquartile range (IQR); the whiskers represent 1.5 times the IQR. Each dot represents the percentage of cellular responses for an individual. Data were analyzed using the Kruskal–Wallis test with the false discovery rate method for multiple comparisons, and only p values of <0.05 (indicating significance) are shown and are represented as $*p < 0.05$ and $**p < 0.01$.

was capable of neutralizing early VOCs (Alpha, Beta, and Delta) and sarbecoviruses identified in bats and pangolins [23], which implies that a booster vaccine dose in SARS-CoV-1 survivors may generate more potent neutralizing antibodies against early VOCs and Omicron variants. By assessing neutralizing antibodies in Ad5-nCoV-boosted SARS-CoV-1 survivors, we found that a booster shot enhanced neutralizing antibodies against WA1 compared to boosted NHIs. Moreover, the boosted SARS-CoV-1 survivors produced a comparable cross-neutralizing activity against Beta and Delta variants observed for WA1. However, less or complete loss of neutralizing activity against the Omicron variant was observed. The enhanced antibody response and neutralizing activity to Beta and Delta may be due to the broad and robust neutralizing activity of antibodies produced by the evolved memory B cells that were recruited into the plasma cell compartment [34–36]. In addition, Omicron receptor-binding domain (RBD) memory B-cell recognition was significantly reduced to 42% compared with other variants [37]. These data suggest that certain Omicron mutations may specifically evade broad sarbecovirus neutralizing antibodies, which are substantially enriched in vaccinated SARS-CoV-1 survivors [23].

Apart from most boosted SARS-CoV-1 survivors who developed an enhanced humoral response against WA1 and the tested VOC, we observed that most boosted SARS-CoV-1 survivors had detectable SARS-CoV-2-S-specific $CD4^+$ and $CD8^+$ T-cell responses. In contrast, despite the limited humoral response to WA1 and the tested VOC in boosted NHIs, most of them produced comparable SARS-CoV-2-S-specific $CD4^+$ and $CD8^+$ T-cell responses related to boosted SARS-CoV-1 survivors. These data indicate that boosted SARS-CoV-1 survivors have induced strong humoral and T-cell responses, whereas boosted NHIs elicited a skew T-cell response. The T-cell response is a critical component of the antiviral immune response. Although T-cell responses do not prevent viral infection, $CD4^+$ T cells are indispensable for generating protective neutralizing antibody responses and supporting the maturation of $CD8^+$

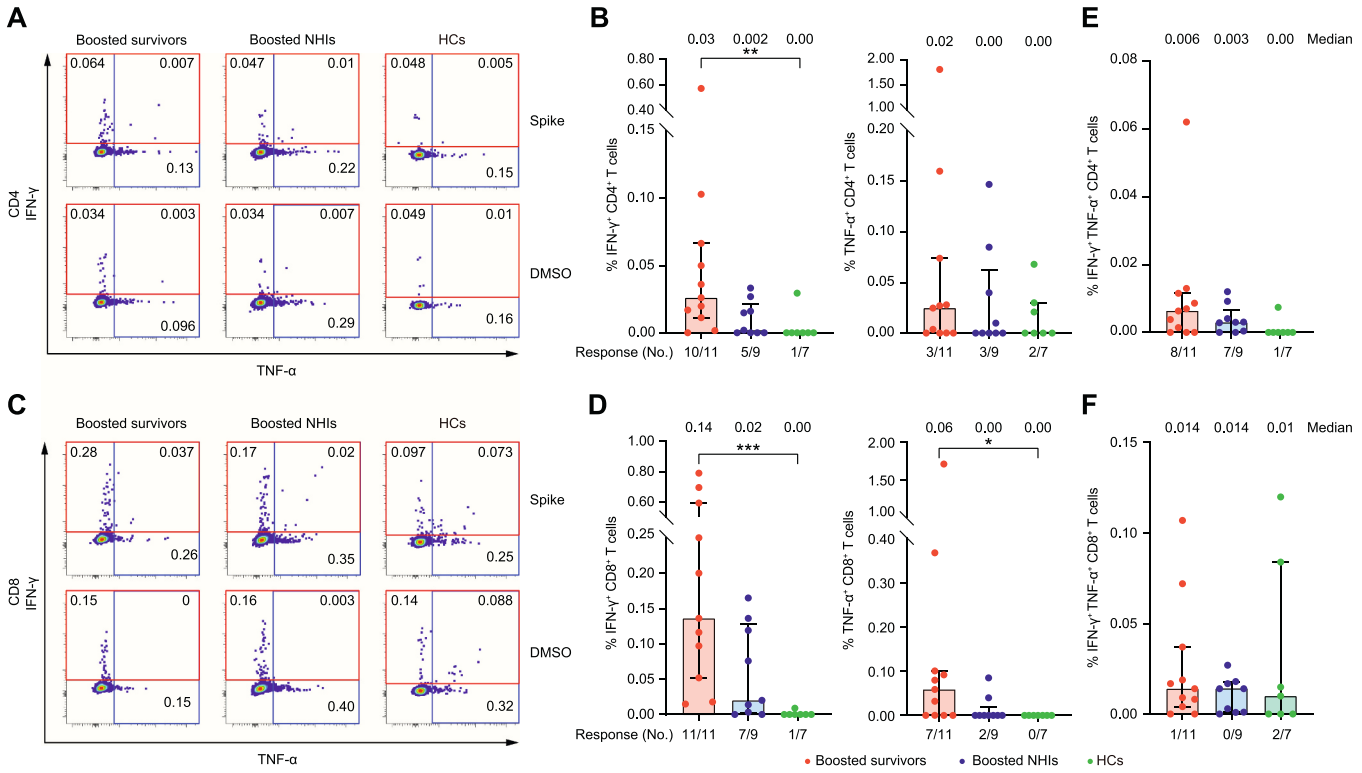

Fig. 3. The functionality of SARS-CoV-2-specific CD4$^+$ and CD8$^+$ T-cell responses in boosted SARS-CoV-1 survivors and NHIs. (A, C) Representative flow cytometric plots of SARS-CoV-2-spike-specific CD4$^+$ T cells (A) and CD8$^+$ T cells (C) expressing IFN-γ and TNF-α by intracellular cytokine staining assays. (B, D) Comparison of SARS-CoV-2-specific CD4$^+$ (B) and CD8$^+$ T cells (D) expressing IFN-γ and TNF-α in boosted SARS-CoV-1 survivors (n = 11), boosted naïve healthy individuals (NHIs, n = 9) and healthy controls (HCs). (E and F) Comparison of SARS-CoV-2-specific IFN-γ$^+$ CD4$^+$ (E) and CD8$^+$ (F) T cells producing TNF-α between groups. Box plots show all data points and indicate the median and interquartile range (IQR); the whiskers represent 1.5 times the IQR. Each dot represents the percentage of cellular responses for an individual. Data were analyzed using the Kruskal–Wallis test with the false discovery rate method for multiple comparisons, and only p values of <0.05 (indicating significance) are shown and are represented as $^{**}p < 0.01$ and $^{***}p < 0.001$.

T cells. A previous study showed that CD8$^+$ T cells provided partial protective immunity in the context of suboptimal antibody titers in macaques [38]. Hence, given the ability of VOCs to escape neutralization, the generation and maintenance of SARS-CoV-2-specific T-cell responses may contribute to lasting vaccine efficacy against severe disease. Although vaccine- and infection-induced T-cell responses decay after antigen clearance [26,39], SARS-CoV-2-specific CD8$^+$ T cells displayed the hallmarks of long-lasting cells [40], and T-cell responses to SARS-CoV-1 infection were detectable 17 years after infection [19]. Moreover, very recently, it has been suggested that there is a limited impact of the T-cell response against the Omicron than the antibody responses at the population level [37,41–44]. Together, we showed that booster vaccination in both SARS-CoV-1 survivors and NHIs elicits a strong overall T-cell response, which may provide protection from severe disease and contribute to the apparent milder outcomes for the infection.

Our study had several limitations. We included a rather low number of SARS-CoV-1 survivors due to the inability to obtain contact information for more survivors, and all of them were females. Thus, confirmation of our results from larger-scale cohorts and exposure to other COVID-19 vaccines would provide further reassurance of humoral and T-cell responses in SARS-CoV-1 survivors after booster vaccination. We studied humoral and T-cell responses approximately one month after booster vaccination. The longer-term durability of the SARS-CoV-2-specific antibody response and T cells remains to be determined. We used 15-mer peptides with 11 amino acid overlap to assess the SARS-CoV-2-specific T-cell response, which is ideal for CD4$^+$ T-cell stimulation, but SARS-CoV-2-specific CD8$^+$ T cells may be underestimated because major histocompatibility complex class I preferentially binds shorter peptides (9-mer or 10-mer peptides) [45].

Overall, our data show that a second Ad5-nCoV booster vaccination has advantages in eliciting a broader neutralizing antibody against WA1 and VOCs and a robust T-cell response in SARS-CoV-1 survivors, although further investigations are needed. Unlike the immune response in boosted SARS-CoV-1 survivors, boosted vaccination in NHIs elicited a partial humoral response but a comparable T-cell response. It remains to be defined whether T-cell-mediated immunity provides protection from severe disease and contributes to the apparent milder outcomes for the infection. Moreover, despite a robust T-cell response, low levels of neutralizing antibodies after booster vaccination suggested that a more potent regimen to improve antibody response should be warranted in case more highly mutated VOCs emerge in the future.

Author contributions

MJM conceived the study. LBN, XMC, and MJM collected blood samples. KLZ, LY, and XJW performed the pseudovirus neutralization assay, and LBN, KLZ, and LY performed the flow cytometry assay. LBN, KLZ, and LY analyzed the data and produced the figures. MJM drafted the manuscript. All authors reviewed and approved the final manuscript.

Declaration of Competing Interest

We declare no competing interests.

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Appendix A. Supplementary data

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