

LETTER TO EDITOR

T_{FH}2 cells associate with enhanced humoral immunity to SARS-CoV-2 inactivated vaccine in patients with allergic rhinitis

To the Editor:

We report that allergic rhinitis (AR) patients displayed enhanced humoral immune response to SARS-CoV-2 inactivated vaccine as compared to healthy controls, and highlight a pivotal role of type 2 T follicular helper cells in this response. Vaccination is considered as the best strategy to reduce SARS-CoV-2 infections and prevent severe illness after breakthrough infections.^{1,2} Although SARS-CoV-2 vaccines are highly protective against COVID-19 in healthy individuals, the vaccine efficacy may be compromised in patients with pre-existing conditions, resulting in dysregulated immune systems. Recent data described poorer humoral immunity to COVID-19 vaccines in individuals with kidney transplantation, undertaking dialysis, or cancer, compared to healthy controls.^{1,2} Allergic diseases, including AR, atopic dermatitis and asthma, are caused by the immune system hypersensitivity to innocuous environmental antigens and characterized by skewed type 2 immune responses.³ Such chronic immunological disorders are highly prevalent and estimated to affect up to 50% of the world population.³ Allergic airway diseases have been revealed to have a potential protective role in COVID-19, possibly because of the reduction of SARS-CoV-2 receptor angiotensin-converting enzyme 2 in airway epithelial cells caused by type 2 cytokines and the abundant infiltration of eosinophils in airways.⁴ However, there are no studies formally investigating whether allergic diseases modulate the humoral response following vaccination against SARS-CoV-2. In the present study, we compare immunological response after two-dose inactivated SARS-CoV-2 immunization between healthy subjects and patients with AR.

We conducted a prospective study to evaluate the potential impact of AR on the immune response after two-dose inactivated SARS-CoV-2 immunization (Figure 1A). The trial was registered at <https://clinicaltrials.gov> (NCT05009134). Twenty-five healthy adults and 32 patients

with AR were recruited at Tongji Hospital (Table 1). AR was diagnosed based on the concordance between typical allergic symptoms and atopic status.⁵ Atopic status was assessed by skin-prick testing (SPT) and/or allergen-specific immunoglobulin E (IgE) levels.⁶ AR patients had at least 1-year disease history and had never been infected with SARS-CoV-2. The exclusion criteria included (i) the presence of sinusitis, (ii) pregnancy or breastfeeding, (iii) with cardiovascular diseases, severe immunologic diseases, chronic obstructive pulmonary disease, chronic infections, diabetes, tumours, chronic kidney diseases or stroke, and (iv) use of intranasal steroid or antihistamines in the previous 1 week or oral steroids in the previous 3 months before this study. Healthy subjects had negative SPT and specific IgE test and had no history of allergy.⁶ All participants received two doses of inactivated SARS-CoV-2 vaccines (WIBP-CorV, Sinopharm, Wuhan) with 1 month apart. Peripheral blood samples were collected on days 0, 7, 30 (before the second dose), 37 (7 days post the second dose) and 60 (30 days post the second dose) to analyze humoral immune responses to vaccination (Figure 1A). None was lost to follow-up. In addition, a complementary approach was adopted to further investigate the influence of AR on the antibody response to natural SARS-CoV-2 infection in 78 patients recovered from COVID-19 (64 control subjects without AR and 14 AR patients), whose peripheral bloods were collected at 10–12 months post the infection. The Ethics Committee of Tongji Hospital reviewed and approved this trial, and informed consent was provided by every participant. More information regarding subjects and methods is provided in Tables S1–S3.

There was no noticeable difference in the incidence of adverse reactions between healthy subjects and patients with AR (Table S1). Protective antibody responses to WIBP-CorV were assessed by the detection of neutralizing antibodies targeting the receptor-binding domain (RBD) of SARS-CoV-2 spike (S) 1 protein and IgG and IgM against

This is an open access article under the terms of the [Creative Commons Attribution](#) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2022 The Authors. *Clinical and Translational Medicine* published by John Wiley & Sons Australia, Ltd on behalf of Shanghai Institute of Clinical Bioinformatics

TABLE 1 Demographic characteristics of subjects in the study of inactivated SARS-CoV-2 vaccination

	Healthy subjects	AR patients	p-Value
Total subjects, <i>n</i>	25	32	–
Gender, male/female	9/16	11/21	.899
Age (years)	24 (23, 27)	24 (22, 26)	.197
Body mass index	21.1 (19.1, 22.3)	20.8 (19.2, 22.4)	.908
Patients with asthma, <i>n</i> (%)	0	1 (3.1%)	1.000
Patients with atopic eczema, <i>n</i> (%)	0	1 (3.1%)	1.000
Sensitization pattern, <i>n</i> (%)			
Dermatophagoides pteronyssinus	0	30 (94.8%)	
Dermatophagoides farinae	0	30 (94.8%)	
Cockroach	0	2 (6.4%)	
Cat dander	0	5 (15.6%)	
Dog dander	0	4 (12.5%)	
Artemisia	0	1 (3.1%)	
Platanus	0	1 (3.1%)	
Alternaria	0	3 (9.4%)	
VAS symptom score	0 (0, 0)	5.0 (3.3, 7.0)	<.001

Note: For continuous variables, data are expressed as medians and interquartile ranges.

Abbreviations: AR, allergic rhinitis; VAS, visual analogue scale.

the S and nucleocapsid proteins. The inactivated SARS-CoV-2 vaccine elicited robust serological responses, with gradual increase in neutralizing antibody, IgG and IgM following vaccination (Figure 1B). Although neutralizing antibody, IgG and IgM levels were low following the first immunization, the second injection boosted their titres by ~35-, 161- and 16-fold (mean) at day 60 relative to day 0 (baseline), respectively (Figure S1A). As reported in COVID-19 infection or vaccination,⁷ the levels of neutralizing antibody strongly correlated with IgG levels (Figure S1B).

Of a particular interest, serological responses in AR patients were stronger than those in healthy controls, showing higher levels of neutralizing antibody at days 30, 37 and 60, and anti-SARS-CoV-2 IgG on days 37 and 60, and anti-SARS-CoV-2 IgM on day 60 (Figure 1C; Figure S1C). Higher frequencies of CD19⁺CD27⁺CD38⁺⁺ circulating plasmablasts were found in patients with AR at day 60, although there was no noticeable difference in CD3⁺CD19⁺ total B cells and its subsets (IgD⁺CD27⁺ double negative, IgD⁺CD27⁺ switched memory, IgD⁺CD27⁺ naive and IgD⁺CD27⁺ nonswitched memory B cells) between healthy subjects and AR patients (Figures S2 and S3). To explore the immune memory after vaccination, we also analyzed memory B-cell response specific to RBD in the peripheral blood (Figure S2). Flow cytometric analysis revealed higher frequencies of RBD-specific memory B cells, again, in AR patients compared to healthy subjects at day 60 (Figure 1D). As the negative controls, RBD-specific memory B cells were undetectable in samples col-

lected before vaccination (Figure 1D). These results suggest AR patients demonstrated enhanced immune responses to inactive SARS-CoV-2 vaccine than control subjects.

T follicular helper (T_{FH}) cells essentially support B cells for the generation of neutralizing antibodies and long-lived humoral immunity after vaccination.⁸ We assessed vaccination-induced T_{FH} activation by examining circulating CXCR5⁺ICOS^{high}PD-1^{high} T_{FH} (ICOS^{high}PD-1^{high} cT_{FH}) cells (Figure S4).⁶ In both groups, inactivated SARS-CoV-2 vaccination induced a modest expansion of ICOS^{high}PD-1^{high} cT_{FH} cells, 7 days after the first immunization and a drastic expansion 7 days after the second immunization (day 37), while there was no significant difference in the frequencies of ICOS^{high}PD-1^{high} cT_{FH} cells at all the time points between the two groups (Figure 2A). To reduce the impact introduced by individual variation, we normalized the frequencies of ICOS^{high}PD-1^{high} cT_{FH} cells to the baseline at day 0 and detected higher frequencies of ICOS^{high}PD-1^{high} cT_{FH} cells at days 7, 37 and 60 in AR patients than control subjects (Figure 2B). In contrast, total CD4⁺ T cells, CXCR5⁺ total cT_{FH} cells, T_{REG} cells and T_{FR} cells were not affected by vaccination and remained comparable between two groups (Figure S5A,B). Therefore, both AR patients and control subjects mounted potent T_{FH} activation by two-dose of WIBP-CorV vaccination, with a stronger signature by the former group.

As both T_{FH} activation and the production neutralizing antibody were strongly elicited after the second dose of vaccine, we focused on the memory response after the second dose in order to understand the relationship between

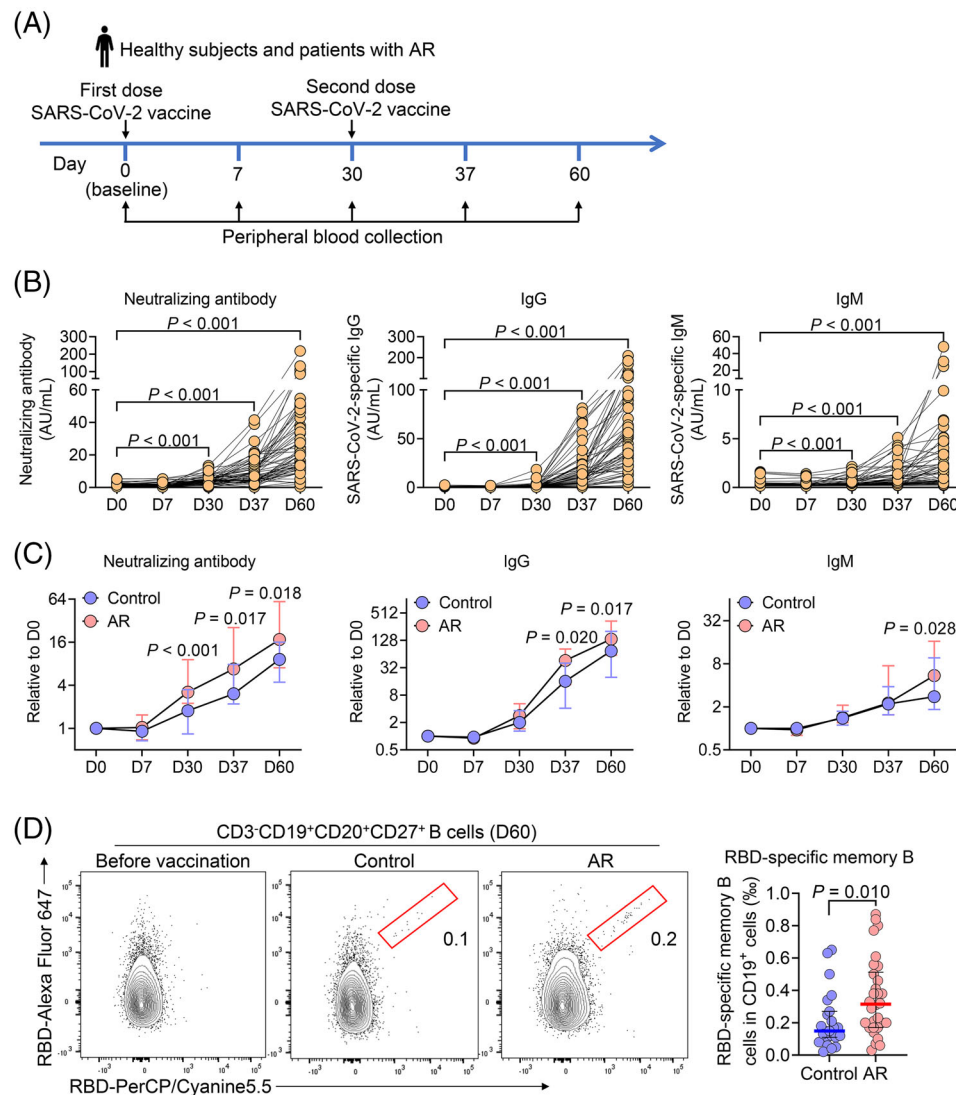


FIGURE 1 Enhanced antibody responses in patients with allergic rhinitis (AR) following inactivated SARS-CoV-2 vaccination. (A) Healthy subjects ($n = 25$) and patients with AR ($n = 32$) were enrolled and received inactivated SARS-CoV-2 vaccine at days 0 and 30. Peripheral blood was collected at days 0 (baseline), 7, 30, 37 and 60. (B) Plasma neutralizing antibodies against the RBD of the SARS-CoV-2 S1 protein and IgG and IgM against the SARS-CoV-2 S and N proteins were measured by chemiluminescent immunoassay. Data are analyzed by two-sided paired-sample t -test. (C) Fold changes of SARS-CoV-2 neutralizing antibody, IgG and IgM in control subjects and AR patients by normalizing to the baseline levels. (D) Frequencies of circulating RBD-specific memory B cells at day 60 were analyzed by flow cytometry. Numbers indicate the frequency of cells in the gated region. For (C) and (D), data are presented as median and interquartile range and analyzed by Mann-Whitney U -test

T_{FH} function and protective antibody response. In patients with AR, the fold changes of ICOS^{high}PD-1^{high} cT_{FH} at day 37 positively correlated with the fold changes of IgG and IgM at day 60 but, intriguingly, not the fold changes of neutralizing antibody, which are more important in evaluating protective humoral immunity (Figure 2C; Figure S5C). Based on CXCR3 and CCR6 expression, cT_{FH} cells can be classified into three major subsets, referred as T_{FH1}, T_{FH2} and T_{FH17} cells.⁶ T_{FH2} and T_{FH17} cells are reported to support chronic humoral immunity, such as autoantibody production in autoimmune diseases, whereas T_{FH1}

cells can support antibody response in infection and vaccine with relatively short duration.⁷ With ICOS^{high}PD-1^{high} cT_{FH} cells, the T_{FH1} and T_{FH2}, but not T_{FH17} subsets, were strongly induced by the vaccination (Figure 2D,E; Figure S6A). Importantly, we noted a marked increase in the frequencies of T_{FH2} cells among either ICOS^{high}PD-1^{high} cT_{FH} cells or total CD4⁺ T cells in AR patients compared with healthy subjects (Figure S6A). As expected, the fold changes of T_{FH2} cells to baseline were also elevated in AR patients at days 7 and 37 (Figure 2E). Furthermore, only T_{FH2} activation, not T_{FH1} and T_{FH17} activation, was found

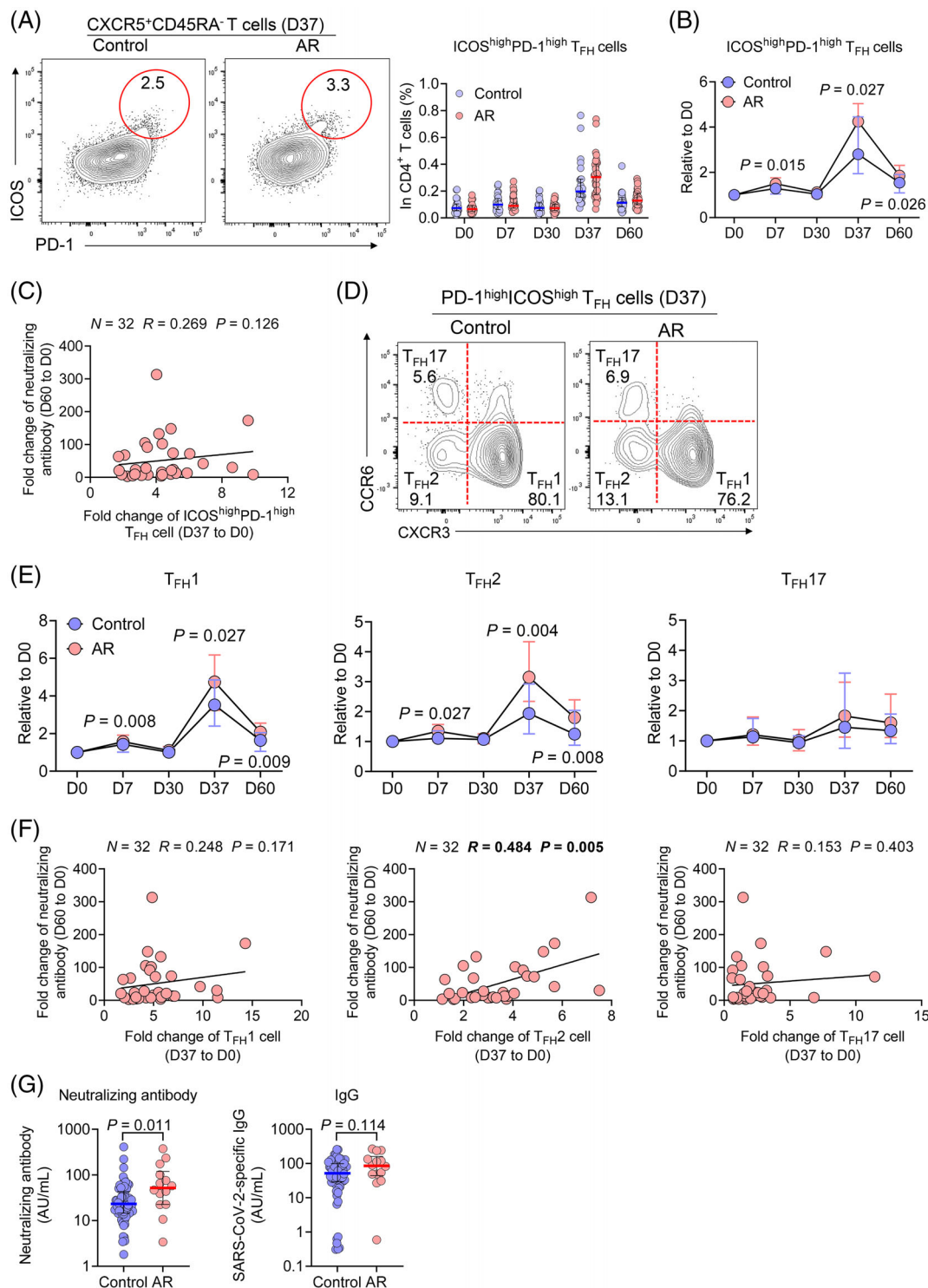


FIGURE 2 Increased circulating T_{FH}2 cells associate with protective antibodies in patients with allergic rhinitis (AR) following vaccination. (A) Frequencies of circulating ICOS^{high}PD-1^{high} T_{FH} cells were analyzed by flow cytometry. (B) Changes of ICOS^{high}PD-1^{high} T_{FH} cells at the indicated time points were normalized to the baseline levels and represented as fold changes. (C) Correlation of fold changes of ICOS^{high}PD-1^{high} T_{FH} cells at day 37 with fold changes of SARS-CoV-2 neutralizing antibody at day 60 relative to those at baseline in patients with AR. (D and E) Frequencies of circulating ICOS^{high}PD-1^{high} T_{FH} cell subsets were analyzed by flow cytometry. Changes of ICOS^{high}PD-1^{high} T_{FH} cell subsets at the indicated time points were normalized to the baseline levels and represented as fold changes. (F) Correlations of fold changes of ICOS^{high}PD-1^{high} T_{FH} cell subsets at day 37 with fold changes of SARS-CoV-2 neutralizing antibody at day 60 in patients with AR. (G) Plasma SARS-CoV-2 neutralizing antibody and IgG levels in recovered COVID-19 patients at 10–12 months after infection ($n = 64$ for controls without AR and $n = 14$ for those with AR). Numbers indicate the frequency of cells in the gated region. For (A), (B), (E) and (G), data are presented as median and interquartile range and analyzed by Mann-Whitney U -test. For (C) and (F), data are analyzed by Spearman's rank correlation

to be positively correlated with neutralizing antibodies in patients with AR (Figure 2F), despite positive correlations between T_{FH1} or T_{FH17} activation and IgG and IgM in AR patients (Figure S6B). Therefore, such results suggest that T_{FH2} subset might play a prominent role in promoting protective humoral response to two-dose inactivated vaccination against SARS-CoV-2.

To verify the influence of AR on the humoral response to SARS-CoV-2, we additionally recruited 78 recovered COVID-19 patients, including 64 without AR and 14 with AR, who showed no difference in demographic characteristics (Table S2). Similar to the humoral response elicited by inactivated SARS-CoV-2 vaccine, patients with pre-existing AR displayed higher levels of neutralizing antibody 10–12 months after infection than control subjects, while the difference of SARS-CoV-2-specific IgG did not reach statistical difference (Figure 2G).

Our study of AR patients for the antibody response to SARS-CoV-2 induced by inactivated vaccine or infection demonstrates that the protective humoral immune response was enhanced rather than compromised in AR patients. The prospective design in the vaccination study allowed us to measure both neutralizing antibody and RBD-specific memory B cells, both supporting the above conclusion. As viral infection and vaccination, especially with influenza, induce a strong T_H1 immune response, the generation and function of the T_{FH1} subset associated with T_H1 response has been extensively investigated in viral infection and vaccination. Notably, COVID-19 infection induces both T_H1 and T_H2 responses.⁷ Despite the T_{FH1} subset was variously activated by inactivated SARS-CoV-2 vaccine, our study revealed an unappreciated role of the T_{FH2} subset following vaccination. We have previously reported an increased T_{FH2} cells in patients with AR.⁶ Our new results demonstrate that the activation of T_{FH2} rather than T_{FH1} subset correlated with the induction of neutralizing antibodies in AR patients. Indeed, a recent study showed that IL-4, a signature cytokine from T_{FH2} cells, plays a critical role in supporting broadly protective antibody response in viral infection.⁹ Although differing in intensity, similar humoral immune responses have been elicited by different SARS-CoV-2 vaccines.¹⁰ Whether AR patients have comparable immune responses to other SARS-CoV-2 vaccines, such as BNT162b2 mRNA vaccine, deserves further investigations.

In summary, our study provides the necessary evidence to justify the recommendation of SARS-CoV-2 vaccination to patients with AR and potentially other allergic diseases. Although the precise molecular mechanisms underlying the enhanced protective humoral immunity to COVID-19 vaccine in patients with AR remain to be elucidated, the function of T_{FH2} cells in regulating anti-SARS-CoV-2 humoral immune response should be a key area deserving

a future investigation. In addition, it is also critical to understand whether type 2 response-modifying treatments, such as allergen immunotherapy and biologics, will impair the efficacy of SARS-CoV-2 vaccination.

ACKNOWLEDGEMENTS

We thank Zhao-Qin Lian, Meng-Chen Wang, and Yin Wang for blood sample collection. This study was supported by the National Natural Science Foundation of China (NSFC) grants 8192010801, 82130030 and 81630024 (Zheng Liu), and 82101198 (Yin Yao) and the Leader Fellowship GNT2009554 from Australian National Health and Medical Research Council (Di Yu).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

Yin Yao¹

Zhe-Zheng Wang¹

Ao Huang¹

Yan Liu¹

Nan Wang¹

Zhi-Chao Wang¹

Lin Yang²

Hui-Jun Li³

Jun-Gang Xie⁴

Rong-Fei Zhu²

Li-Ming Cheng³

Di Yu⁵

Zheng Liu¹ 

¹ Department of Otolaryngology-Head and Neck Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

² Department of Allergy, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

³ Department of Laboratory Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

⁴ Department of Respiratory and Critical Care Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

⁵ The University of Queensland Diamantina Institute, Faculty of Medicine, The University of Queensland, Brisbane, Queensland, Australia

Correspondence

Zheng Liu, Department of Otolaryngology-Head and Neck Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, No. 1095 Jiefang Ave, Wuhan 430030, P.R. China.
Email: zhengluiuent@hotmail.com

Di Yu, The University of Queensland Diamantina Institute, Faculty of Medicine, The University of Queensland, 37 Kent St, Woolloongabba, QLD 4102, Australia.

Email: di.yu@uq.edu.au

Li-Ming Cheng, Department of Laboratory Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, No. 1095 Jiefang Ave, Wuhan 430030, P.R. China.

Email: chengliming2015@163.com

Rong-Fei Zhu, Department of Allergy, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, No. 1095 Jiefang Ave, Wuhan 430030, P.R. China.

Email: zrf13092@163.com

Yin Yao, Zhe-Zheng Wang and Ao Huang contributed equally to this work.

ORCID

Zheng Liu  <https://orcid.org/0000-0002-4168-6702>

REFERENCES

1. Rincon-Arevalo H, Choi M, Stefanski AL, et al. Impaired humoral immunity to SARS-CoV-2 BNT162b2 vaccine in kidney transplant recipients and dialysis patients. *Sci Immunol*. 2021;6:eabj1031.
2. Ehmsen S, Asmussen A, Jeppesen SS, et al. Antibody and T cell immune responses following mRNA COVID-19 vaccination in patients with cancer. *Cancer Cell*. 2021;39:1034-1036.

3. Yao Y, Chen CL, Yu D, Liu Z. Roles of follicular helper and regulatory T cells in allergic diseases and allergen immunotherapy. *Allergy*. 2021;76:456-470.
4. Ding M, Dong X, Sun YL, et al. Recent advances and developments in COVID-19 in the context of allergic diseases. *Clin Transl Allergy*. 2021;11:e12065.
5. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy*. 2008;63(86):8-160.
6. Yao Y, Chen CL, Wang N, et al. Correlation of allergen-specific T follicular helper cell counts with specific IgE levels and efficacy of allergen immunotherapy. *J Allergy Clin Immunol*. 2018;142:321-324.
7. Juno JA, Tan HX, Lee WS, et al. Humoral and circulating follicular helper T cell responses in recovered patients with COVID-19. *Nat Med*. 2020;26:1428-1434.
8. Yao Y, Chen Z, Zhang H, et al. Selenium-GPX4 axis protects follicular helper T cells from ferroptosis. *Nat Immunol*. 2021;22:1127-1139.
9. Miyauchi K, Adachi Y, Tonouchi K, et al. Influenza virus infection expands the breadth of antibody responses through IL-4 signalling in B cells. *Nat Commun*. 2021;12:3789.
10. Mok CKP, Cohen CA, Cheng SMS, et al. Comparison of the immunogenicity of BNT162b2 and CoronaVac COVID-19 vaccines in Hong Kong. *Respirology*. 2021. <https://doi.org/10.1111/resp.14191>

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Online Data Supplement

T_{FH}2 cells associate with enhanced humoral immunity to SARS-CoV-2 inactivated vaccine in patients with allergic rhinitis

Yin Yao, MD, PhD^{1*}, Zhe-Zheng Wang, MD, PhD^{1*}, Ao Huang, MD^{1*}, Yan Liu,
MD¹, Nan Wang, MD, PhD¹, Zhi-Chao Wang, MD, PhD¹, Lin Yang, PhD², Hui-Jun Li,
MD³, Jun-Gang Xie, MD, PhD⁴, Rong-Fei Zhu, MD, PhD², Li-Ming Cheng, MD,
PhD³, Di Yu, PhD⁵, Zheng Liu, MD, PhD¹

¹Department of Otolaryngology-Head and Neck Surgery, Tongji Hospital, Tongji
Medical College, Huazhong University of Science and Technology, Wuhan, China

²Department of Allergy, Tongji Hospital, Tongji Medical College, Huazhong
University of Science and Technology, Wuhan, China

³Department of Laboratory Medicine, Tongji Hospital, Tongji Medical College,
Huazhong University of Science and Technology, Wuhan, China

⁴Department of Respiratory and Critical Care Medicine, Tongji Hospital, Tongji
Medical College, Huazhong University of Science and Technology, Wuhan, China

⁵The University of Queensland Diamantina Institute, Faculty of Medicine, The
University of Queensland, Brisbane, Australia

*These authors contributed equally to this work.

METHODS

Clinical study design and participants

We first conducted a prospective cohort study to investigate the potential impact of AR on immune response and adverse events to SARS-CoV-2 vaccination. The trial is registered at <https://clinicaltrials.gov> (NCT05009134). Twenty-five healthy adults and 32 patients with AR were recruited at Tongji Hospital. The diagnosis of AR was based on the concordance between atopic status and typical allergic symptoms according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guideline^{S1}. Atopic status was evaluated by the skin prick test and/or ImmunoCAP (Phadia, Uppsala, Sweden) to detect specific IgE for common inhalant allergens in our region^{S2}. AR patients had at least 1 year disease history and had never been infected with SARS-CoV-2 (no history of positive polymerase chain reaction results on nasopharyngeal or pharyngeal swab samples and levels of anti-SARS-CoV-2 spike and nucleocapsid protein IgG and IgM less than 10 AU/mL before vaccination). The exclusion criteria included: (i) the presence of sinusitis, (ii) pregnancy or breastfeeding, (iii) with severe immunologic diseases, diabetes, tumors, chronic kidney diseases, chronic obstructive pulmonary disease, cardiovascular diseases, stroke, or chronic infections, and (iv) used antihistamines or intranasal steroid in the past 1 week or oral steroids in the past 3 months prior to this study. Concomitant asthma and atopic eczema were diagnosed according to Global Initiative for Asthma guideline^{S3} and the Williams criteria^{S4}, respectively. AR patients received intranasal antihistamine or intranasal steroid treatment as needed, and no systemic medication

including oral steroids and antihistamines were allowed during this study. A visual analog scale (VAS) ranging from 0 (not at all bothersome) to 10 cm (extremely bothersome) was used to quantify the global perception of severity of combined nasal symptoms. Healthy controls had no history of allergy and had negative skin prick test and allergen specific IgE test.^{S5}

All participants received an inactivated SARS-CoV-2 vaccine (WIBP-CorV, Sinopharm, Wuhan) on day 0 and day 30. Adverse events related to vaccination were recorded. Peripheral blood samples were collected at day 0 (baseline, before vaccination), day 7 (7 days after first vaccination), day 30 (30 days after first vaccination), day 37 (7 days after second vaccination), and day 60 (30 days after second vaccination). None were lost to follow-up. Plasma and peripheral blood mononuclear cells (PBMCs) were collected and stored as we previously described.^{S6}

In addition, 78 recovered COVID-19 cases, who were infected with SARS-CoV-2 during January 13, 2020, to March 9, 2020, were retrospectively enrolled to validate the effect of AR on protective antibody response to SARS-CoV-2. Peripheral bloods were collected at 10 to 12 months after symptom onset. The diagnosis of COVID-19 was based on the guidance for diagnosis and management of COVID-19 released by World Health Organization and confirmed by SARS-CoV-2 polymerase chain reaction detection of nasopharyngeal or pharyngeal swab specimens at Tongji Hospital.^{S7} AR, asthma, and atopic eczema were determined based on patients' self-report on admission and further conformed by experienced physicians. Patients with bronchiectasis, cystic fibrosis, severe immunologic diseases, tumors,

diabetes, chronic kidney diseases, chronic obstructive pulmonary disease, cardiovascular diseases, stroke, and sinusitis were excluded from the study. COVID-19 disease severity was classified as we previously reported.^{S7} The exclusion criteria led to only subjects with mild and moderate COVID-19 included in this retrospective study.

This study was approved by the Tongji Hospital Ethics Committee. Informed consent was obtained from every participant. All blood samples were processed and analyzed by investigators blinded to clinical data of patients. All samples were used in accordance with approved guidelines and regulations.

Adverse events

For the first 7 days after each dose, participants involved in vaccine study were provided with a daily record card for recording the injection site symptoms (pain, redness, and swelling), systematic symptoms (fatigue, fever, headache, and myalgia), digestive symptoms (diarrhea, vomiting, and nausea), respiratory symptoms (runny nose, cough, stuffy nose, and sore throat), and allergic symptoms (pruritus, hives, itchy throat, swelling of mouth or throat, shortness of breath, and anaphylaxis).^{S8} From day 8 to day 28 after each dose, safety data were collected by spontaneous report from the participants combined with the regular visit. Adverse events were further verified by investigators and the causal association between adverse events and vaccination was determined by the investigators.

Plasma antibodies detection

The neutralizing antibody against the receptor-binding domain (RBD) of the SARS-CoV-2 spike 1 protein in plasma were measured by chemiluminescent immunoassay using iFlash 2019-nCoV neutralization assay kits (YHLO Biotech Co, Shenzhen, China) according to the manufacture's instruction. This surrogate neutralization assay detects antibodies that are able to compete with binding of a recombinant extracellular domain of the SARS-CoV-2 receptor angiotensin-converting enzyme 2 to a recombinant RBD of the SARS-CoV-2 spike 1 protein coated on microparticles and thus indicates the neutralization activity of sera.^{S9} The SARS-CoV-2 neutralizing antibody concentrations were measured by an iFlash3000 Chemiluminescence Immunoassay Analyzer (YHLO Biotech Co). Plasma IgM and IgG specific to the spike and the nucleocapsid proteins of the SARS-CoV-2 were detected using chemiluminescent immunoassay kits (Yhlo Biotech Co.) as we previously reported.^{S10}

Flow cytometry

After blocking with 5% fetal bovine serum (FBS, Thermo Fisher Scientific, Waltham, MA, USA), PBMCs were stained with Zombie Aqua (Biolegend, San Diego, CA, USA) to exclude dead cells. Then, cells were incubated with fluorochrome-labeled antibodies for 30 min at 25°C to label surface marker. Isotype controls were used as negative controls. Fluorescence minus one control for each fluorochrome was used to set the gate for positive populations. Data were analyzed using a BD LSRFortessa™

X-20 (BD Bioscience) instrument and FlowJo software (TreeStar, Ashland, OR, USA) as previously described.^{S6} Details of antibodies used flow cytometry are tabulated in Table S3.

To detect SARS-CoV-2-specific B cells, biotinylated recombinant SARS-CoV-2 Spike RBD protein antigens (BT10500, R&D systems) were individually multimerized with fluorescently labeled streptavidin at 4°C for 1 hour as previously described.^{S11,12} Briefly, recombinant SARS-CoV-2 RBD protein was mixed with AF647-streptavidin (Biolegend) or PerCP5.5-streptavidin (Biolegend) at 2:1 ratio (~4:1 molar ratio) at 4°C for 1 hour. The antigen probes prepared individually as above were then mixed in 50 mM free d-biotin (Macklin) in PBS to reduce cross-reactivity. PE-streptavidin (BioLegend) was used as a decoy probe to gate out SARS-CoV-2 non-specific streptavidin-binding B cells. PBMC (5×10^6) were prepared in U-bottom 96-well plates and stained with 50 μ L of antigen probe cocktail containing 50 ng of RBD and 20 ng of streptavidin-PE at 4°C for 30 min. After washing, cells were then stained with 50 μ L of antigen probe cocktail containing.

Statistical analysis

All statistical analyses were carried out with GraphPad Prism Software v.9.0 (GraphPad Software). Data are presented in dot plots by medians and interquartile ranges unless specifically stated. Data were analyzed by the Mann–Whitney *U*-test or paired-sample *t*-test. For categorical data, chi-squared test or Fisher's exact test was performed. Spearman's rank correlation analysis was used to analyze associations. A

133 P value < 0.05 was considered statistically significant.

REFERENCES:

- S1. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008;63(suppl 86):8-160.
- S2. Zhu R, Wang J, Wu Y, et al. Allergic Rhinitis Control Test questionnaire-driven stepwise strategy to improve allergic rhinitis control: a prospective study. *Allergy* 2016;71:1612-1619.
- S3. Bateman ED, Hurd SS, Barnes PJ, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008;31:143-78.
- S4. Williams HC, Burney PG, Hay RJ, et al. The U. K. Working Party's Diagnostic Criteria for Atopic Dermatitis. I. Derivation of a minimum set of discriminators for atopic dermatitis. *Br J Dermatol* 1994;131:383-396.
- S5. Yao Y, Wang ZC, Wang N, et al. Allergen immunotherapy improves defective follicular regulatory T cells in patients with allergic rhinitis. *J Allergy Clin Immunol* 2019;144:118-128
- S6. Yao Y, Chen Z, Zhang H, et al. Selenium-GPX4 axis protects follicular helper T cells from ferroptosis. *Nat Immunol* 2021;22:1127-1139.
- S7. Song J, Zeng M, Wang H, et al. Distinct effects of asthma and COPD comorbidity on disease expression and outcome in patients with COVID-19. *Allergy* 2021; 2021;76:483-496.
- S8. Jara A, Undurraga EA, Gonzalez C, et al. Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Chile. *N Engl J Med* 2021;385:875-884.

- 156 S9. Tenbusch M, Schumacher S, Vogel E, et al. Heterologous prime-boost vaccination
157 with ChAdOx1 nCoV-19 and BNT162b2. *Lancet Infect Dis* 2021;21:1212-1213.
- 158 S10. Liu L, Chen HG, Li Y, et al. Temporal profiles of antibody responses,
159 cytokines, and survival of COVID-19 patients: A retrospective cohort in Wuhan,
160 China. *Engineering (Beijing)* 2021;7:958-965.
- 161 S11. Dan JM, Mateus J, Kato Y, et al. Immunological memory to SARS-CoV-2
162 assessed for up to 8 months after infection. *Science* 2021;371:eabf4063.
- 163 S12. Zhang H, Liu Y, Liu D, et al. Time of day influences immune response to an
164 inactivated vaccine against SARS-CoV-2. *Cell Research* 2021; 31:1215-1217.

Figure Legends

Figure S1 Changes of SARS-CoV-2 neutralizing antibody, IgG, and IgM levels after inactivated SARS-CoV-2 vaccination. Healthy subjects ($n = 25$) and patients with AR ($n = 32$) were enrolled and received inactivated SARS-CoV-2 vaccine at day 0 and day 30. Peripheral blood was collected at day 0 (baseline), day 7, day 30, day 37, and day 60. **a**, Fold changes of SARS-CoV-2 neutralizing antibody, IgG, and IgM levels normalized to the baseline levels (day 0). Data are analyzed by two-sided paired-sample t -test. **b**, Correlation of the levels of SARS-CoV-2 neutralizing antibody and IgG. Data are analyzed by Spearman's rank correlation. **c**, SARS-CoV-2 neutralizing antibody, IgG, and IgM levels in healthy controls and patients with AR. Data are presented as median and interquartile range and analyzed by Mann–Whitney U -test.

Figure S2 Flow cytometric gating strategy of B cell subsets in human peripheral

bloods. Within viable $CD3^{-}CD19^{+}CD20^{+}$ cells, naive B cells were defined as $CD27^{-}IgD^{+}$, nonswitched memory B cells as $CD27^{+}IgD^{+}$, switched memory B cells as $CD27^{+}IgD^{-}$, and double negative B cells as $CD27^{-}IgD^{-}$. Within viable $CD3^{-}CD19^{+}$ cells, plasmablasts were defined as $CD27^{+}CD38^{++}$.

Figure S3 Circulating B cell subsets at day 60 after inactivated SARS-CoV-2

vaccination. Frequencies of circulating B cell subsets in healthy controls ($n = 25$) and AR patients ($n = 32$) were analysed by flow cytometry. Data are presented as median and interquartile range and analyzed by Mann–Whitney U -test.

Figure S4 Flow cytometric gating strategy of T cell subsets in human peripheral

bloods. Within viable $CD3^{+}CD8^{-}CD4^{+}$ T cells, T_{REG} cells were defined as

$CD25^{high}CD127^{low}$ cells, T_{FR} cells as $CD45RA^{-}CXCR5^{+}T_{REG}$ cells, circulating T_{FH}

cells as $CD25^{-/low}CD45RA^{-}CXCR5^{+}ICOS^{high}PD-1^{high}$ cells, T_{FH1} cells as

$CXCR3^{+}CCR6^{-}T_{FH}$ cells, T_{FH2} cells as $CXCR3^{-}CCR6^{-}T_{FH}$ cells, and T_H17 cells as

$CXCR3^{-}CCR6^{+}T_{FH}$ cells.

Figure S5 Changes of circulating T cell subsets after inactivated SARS-CoV-2 vaccination. **a**, Frequencies of circulating T cell subsets in healthy controls ($n = 25$) and patients with AR ($n = 32$) were analysed by flow cytometry. **b**, Changes of frequencies of T cell subsets at the indicated time points were normalised to the baseline levels and represented as fold changes. Data are presented as median and interquartile range and analyzed by Mann–Whitney U -test. **c**, Correlations of fold changes of T_{FH} cells at day 37 relative to those at day 0 with changes of levels of SARS-CoV-2 IgG and IgM at day 60 relative to those at day 0 in patients with AR. Data are analyzed by Spearman’s rank correlation.

Figure S6 Changes of circulating T_{FH} cell subsets after inactivated SARS-CoV-2

vaccination. a, Frequencies of circulating ICOS^{high}PD-1^{high} T_{FH} cell subsets in healthy controls ($n = 25$) and AR patients ($n = 32$) were analysed by flow cytometry. Data are presented as median and interquartile range and analyzed by Mann–Whitney *U*-test. **b,** Correlations of fold changes of ICOS^{high}PD-1^{high} T_{FH} cell subsets at day 37 relative to those at day 0 with changes of levels of SARS-CoV-2 IgG and IgM at day 60 relative to those at day 0 in patients with AR. Data are analyzed by Spearman's rank correlation.

212 **Table S1 Adverse events related to COVID-19 vaccination**

	First dose			Second dose		
	Healthy subjects (<i>n</i> = 25)	AR patients (<i>n</i> = 32)	<i>p</i> value	Healthy subjects (<i>n</i> = 25)	AR patients (<i>n</i> = 32)	<i>p</i> value
Participants with adverse events, <i>n</i> (%)	10 (40%)	13 (43.8%)	0.962	9 (36%)	11 (34.4%)	0.899
Injection site symptom						
Pain, <i>N</i> (%)	9 (36%)	10 (31.2%)	0.706	8 (32%)	7 (21.9%)	0.389
Redness, <i>N</i> (%),	1 (4%)	4 (12.5%)	0.513	1 (4%)	3 (9.4%)	0.790
Swelling, <i>N</i> (%)	1 (4%)	2 (6.3%)	0.826	0	2 (6.3%)	0.499
Systematic symptom						
Fever, <i>N</i> (%)	0	2 (6.3%)	0.499	0	0	-
Fatigue, <i>N</i> (%)	4 (16%)	8 (25%)	0.408	1 (4%)	4 (12.5%)	0.513
Headache, <i>N</i> (%)	1 (4%)	1 (3.1%)	1.000	0	1 (3.1%)	1.000
Myalgia, <i>N</i> (%)	3 (12%)	4 (12.5%)	0.727	1 (4%)	1 (3.1%)	1.000
Digestive symptom						
Diarrhea, <i>N</i> (%)	0	0	-	0	0	-
Vomiting, <i>N</i> (%)	0	0	-	0	0	-
Nausea, <i>N</i> (%)	0	0	-	0	1 (3.1%)	1.000
Respiratory symptom						
Runny nose, <i>N</i> (%)	0	1 (3.1%)	1.000	0	1 (3.1%)	1.000
Cough, <i>N</i> (%)	0	0	-	0	0	-
Stuffy nose, <i>N</i> (%)	0	1 (3.1%)	1.000	0	1 (3.1%)	1.000
Sore throat, <i>N</i> (%)	1 (4%)	2 (6.3%)	0.826	0	0	-
Allergic symptom						
Pruritus, <i>N</i> (%)	1 (4%)	1 (3.1%)	1.000	0	1 (3.1%)	1.000

Hives, N (%)	0	0	-	0	0	-
Itchy throat, N (%)	0	0	-	0	0	-
Swelling of mouth or throat, N (%)	0	0	-	0	0	-
Shortness of breath, N (%)	0	0	-	0	0	-
Anaphylaxis, N (%)	0	0	-	0	0	-

213 AR, allergic rhinitis

214

215 **Table S2 Demographic characteristics of recovered COVID-19 cases**

	Without AR	With AR	<i>p</i> value
Total subjects, n	64	14	-
Gender, male/female	10/54	2/12	0.777
Age (years)	31 (27, 36)	29 (27, 32)	0.849
Patients with asthma, n (%)	0	1 (7.1%)	0.180
Patients with atopic eczema, n (%)	0	1 (7.1%)	0.180
Disease severity			
Mild, n (%)	18 (28.1%)	3 (21.4%)	0.858
Moderate, n (%)	46 (71.9%)	11 (78.5%)	0.858
Sampling time after symptom onset (months)	11 (11, 12)	11 (11, 12)	0.635

216 For continuous variables, data are expressed as medians and interquartile ranges. AR,

217 allergic rhinitis

218

219 **Table S3 Antibodies used for flow cytometry**

Antibody	Parameter	Clone ID	Source	Isotype	Manufacturer	Dilution
CCR6	PE	G034E3	mouse	IgG2b, κ	Biolegend (San Diego, CA, USA)	1:100
CCR7	Alexa Fluor® 647	G043H7	mouse	IgG2a κ	Biolegend	1:100
CXCR3	PE-Cy7	G025H7	mouse	IgG1, κ	Biolegend	1:100
CXCR5	BB515 (FITC)	RF8B2	Rat	IgG2b, κ	BD Biosciences (San Jose, CA, USA)	1:100
CD127	Brilliant Violet 711	A019D5	mouse	IgG1, κ	Biolegend	1:100
CD19	Alexa Fluor® 700	H1B19	mouse	IgG1, κ	Biolegend	1:200
CD20	Brilliant Violet 785	2H7	mouse	IgG2b, κ	Biolegend	1:200
CD25	APC-Cy7	BC96	mouse	IgG1, κ	Biolegend	1:50
CD27	PE-Cy7	M-T271	mouse	IgG1, κ	Biolegend	1:100
CD3	Brilliant Violet 711	OKT3	mouse	IgG2a, κ	Biolegend	1:200
CD38	BB515 (FITC)	HIT2	mouse	IgG1, κ	Biolegend	1:200
CD4	Brilliant Violet 605	RPA-T4	mouse	IgG1, κ	Biolegend	1:200
CD45RA	PerCP-Cy5.5	HI100	mouse	IgG2b, κ	Biolegend	1:200
CD8	Alexa Fluor® 700	RPA-T8	mouse	IgG1, κ	Biolegend	1:200
ICOS	Brilliant Violet 785	C398.4A	Armenian Hamster	IgG	Biolegend	1:100
IgD	APC-Cy7	IA6-2	mouse	IgG2a, κ	BD Biosciences	1:200
IgG	Brilliant Violet	M1310G05	Rat	IgG2a, κ	Biolegend	IgG1, κ

421

IgM	Brilliant Violet 605	MHM-88	Mouse	IgG1, κ	IgG1, κ	IgG1, κ
PD-1	Brilliant Violet 421	EH12.2H7	mouse	IgG1, κ	IgG1, κ	1:100

220 PE, phycoerythrin; APC, allophycocyanin; PerCP, peridinin chlorophyll protein

221 complex; FITC, fluorescein isothiocyanate.

Figure S1

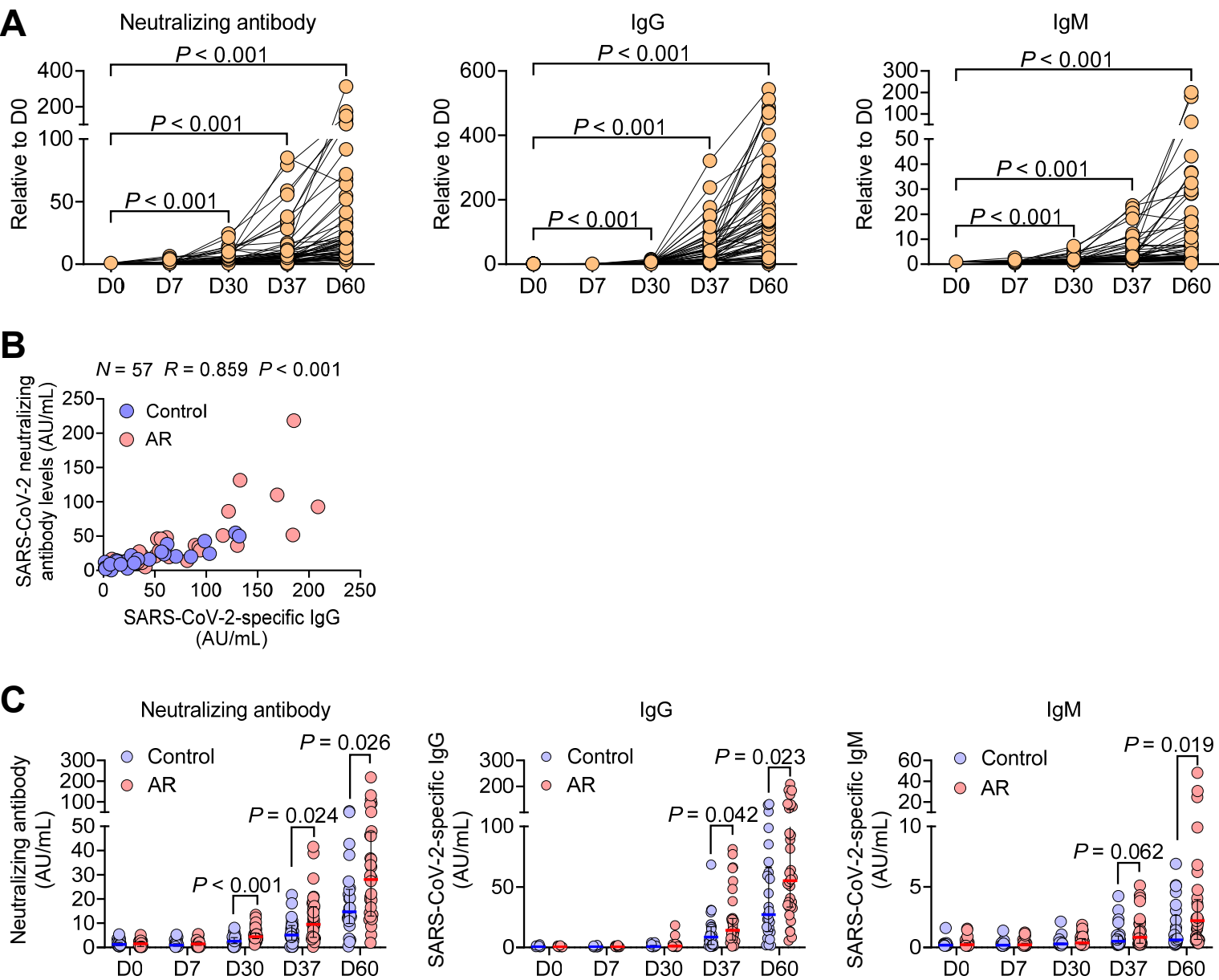


Figure S2

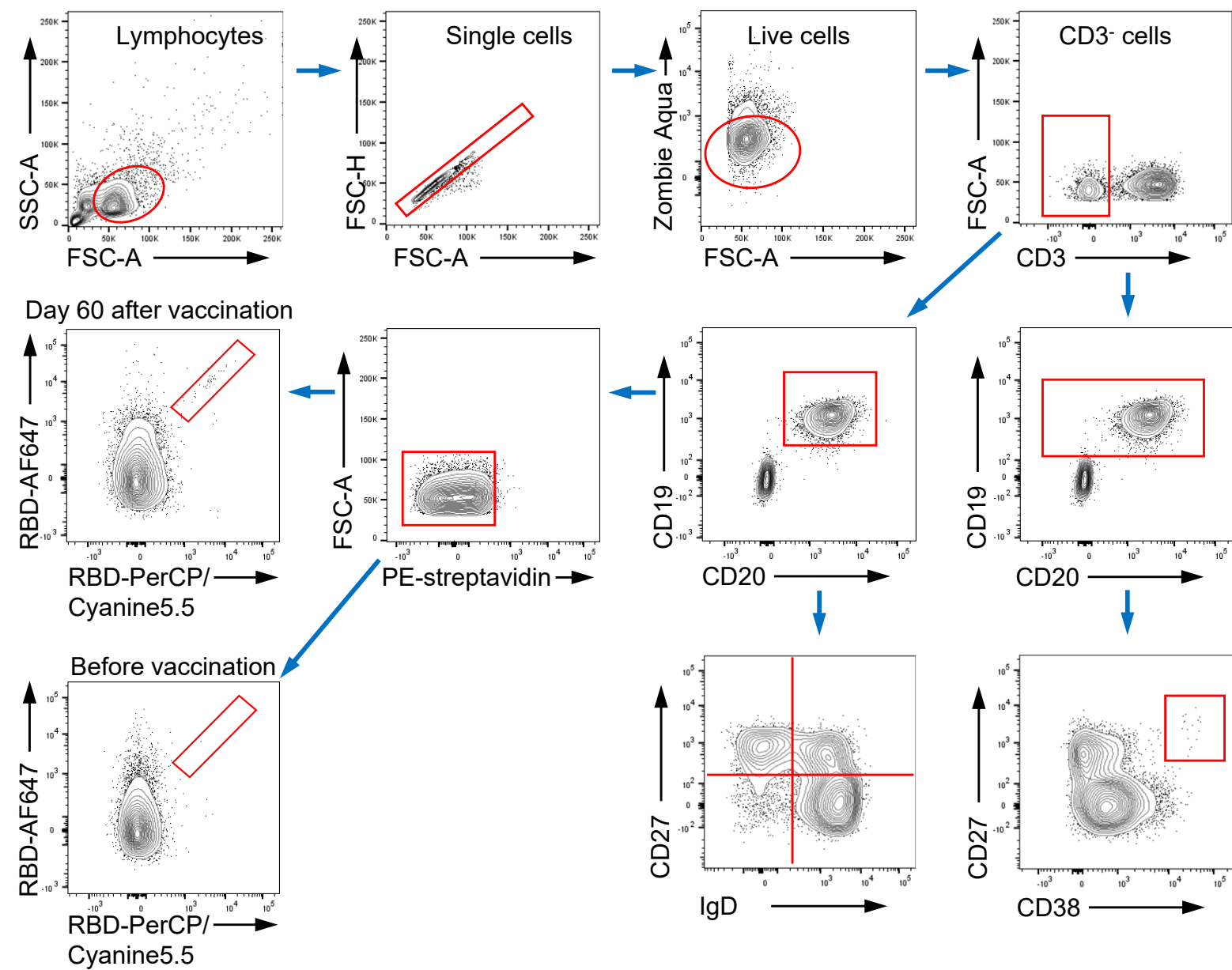
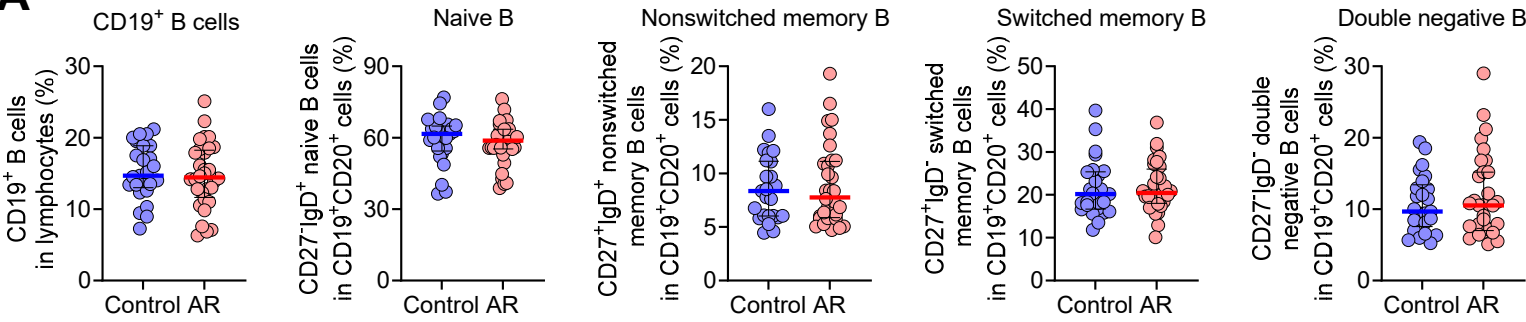


Figure S3

A



B

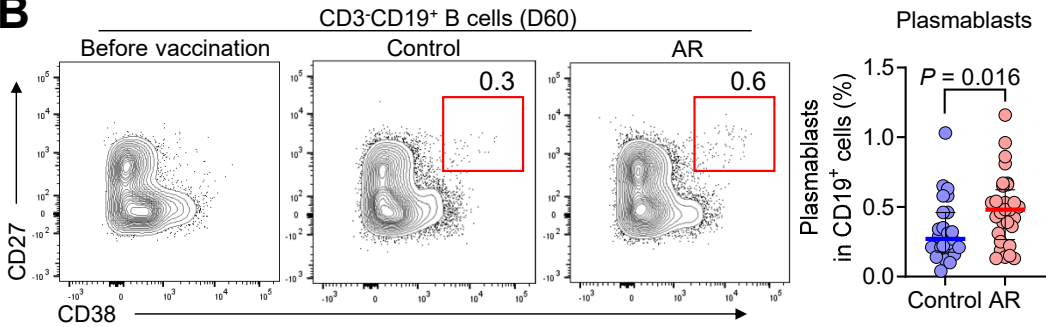


Figure S4

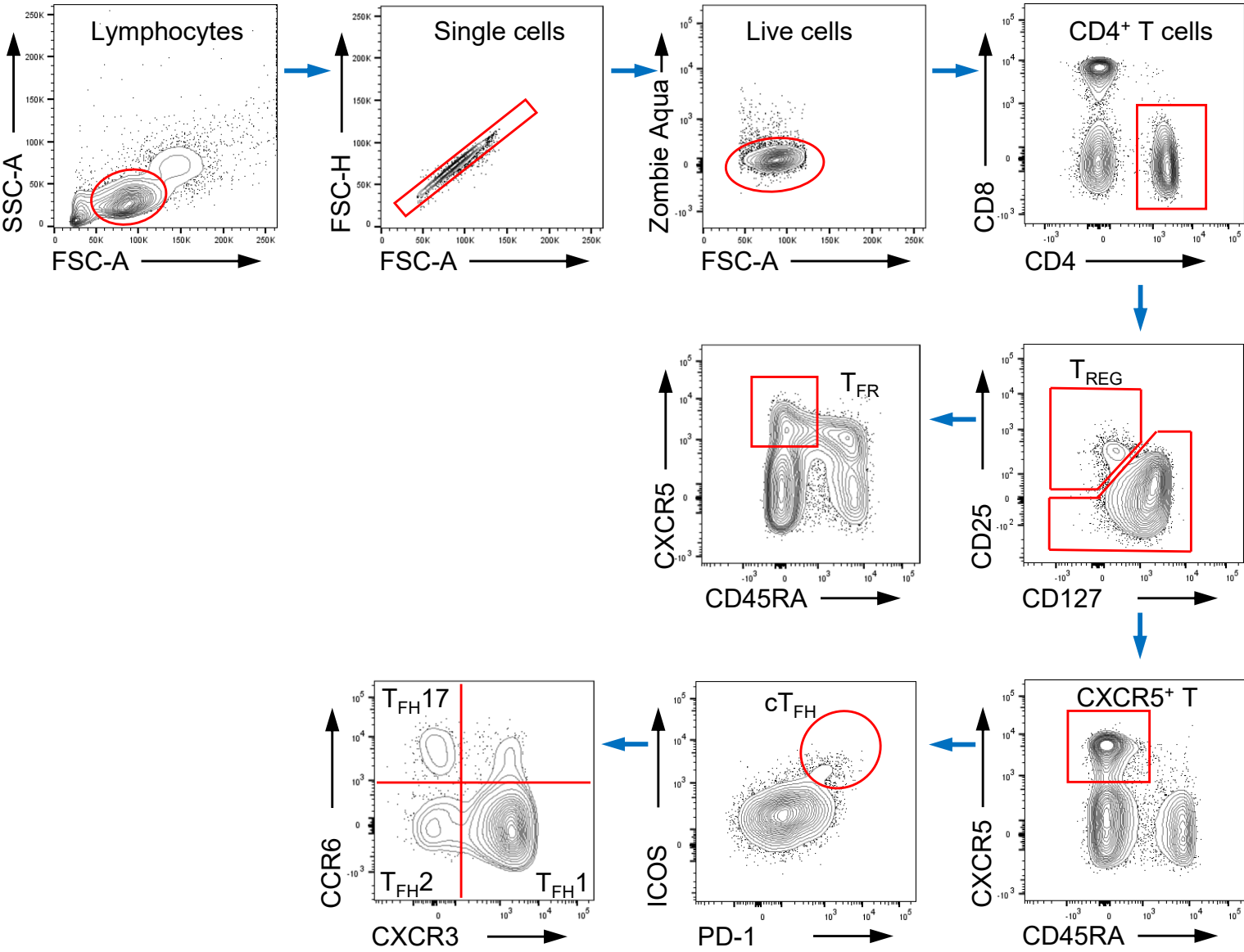


Figure S5

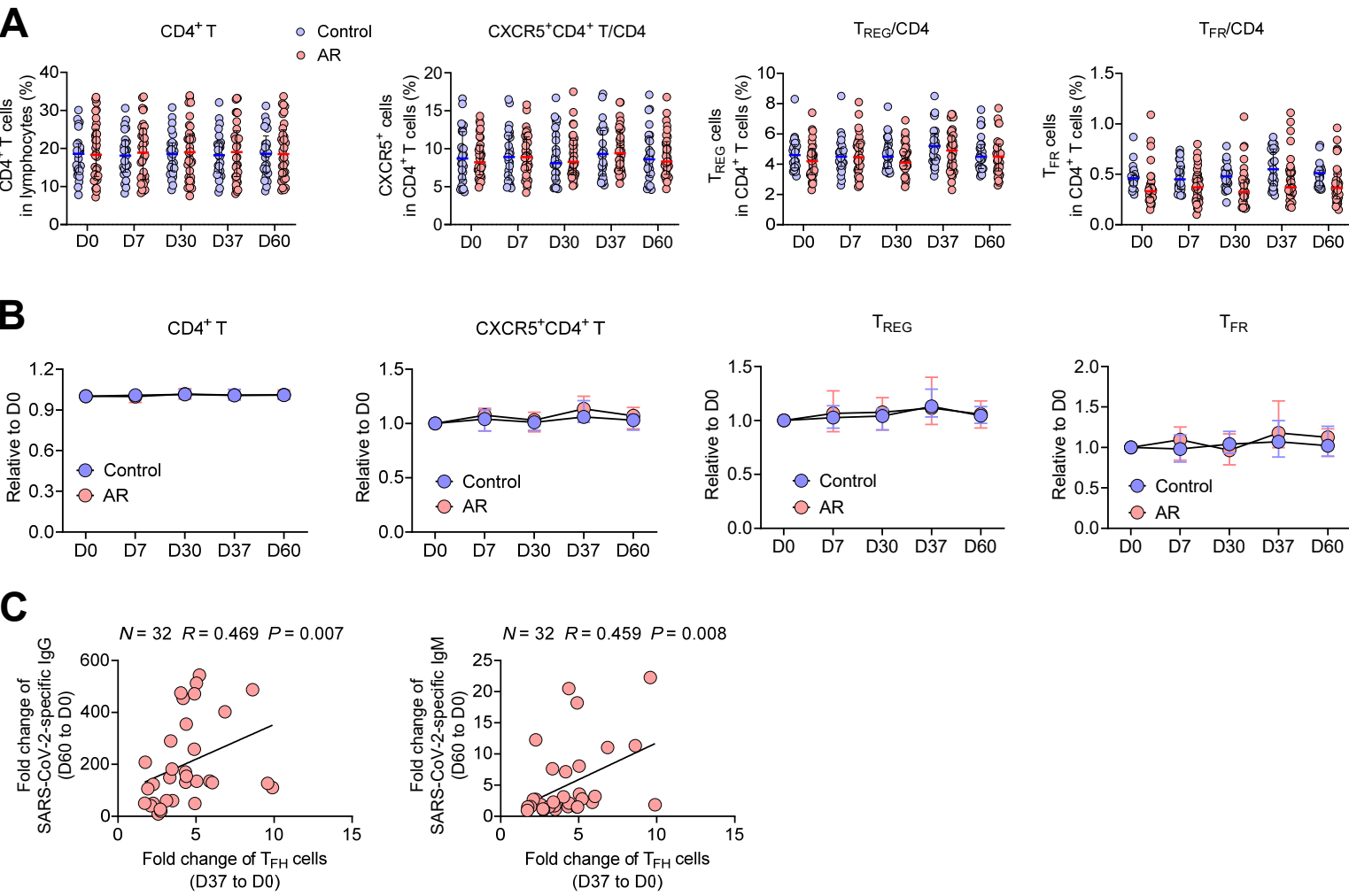
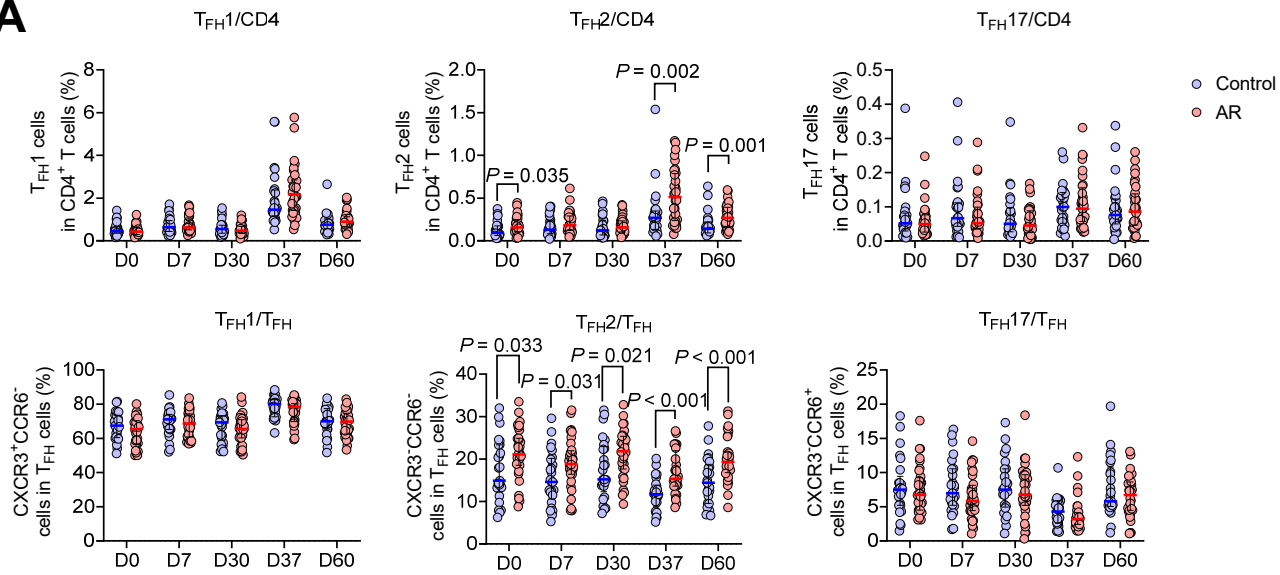


Figure S6

A



B

