Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Distinct B and NKT cell responses shape the delayed response to ChAdOx1 nCoV-19 vaccine in end-stage renal disease

Dear Editor,

Tang and colleagues conducted a meta-analysis of solid organ transplant recipients and reported, in this Journal, significantly lower anti-SARS-CoV-2 IgG seroconversion rates than healthy control following mRNA vaccine inoculation (1). Increased concerns are directed toward immunocompromised patients who responded poorly to SARS-CoV-2 vaccination, as they are predisposed to higher morbidity and mortality when contracted Coronavirus disease-19 (COVID-19) (2). Similarly, patients with end-stage renal disease (ESRD) showed a blunted response to SARS-CoV-2 vaccination, with reported response rates of 96% to as low as 29%, even after two doses of vaccination (reviewed by Yen et al. (3)), and the antibody titer (AT) generated is significantly lower than healthy individuals receiving the same vaccine (4). Studies of response to SARS-CoV-2 vaccination in the ESRD cohort mainly employed the mRNA vaccine platform and observed humoral immune responses (3). Less is known about the role of cellular immunity.

This study aimed to unravel the kinetics of immune response following vaccination with the ChAdOx nCOV-19 (AstraZeneca), an adenovirus-vectored vaccine, in an ESRD cohort with maintenance dialysis. Peripheral blood was collected from 53 patients at four time-points (**Supplementary Figure S1**). Time 0 (T0), 0–7 days before the first dose of vaccine, and Time 1 (T1) taken 14–20 days after the first dose of vaccine. Time 2 (T2) was taken day 0–4 before the second dose of vaccine. Given the recommended ChAdOx nCOV-19 dosing interval of 8–10 weeks, the T2 blood was drawn approximately 70 days following the T0 sampling. Lastly, Time 3 (T3) was taken on days 21–35 following the second dose of vaccine (about 28 days after the T2 sampling). Anti-SARS-CoV-2 IgG quantification was determined using a chemiluminescent microparticle immunoassay (SARS-CoV-2 IgG II Quant assay on an ARCHITECHT analyzer, Abbott) according to the manufacturer's protocol. An AT of $\geq$50 arbitrary units per milliliter (AU/mL) was considered a positive antibody response. We observed 32 patients who showed positive AT response (termed as responder group). Instead, 21 patients (40%) did not yield positive AT (termed as delayed responder, DR following the first dose of vaccination (T2) (**Fig. 1A**). There was no significant difference in clinical and demographic characteristics among the two groups (**Table 1**). Most DR..... eventually showed improvement of the AT after the second dose of vaccination (T3). However, the AT was lower quantitatively than that of the responders (**Fig. 1B).** The antibody response from two patients (3.78%) remained negative despite two vaccination doses.

Additionally, peripheral blood mononuclear cells (PBMCs) were collected at the T2 and incubated with or without the presence of recombinant SARS-CoV-2 S protein (SP) (BioLegend) to mimic immune cell response following SARS-CoV-2 infection, and later subjected to flowcytometry assay. Following the first dose of the vaccine, the studied immune cell profile, including B cells, NK cells, total T cells, and Th and Tc cells, did not differ between antibody response groups (data not shown). Despite the antibody response, early active ($CD69^+$) B and T cells were increased following the SP challenge. The responder group exhibited a significant increase of total B cells and early active NK and Tc cells **(Fig. 1C)**. On the other hand, the DR..... group revealed no rise in B cells and Tc cells, suggesting inadequately articulated cellular immune response following vaccination. Instead, the DR..... group exhibited a unique expansion of NKT subsets, including the early active NKT, cytotoxic NKT, as well as total NKT cell counts (**Fig. 1D**). A separate investigation on the non-responders is provided in the supplementary materials.

The current information on vaccine immunogenicity in the ESRD cohort is mainly derived from mRNA vaccines, with scarce evidence from other vaccine platforms (5). Ancillary factors include age, lymphocyte count (4), ethnicity, the length of the on-dialysis period, the serum albumin level, and the use of immunosuppressive therapy (5, 6) have been reported to shape the dynamic of antibody response.

Tight regulation of T and B cell responses is key to long-lasting immunity against the virus. In a phase 1/2 clinical trial of ChAdOx1 nCoV-19 among the healthy population, a single vaccine dose induced a Th1-biased response, followed by Tc cells of monofunctional, polyfunctional, and cytotoxic phenotypes (7). We did not find a prominent Th1 response even among the responders in our ESRD cohort, possibly pointing out a discrepancy in immune cell capacity. Contrary to the responders, an inadequacy in neutralizing the humoral immune response in the DR..... group may accentuate the activation of NKT cells, a critical process in immunogenicity maturation following the antigen stimulation (8). Studies have proposed important roles of NKT cells during SARS-CoV-2 infection, notably during the acute phase. It promotes viral clearance through direct cytotoxicity and the mediation of the antibody-dependent cell-mediated cytotoxicity effect (9). Noticeable decreases of NKT cells are observed in patients with severe COVID-19 and may serve as a biomarker for outcome prediction (10).

The present study measured the immune response as expression of representative markers of each cell, indicating approximate cell numbers in the studied PBMC population. However, this approach could not precisely describe the function of the immune cells, and further studies are needed to enrich the information.

Abbreviations: AT, antibody titer; DR, delayed responders; ESRD, end-stage renal disease; PBMC, peripheral blood mononuclear cells; SP, S protein; URR, urea reduction ratio.

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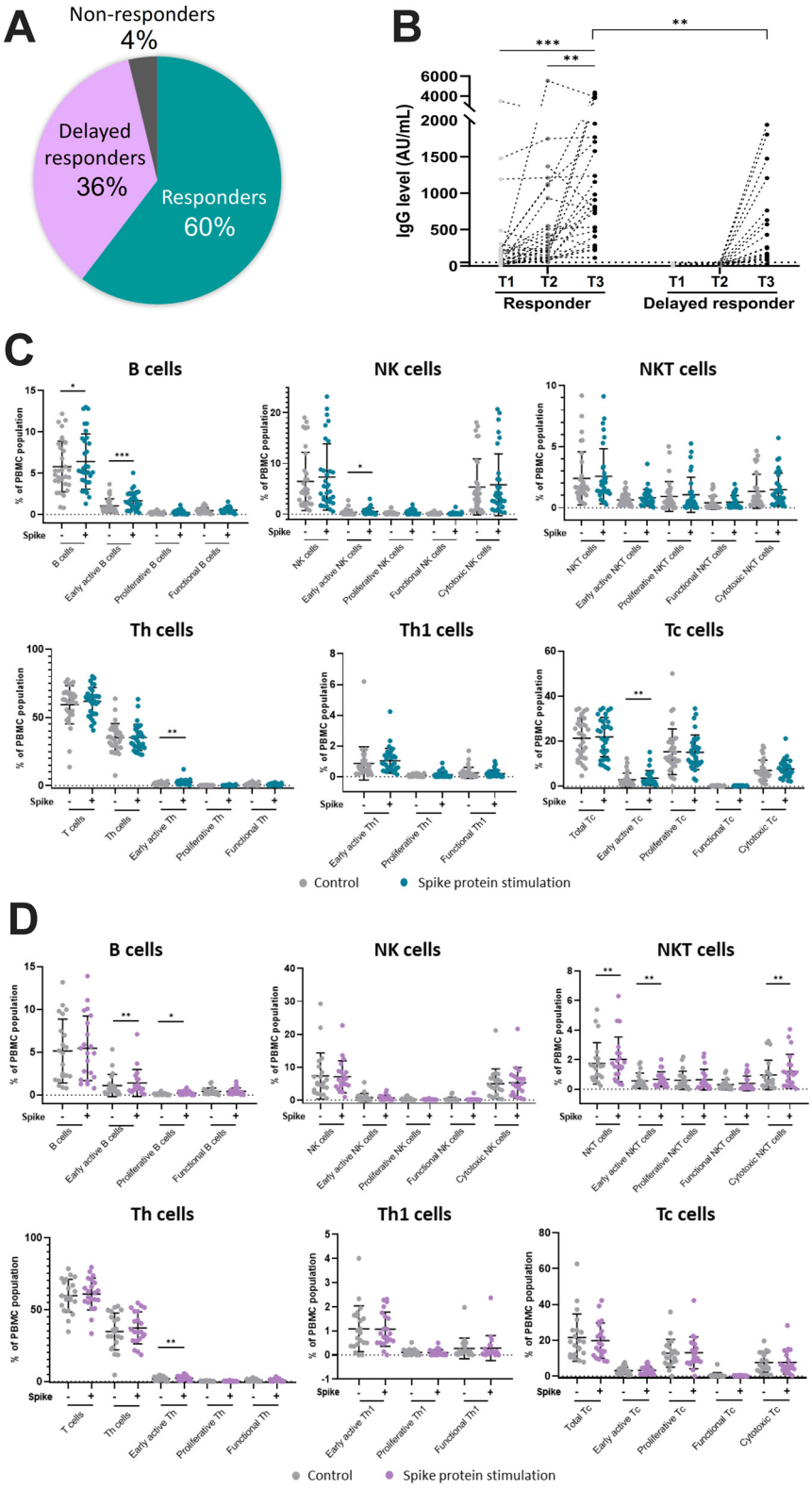

In an ESRD cohort, the study revealed a substantial proportion (40%) of patients showing suboptimal AT until the second vaccination dose, while 3.7% ($n = 2$) were non-responders to two doses of vaccine. SP challenge triggered activation of circulating $CD69^{+}$ B and T cells. The responder group elicited prominent increase of B and early active Tc cells, while the DR..... group interestingly showed an increased number of NKT cell population. Despite the minimal antibody response to vaccination, the understanding of early immune cell activation sparked a notion of potential attempt to modulate the cellular immune response, notably in immunocompromised individuals. Our findings also highlighted the concern of impaired immune response in this population and necessitated the need for a thorough discussion on current and future vaccination programs. A globally

Table 1
Demographic and clinical characteristics of the 53 patients of end-stage renal disease.

	Responders $n = 32$	Delayed responders $n = 19$	Non-responders #26	#40
Age (year)	64.3 ± 10.3	66.0 ± 12.2	85	81
Sex			Male	Male
Female n (%)	14 (43.8)	5 (26.3)		
Male n (%)	18 (56.3)	14 (73.7)		
Body mass index (kg/m^2)	23.8 ± 4.7	24.0 ± 3.9	23.14	27.3
Kt/V	1.59 ± 0.22	1.64 ± 0.22	1.17	1.68
URR (%)	74.3 ± 4.1	75.1 ± 4.0	64.89	76.19
D-dimer (mg/L FEU)	2.0 ± 2.7	1.4 ± 1.3	1.48	1.44
Ferritin (ng/ml)	314.0 ± 257.1	354.1 ± 265.2	626.7	11,104
Uric acid (mg/dl)	7.6 ± 1.9	7.0 ± 1.6	8.7	8
Hemoglobin (g/dl)	10.7 ± 0.7	10.0 ± 1.3	10.7	10.4
Albumin (g/dl)	3.8 ± 0.3	3.7 ± 0.3	4	3.6
Diabetes Mellitus n (%)	16 (50.0)	9 (47.4)	Yes	No
Hypertension n (%)	29 (90.6)	17 (89.5)	Yes	Yes
Dialysis vintage (year)	6.6 ± 5.3	6.7 ± 6.9	8	5.6

URR, urea reduction ratio. Data on the responders and delayed responders were presented as mean±SD. No statistical difference of the studied parameters was observed among the two groups.

coordinated and standardized method to analyze the seroconversion and immune cell activation following vaccination is also prompted.

Ethical statement

The Joint Institutional Review Board of Taipei Medical University approved this retrospective study, and informed consent was obtained from each participant (TMU-JIRB N202106049).

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Declaration of Competing Interest

The authors declare no competing interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.02.027.

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Denise Utami Putri
Pulmonary Research Center, Wan Fang Hospital, Taipei Medical University, Taipei 116081, Taiwan
Division of Pulmonary Medicine, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei 116081, Taiwan

Chiou-Feng Lin
Department of Microbiology and Immunology, School of Medicine, College of Medicine, Taipei Medical University, Taipei 110301, Taiwan
Core Laboratory of Immune Monitoring, Office of Research and Development, Taipei Medical University, Taipei 110301, Taiwan
Graduate Institute of Medical Sciences, College of Medicine, Taipei Medical University, Taipei, 110301, Taiwan
International Ph.D. Program in Cell Therapy and Regenerative Medicine, College of Medicine, Taipei Medical University, Taipei, 110301, Taiwan

Ching-Sheng Hung
Ph.D. Program in Medical Biotechnology, College of Medical Science and Technology, Taipei Medical University, Taipei 110301, Taiwan
Department of Laboratory Medicine, Wan Fang Hospital, Taipei Medical University, Taipei 116081, Taiwan

Chun-Kai Huang
Department of Laboratory Medicine, Wan Fang Hospital, Taipei Medical University, Taipei 116081, Taiwan
School of Medical Laboratory Science and Biotechnology, College of Medical Science and Technology, Taipei Medical University, Taipei 110301, Taiwan

Tsong-Yih Ou
Division of Infectious Diseases, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei 116081, Taiwan
Division of Infectious Diseases, Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei 110301, Taiwan

Chun-Yi Lai, Po-Chun Tseng
Department of Microbiology and Immunology, School of Medicine, College of Medicine, Taipei Medical University, Taipei 110301, Taiwan
Core Laboratory of Immune Monitoring, Office of Research and Development, Taipei Medical University, Taipei 110301, Taiwan

Chung-Yi Cheng**
Taipei Medical University Research Center of Urology and Kidney, Taipei 110301, Taiwan
Division of Nephrology, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei 116081, Taiwan
Division of Nephrology, Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei 110301, Taiwan

Chih-Hsin Lee*
Pulmonary Research Center, Wan Fang Hospital, Taipei Medical University, Taipei 116081, Taiwan
Division of Pulmonary Medicine, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei 116081, Taiwan
Division of Pulmonary Medicine, Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei 110301, Taiwan

*Corresponding authors at: Tuberculosis Center and Pulmonary Research Center, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan, 111, Sec. 3, Xinglong Rd., Wenshan Dist., Taipei 116081, Taiwan, R.O.C.
**Co-corresponding author at: Division of Nephrology, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan, 111, Sec. 3, Xinglong Rd., Wenshan Dist., Taipei 116081, Taiwan, R.O.C.
E-mail addresses: 94426@w.tmu.edu.tw (C.-Y. Cheng), chleetw@tmu.edu.tw (C.-H. Lee)