
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.

# Disparity between levels of anti-RBD IgG and anti-nucleocapsid protein IgG antibodies in COVID-19–recovered patients who received a kidney transplant

**To the editor:** We read with great interest the study by Chavarot *et al.*,[1] which demonstrated that anti–severe acute respiratory syndrome coronavirus disease 2 (SARS-CoV-2) anti-nucleocapsid (N) protein IgG declines rapidly following SARS-CoV-2 infection in patients who received a kidney transplant (KTx-pts), independent of illness severity, but did not address the dynamic interplay with IgG antibodies against the spike protein–receptor binding domain (spike-RBD).

We studied 25 KTx-pts and 23 normal control patients, all of whom had nasopharyngeal coronavirus disease 2019 (COVID-19) confirmed by reverse transcription polymerase chain reaction (1 control patient confirmed by blood enzyme-linked immunosorbent assay [ELISA]) and subsequently tested negative for SARS-CoV-2 and recovered. All patients had stable engraftments for an average of 18.6 months (1–52 months) at the time of viral infection.

We used multiplexed microsphere-based assays for the detection of IgG antibodies against the viral N protein and spike-RBD. Most KTx-pts (22 of 25; 88%) were positive for anti–spike-RBD IgG antibodies, and only 28% were positive for anti-N IgG antibodies (Figure 1a and Supplementary Table S1). All 23 controls developed both anti-N and anti-RBD IgG antibodies (Supplementary Figure S1A). In a subgroup of KTx-pts (n = 12), in which both age (54.5 years old) and infection time (35.8 days) were comparable to a subgroup of control patients (n = 16), we found that although the levels of anti-RBD IgG antibodies were very heterogenous, they were not statistically different from those of normal control patients ($P = 0.60$). Levels of anti-N IgG antibodies in patients who received a transplant, on the other hand, were significantly reduced, when compared to those of the control patients ($P = 0.0022$) or compared to the level of anti-RBD IgG in the same group of patients who received a transplant ($P = 0.0449$). This result (Supplementary Figure S1B) suggests that anti-N IgG antibodies, but not anti-RBD IgG antibodies, were predominately affected in KTx-pts.

Longitudinal analyses of anti-N and anti–spike-RBD antibodies were studied in 6 KTx-pts with multiple sera samples available. Figure 1b shows heterogenous yet rapid induction of anti-RBD IgG antibodies, with persistence for at least 100 days (median fluorescence intensity [MFI] >700) and still present at 200 days in 4 patients. However, significantly lower levels of anti-N antibodies were produced, and by day 100, only 1 patient had anti-N IgG antibodies. This patient was noted to have pre-existing anti-N IgG antibodies detected 138 days prior to SARS-CoV-2 infection, consistent with previous exposure to another type of epitope–sharing corona viruses.[2]

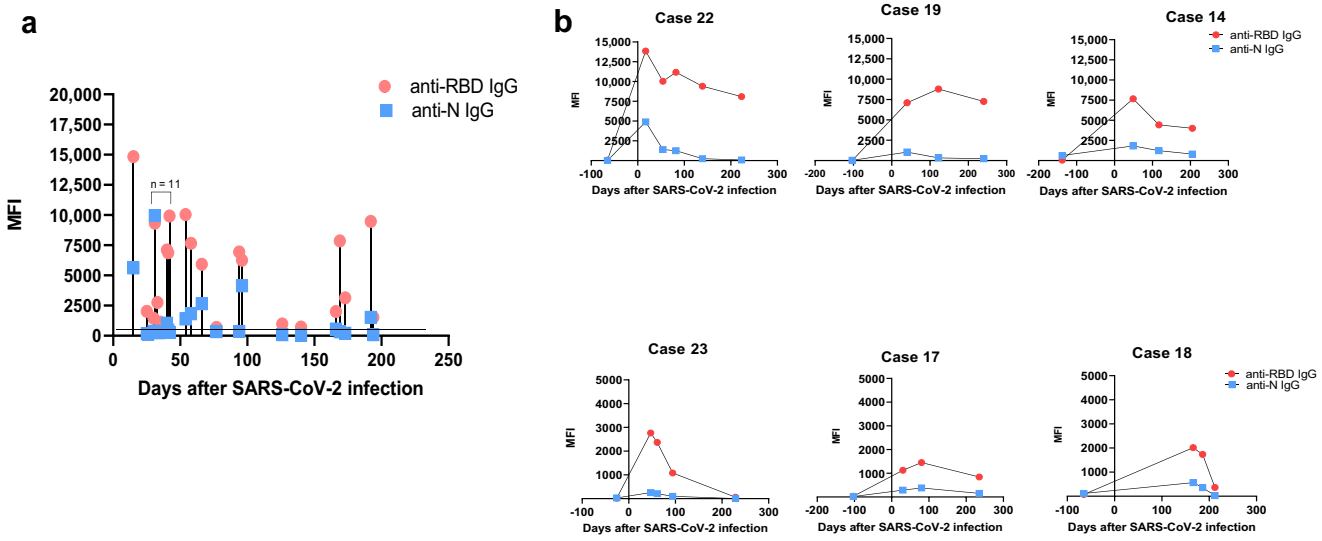


**Figure 1 |** (**a**) Detection of anti-nucleocapsid (N) IgG and anti–receptor binding domain (RBD) IgG antibodies in coronavirus disease 2019 (COVID-19)–recovered kidney transplant patients (KTx-pts). A total of 25 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–positive patients were tested by multiplexed microsphere-based SARS-CoV-2 IgG assays (Luminex Corps). Results are shown as median fluorescence intensity (MFI). The positive threshold (700 MFI) is represented by a horizontal line for both IgG antibodies; each patient is represented by a vertical line. Scatter plot analysis elucidates the level of both types of IgG antibodies at the time (days) of post-COVID confirmation for each patient. (**b**) Longitudinal analysis of anti-viral IgG antibodies in 6 KTx-pts. Samples were analyzed for the presence of anti-N IgG and anti-RBD IgG antibodies after SARS-CoV-2 infection at different time points. For each patient, a sample taken prior to their exposure to SARS-CoV-2 (before February 2020) was used as an internal control, with a value typically <100 MFI. Day 0 is designated as the day the SARS-CoV-2 infection was confirmed. Antibody positivity was set as previously described. Except for 1 patient (case 14) who had underdetectable (656 MFI) anti-N IgG antibodies on a pre-pandemic date, no other patients had pre-existing anti-N or anti-RBD IgG antibodies.

Even with different methodologies, our results are consistent with the findings of Chavarot *et al.*[1] that anti-N protein IgG was induced in KTs-pts and that these antibodies rapidly decline over time. SARS-CoV-2 N protein shares a high degree of amino acid identity with SARS-CoV (90%) and Middle East respiratory syndrome (MERS)–CoV (45%). The role of immunodominant anti-N IgG antibodies in providing protective antiviral immunity is currently unknown. By comparing levels of anti-N antibodies with those of concurrent anti-RBD antibodies over a prolonged period in patients who received a transplant, our findings provide a rare opportunity to look into the immunologic dynamics of these individuals, further extending current understanding of the anti–SARS-CoV-2 immune response in immunocompromised patients. In summary, our results clearly demonstrate a disparity between the levels of anti-N and anti-RBD IgG antibodies in COVID-19–recovered post-transplant patients. Our findings of persistence of anti-RBD IgG antibodies suggest that patients who recovered from a transplant may have developed long-lasting anti-RBD IgG antibodies, with a potential neutralizing effect against common strains[3] or some of the new SARS-CoV-2 variants.[4] Larger studies are needed to estimate the degree of acquired protection against reinfection.

**SUPPLEMENTARY MATERIAL**

Supplementary File (PDF)

**Table S1.** Cohort of coronavirus disease 2019 (COVID-19)–recovered kidney transplant patients (KTx-pts). Forty-one KTx-pts positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) between March 2020 and January 2021 were retroactively identified through Columbia University Irving Medical Center (CUIMC) medical records. The study was approved by the Columbia University Institutional Review Board. Availability of patients' (n = 25) post-infection samples were identified through HistoTrac Software. Positivity for both anti–receptor binding domain (RBD) and anti-nucleocapsid (N) IgG antibodies was preset to 700 median fluorescence intensity (MFI) by the manufacturer. ^Second or more graft recipient; CAD, cadaver donor; LRD, living related donor; LUD, living unrelated donor; na, not available.

**Figure S1.** (**A**) Detection of anti-nucleocapsid (N) IgG and anti–receptor binding domain (RBD) IgG antibodies in coronavirus disease 2019 (COVID-19)–recovered controls. A group of 23 were similarly tested by multiplexed microsphere-based severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) IgG assays. The positive threshold (a vertical line) is as previously described; each individual is represented by a vertical line. (**B**) Decrease in the development of anti-N IgG antibodies in COVID-19–recovered patients who received a kidney transplant (KTx-pts), but not in recovered control patients. Levels of anti-N IgG and anti–spike-RBD IgG in 13 recovered KTx-pts were compared to those in a group of recovered control patients (n = 16) who had a similar age and infection time. Average (range) age for the patient group was 54.5 years (37–72 years); for the control group, the average (range) age was 55.8 years (30–76 years). Average (range) infection days for the patient group was 35.8 days (15–38 days); for the control group, average (range) infection days was 39.1 days (9–36 days). Statistics were performed with the Mann-Whitney test using Graphpad Prism Software. *Significant; **very significant; NR, normal recovered controls; ns, not significant; Tx, KTx-pts.


1. Chavarot N, Leruez-Ville M, Scemla A, et al. Decline and loss of anti–SARS-CoV-2 antibodies in kidney transplant recipients in the 6 months following SARS-CoV-2 infection. *Kidney Int*. 2021;99:486–488.
2. Chia WN, Tan CW, Foo R, et al. Serological differentiation between COVID-19 and SARS infections. *Emerg Microbes Infect*. 2020;9:1497–1505.
3. Wajnberg A, Amanat F, Firpo A, et al. Robust neutralizing antibodies to SARS-CoV-2 infection persist for months. *Science*. 2020;370:1227–1230.
4. Wang P, Nair MS, Liu L, et al. Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. *Nature*; 2021.



Chih-Chao Chang[1], George Vlad[1], Elena-Rodica Vasilescu[1], Syed A. Husain[2,3], Ya Nan Liu[1], Wei-Zen Sun[4], Ming-Fu Chang[5], Nicole Suciu-Foca[1] and Sumit Mohan[2,3]

*[1]Department of Pathology and Cell Biology, Columbia University Irving Medical Center, New York, New York, USA; [2]Department of Medicine, Division of Nephrology, Columbia University Irving Medical Center, New York, New York, USA; [3]Department of Epidemiology, The Columbia University Renal Epidemiology (CURE) Group, Columbia University, New York, New York, USA; [4]Department of Anesthesiology, National Taiwan University Hospital, Taipei, Taiwan; and [5]Institute of Biochemistry and Molecular Biology, National Taiwan University, Taipei, Taiwan*

**Correspondence:** *Chih-Chao Chang, Department of Pathology and Cell Biology, Columbia University Irving Medical Center, 630 West 168th Street, VC15-204, New York, New York 10032 USA. E-mail: cc55@cumc.columbia.edu*



*Kidney International* (2021) **100,** 240–241; https://doi.org/10.1016/j.kint.2021.04.018




# The PMDA's view on the limited pipeline of nephrology drugs in Japan

**To the editor:** We truly appraise the article by Barisoni *et al.* introducing several actions to grow clinical trial infrastructures and calling on the nephrology community to collaborate with patients, clinicians, pathologists, industries, and regulatory agencies.[1] Herein, we would like to share the recent situations of nephrology drugs in Japan.

A retrospective analysis of the new active substances[2] approved in Japan between 2008 and 2020 revealed that nephrology had the smallest number of new active substances among 10 internal medicine specialties (Figure 1). None of those was indicated for kidney diseases themselves or orphan diseases. These results reminded us that drug development in nephrology has been left behind that in other medical specialties, and future drug development should focus more on kidney diseases, such as glomerular diseases. In Japan, end-stage kidney disease involves a serious economic burden to the national medical insurance system, and approximately 4% of the total medical cost is being expensed for dialysis. As a recent update of kidney failure definition in clinical trials by the International Society of Nephrology,[3] further improvements in clinical end points will be needed to facilitate drug development.

Our primary mission is to make truly effective drugs available for patients adequately and timely. We will support