

CORRESPONDENCE

Multiorgan and Renal Tropism of SARS-CoV-2

TO THE EDITOR: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) preferentially infects cells in the respiratory tract,^{1,2} but its direct affinity for organs other than the lungs re-

mains poorly defined. Here, we present data from an autopsy series of 27 patients (see the clinical data in Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM

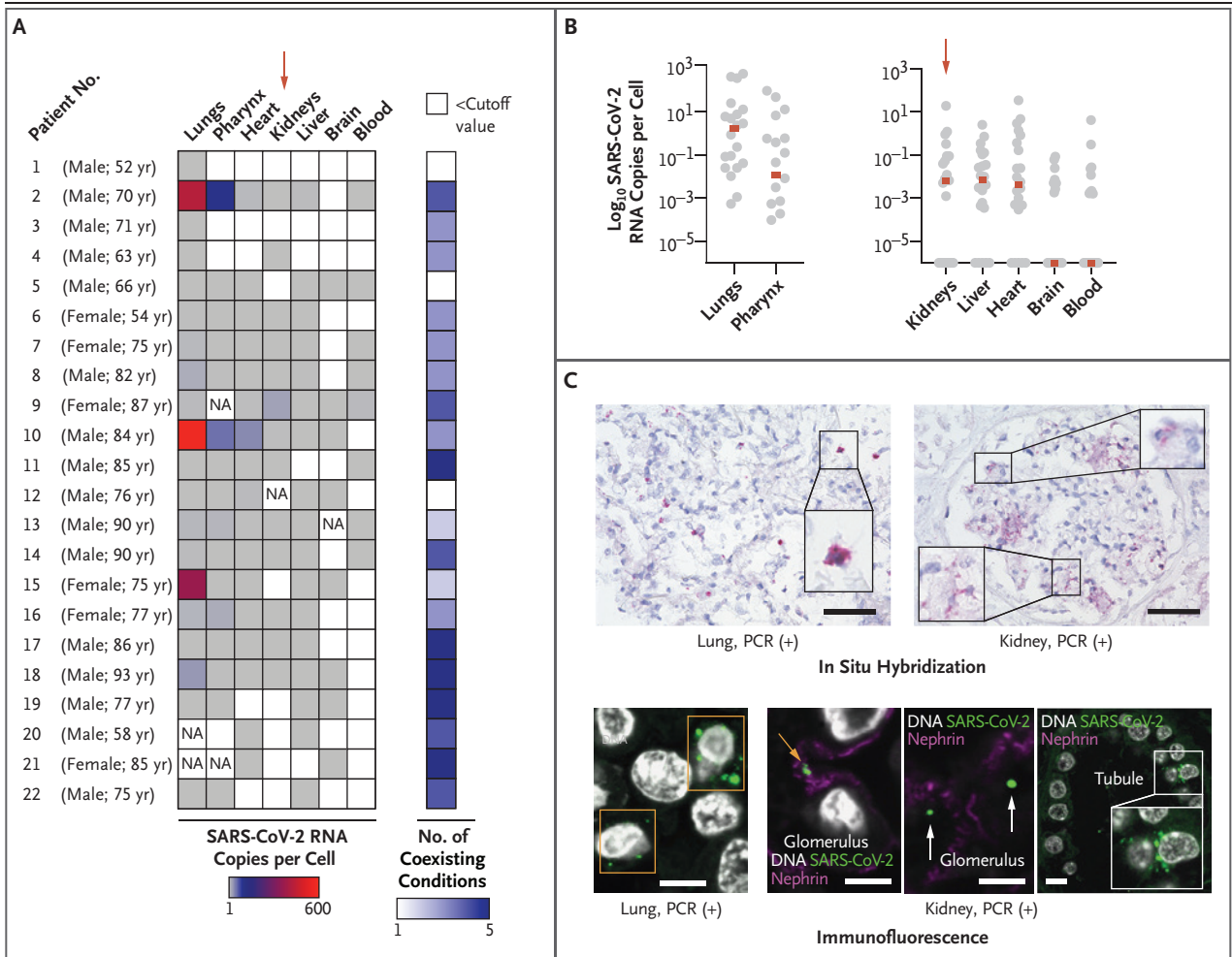


Figure 1. Multiorgan SARS-CoV-2 Tropism and Spatially Resolved Affinity for Kidney Cells.

Panel A shows detection of SARS-CoV-2 in the organs in association with the number of coexisting conditions in each patient. The red arrow highlights the viral load in the kidneys (one of the most common targets of SARS-CoV-2). Viremia as such did not correlate with the detected multiorgan tropism. NA denotes not available. Panel B shows the SARS-CoV-2 viral load in key organs, with a broad organotropism of the virus. The red arrow highlights the viral load in the kidneys, and the red rectangles indicate the median values in all organs. Each gray dot represents data from one patient. Panel C shows renal tropism detected with the use of in situ hybridization (spatially resolved viral RNA detection) and indirect immunofluorescence (spatially resolved viral protein detection) with confocal microscopy. In situ hybridization showed SARS-CoV-2 RNA detected in the lung and renal parenchyma (boxed areas show examples in each organ). Immunofluorescence of the lung specimen showed cells with SARS-CoV-2 protein (boxed areas), and immunofluorescence of the kidney specimen showed SARS-CoV-2 protein in areas of the glomerular epithelial (orange arrow), endothelial (white arrows), and tubular (white outline) cells. Scale bars represent 50 μ m in the in situ hybridization images and 10 μ m in the immunofluorescence images. PCR denotes polymerase chain reaction.

.org) that show that SARS-CoV-2 can be detected in multiple organs, including the lungs, pharynx, heart, liver, brain, and kidneys.

We first quantified the SARS-CoV-2 viral load in autopsy tissue samples obtained from 22 patients who had died from Covid-19. Seventeen patients (77%) had more than two coexisting conditions (Fig. 1A), and a greater number of coexisting conditions was associated with SARS-CoV-2 tropism for the kidneys (Table S2), even in patients without a history of chronic kidney disease (Table S3). The highest levels of SARS-CoV-2 copies per cell were detected in the respiratory tract, and lower levels were detected in the kidneys, liver, heart, brain, and blood (Fig. 1B). These findings indicate a broad organotropism of SARS-CoV-2.

Since the kidneys are among the most common targets of SARS-CoV-2, we performed in silico analysis of publicly available data sets of single-cell RNA sequencing. This analysis revealed that RNA for angiotensin-converting enzyme 2 (*ACE2*), transmembrane serine protease 2 (*TMPRSS2*), and cathepsin L (*CTSL*) — RNA of genes that are considered to facilitate SARS-CoV-2 infection³ — is enriched in multiple kidney-cell types from fetal development through adulthood (Fig. S1). This enrichment may facilitate SARS-CoV-2-associated kidney injury, as previously suggested.⁴

We also quantified the SARS-CoV-2 viral load in precisely defined kidney compartments obtained with the use of tissue microdissection from 6 patients who underwent autopsy (1 patient who was included in the previously mentioned 22 patients as an internal negative control, plus 5 additional patients). Three of these 6 patients had a detectable SARS-CoV-2 viral load in all kidney compartments examined, with preferential targeting of glomerular cells (Fig. S2). We also detected viral RNA and protein with high spatial resolution using in situ hybridization and indirect immunofluorescence with confocal microscopy (Fig. 1C). Data on additional controls are provided in Figures S3 and S4.

On the basis of these findings, renal tropism is a potential explanation of commonly reported new clinical signs of kidney injury in patients with Covid-19,⁵ even in patients with SARS-CoV-2 infection who are not critically ill. Our results indicate that SARS-CoV-2 has an organotropism

beyond the respiratory tract, including the kidneys, liver, heart, and brain, and we speculate that organotropism influences the course of Covid-19 disease and, possibly, aggravates preexisting conditions.

Victor G. Puelles, M.D., Ph.D.

Marc Lütgehetmann, M.D.

Maja T. Lindenmeyer, Ph.D.

Jan P. Sperhake, M.D.

Milagros N. Wong, M.D.

Lena Allweiss, Ph.D.

Silvia Chilla

Axel Heinemann, M.D.

Nicola Wanner, Ph.D.

Shuya Liu, Ph.D.

Fabian Braun, M.D.

Shun Lu, Ph.D.

Susanne Pfefferle, M.D.

Ann S. Schröder, M.D.

Carolin Edler, M.D.

University Medical Center Hamburg–Eppendorf
Hamburg, Germany

Oliver Gross, M.D.

University Medical Center Göttingen
Göttingen, Germany

Markus Glatzel, M.D.

Dominic Wichmann, M.D.

Thorsten Wiech, M.D.

Stefan Kluge, M.D.

Klaus Pueschel, M.D.

Martin Aepfelbacher, M.D.

Tobias B. Huber, M.D.

University Medical Center Hamburg–Eppendorf
Hamburg, Germany
t.huber@uke.de

Drs. Puelles, Lütgehetmann, Lindenmeyer, and Sperhake contributed equally to this letter.

Supported by grants (CRC/1192, to Dr. Puelles; CRC/841, to Dr. Lütgehetmann; and CRC/1192, HU 1016/8-2, HU 1016/11-1, and HU 1016/12-1, to Dr. Huber) from the German Research Foundation and grants (eMed Consortia Fibromap, to Dr. Puelles; and STOP-FSGS-01GM1518C, to Dr. Huber) from the Federal Ministry of Education and Research.

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

This letter was published on May 13, 2020, at NEJM.org.

1. Coronavirus disease 2019 (COVID-2019): situation report — 51. Geneva: World Health Organization, 2020 (<https://www.who.int/docs/default-source/coronavirus/situation-reports/20200311-sitrep-51-covid-19.pdf>).

2. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. *N Engl J Med* 2020;382:1177-9.

3. Sungnak W, Huang N, Bécavin C, et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. *Nat Med* 2020 April 23 (Epub ahead of print).
4. Su H, Yang M, Wan C, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int* 2020 April 9 (Epub ahead of print).
5. Pei G, Zhang Z, Peng J, et al. Renal involvement and early prognosis in patients with COVID-19 pneumonia. *J Am Soc Nephrol* 2020 April 28 (Epub ahead of print).
DOI: 10.1056/NEJMc2011400

Correspondence Copyright © 2020 Massachusetts Medical Society.