Assessing the importance of interleukin-6 in COVID-19 - Authors' reply.

D. E. Leisman
L. Ronner
R. Pinotti
M. D. Taylor
Zucker School of Medicine at Hofstra/Northwell, mtaylor15@northwell.edu
P. Sinha

See next page for additional authors

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Authors

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Assessing the importance of interleukin-6 in COVID-19

Authors’ reply
We thank Luke Chen and colleagues for their interest in our study.1 With respect to potential double counting of participants—this is a valid criticism. Indeed some participants could have been double counted if they were treated at the same hospital in overlapping time periods. Among the identified studies, only small fractions of the study periods overlap. Nevertheless, we recalculated our primary analysis using only one study—whichever was largest—from each group with potentially overlapping cohorts (figure). The results do not change.

Our dataset is publicly available.1 We welcome Chen and colleagues or other researchers to explore additional analyses.

Regarding our study representing predominantly Chinese cohorts—North American and European studies were generally published after our search had been concluded. Findings from these regions are consistent with our results. For example, in 237 critically ill patients with COVID-19 in New York City, NY, USA, median interleukin (IL)-6 concentration was 26 pg/mL (IQR 11–69 pg/mL).2 Patients enrolled in the BACC Bay trial done in Boston, MA, USA, (n=243) had median IL-6 concentration of 24.4 pg/mL (IQR 14.1–45.5 pg/mL).3

Chen and colleagues argue that elevated IL-6 is not a prerequisite for clinical response to IL-6 blockade. Although theoretically true, most randomised trials of anti-IL-6 have shown no benefit so far, as their correspondence notes.4,5 The authors invoke a prediction rather than a causal framework, stating that IL-6 is “the best available biomarker for severity of COVID-19”. IL-6 is associated with disease severity but there are no data to support this superlative designation. Furthermore, unlike C-reactive protein and D-dimer, IL-6 is not a widely available test and often takes days to obtain results, limiting clinical use.

As has been proven for sepsis and acute respiratory distress syndrome before, we maintain that a cytokine storm model is overly reductive and at best unhelpful in COVID-19.

Our dataset is publicly available.1

Figure: Interleukin-6 concentrations in patients with COVID-19 versus comparison disorders
Markers indicate the weighted pooled mean concentration for each disease group. Errors bars indicate 95% CIs. p values and 95% CI were computed for the difference in means between the indicated group versus the comparison disorder.

For the “Identification of CD8+ T cells that are C1D161h and/or IL1BtOh and have rapid drug efflux capacity for toxicity of CAR T cells”, for which he receives royalties from the licensee, Juno Therapeutics; a patent pending for “Methods and compositions related to toxicity associated with cell therapy”; a patent pending for “Methods for the treatment of B cell malignancies using adoptive cell therapy”; and a patent pending for “Biomarkers and uses thereof for selecting pancreas immunotherapy intervention”. MOH is supported in part by the US National Institute of General Medical Sciences, US National Institutes of Health (NIH) (grant K08 GM 132794).

CJT’s institution, the Fred Hutchinson Cancer Research Center, has held equity in Juno Therapeutics; CJT has received research grants and personal fees for advisory board participation from Juno Therapeutics/Bristol Myers Squibb, during the conduct of the study. He declares fees and stock options in relation to a role on the scientific advisory boards of Precision Biosciences, Caribou Biosciences, Eureka Therapeutics, Myeloid Therapeutics, Century Therapeutics, and ArsenaalBio; travel expenses and fees for participation on the advisory boards of Amgen, Novartis, Kite/Gilead, Humanigen, Aptevo, PACT Pharma, AstraZeneca, and Nektar Therapeutics; travel expenses from T-CURX; and research funding from AstraZeneca and Nektar Therapeutics, outside of the submitted work. CJT reports a patent (US patent number 10 653 756; issued May 19, 2020) for the “Identification of CD8+ T cells that are C1D161h and/or IL1BtOh and have rapid drug efflux capacity for toxicity of CAR-T cells”, for which he receives royalties from the licensee, Juno Therapeutics; a patent pending for “Methods and compositions related to toxicity associated with cell therapy”; a patent pending for “Methods for the treatment of B cell malignancies using adoptive cell therapy”; and a patent pending for “Biomarkers and uses thereof for selecting pancreas immunotherapy intervention”. MOH is supported in part by the US National Heart Lung and Blood Institute (RO0 HL 141678). ML discloses research funds from the French Ministry of Health, research support from Shingotec, lecture fees from Baxter and Fresenius, and consulting fees from Novartis. CSD is supported in part by the US National Institute of General Medical Sciences, US NIH (RO1 GM 221102). He has stock options with Enlivex Therapeutics, outside of the submitted work. CSD reports honoraria from Lippincott Williams & Wilkins (Scientific Editor Critical Care Medicine) and the New York University Department of Anesthesiology (visiting professor); non-financial support for participation in the Bernard-Wiggers Task Force (accommodation) and

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*Daniel E Leisman, Lukas Ronner, Rachel Pinotti, Matthew D Taylor, Pratik Sinha, Carolyn S Calfee, Alexandre V Hirayama, Fiore Mastrolanni, Cameron J Turtle, Michael O Harhay, Matthieu Legrand, Clifford S Deutschman
dleisman@mgh.harvard.edu

Department of Medicine (DEL) and Department of Anesthesia, Critical Care, and Pain Medicine (DEL), Massachusetts General Hospital, Boston, MA 02114, USA; Feinstein Institute for Medical Research, Manhasset, NY, USA (DEL, MDT, CSD); Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA, USA (LR); Levy Library, Icahn School of Medicine at Mount Sinai, New York, NY, USA (RP); Department of Pediatrics, Cohen Children’s Medical Center, New Hyde Park, NY, USA (MDT, CSD); Ziskin School of Medicine at Hofstra-Northwell, New York, NY, USA (MDT, CSD); Department of Anesthesiology, Division of Critical Care, Washington University School of Medicine in St Louis, St Louis, MO, USA (PS); Department of Anesthesia and Perioperative Care (CSC, ML), Division of Pulmonary, Critical Care, Allergy, and Sleep Medicine (CSC), and Cardiovascular Research Institute (CSC), University of California, San Francisco School of Medicine, San Francisco, CA, USA; Clinical Research Division (AVH) and Integrated Immunotherapy Research Center (AVH, CJT), Fred Hutchinson Cancer Research Center, Seattle, WA, USA; Division of Pulmonary and Critical Care Medicine, Northwell Health, New York, NY, USA (FM, CJT); Department of Biostatistics, Epidemiology, and Informatics (MOH) and Palliative and Advanced Illness Research Center (MOH), Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA