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.

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.[3-5] The authors invoke a prediction rather than 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.

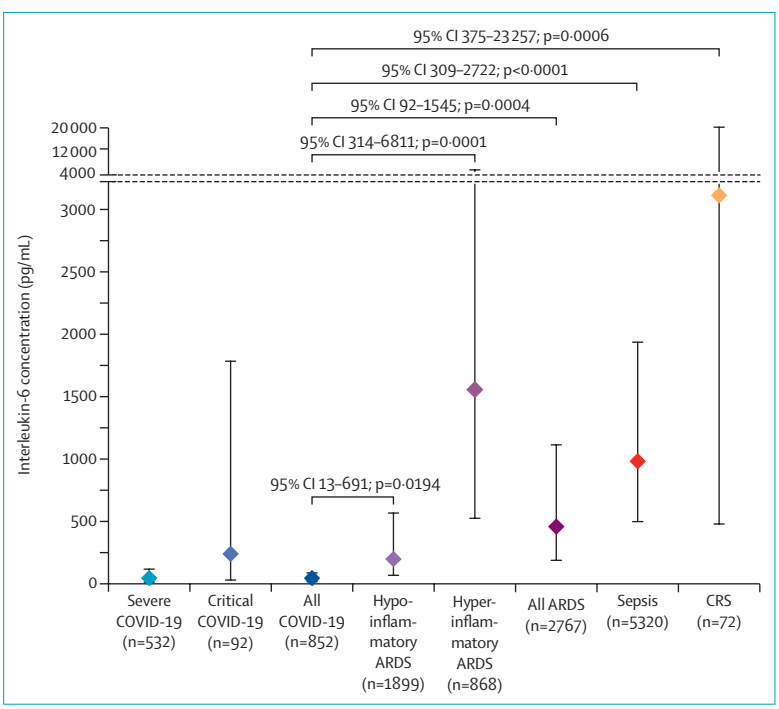

Figure: **Interleukin-6 concentrations in patients with COVID-19 versus comparison disorders**
Markers indicate the weighted pooled mean concentration for each disease group. Errors bars indicate 95% CIs. p values and 95% CI were computed for the difference in means between the indicated group versus COVID-19. ARDS=acute respiratory distress syndrome. CAR=chimeric antigen receptor. CRS=chimeric antigen receptor T cell-induced cytokine release syndrome.

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