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## **Tocilizumab in COVID-19 therapy: who benefits, and how?**

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The RECOVERY Collaborative Group reported statistically significant improvement in survival of patients with COVID-19 who were receiving tocilizumab interleukin (IL)-6 inhibitor, albeit with very modest reduction of mortality (31% vs 35% with usual care,  $p=0.0028$ ).<sup>1</sup> This result adds to a number of studies with tocilizumab and other IL-6 antagonists, such as sarilumab, which showed only minor, or no, reduction in mortality.<sup>2</sup> Given that IL-6 is associated with COVID-19 severity and mortality,<sup>3</sup> the question arises as to why IL-6 antagonist therapy does not substantially improve survival.

In April, 2021, we showed that IL-6 serum concentrations are indeed associated with COVID-19 severity (appendix); however, a better classification of severity is obtained when IL-6 is combined with other cytokine concentrations.<sup>4</sup> Moreover, within each respiratory severity group, IL-6 is not significantly associated with mortality (appendix). It is rather distinct combinations of interferon  $\alpha$ , inteferon  $\beta$ , IL-10, and tumour necrosis factor  $\alpha$  that are better predictors of mortality in different severity groups.<sup>4</sup>

Nevertheless, mortality in the low IL-6 group of patients is significantly lower than in the high IL-6 group of patients (appendix), suggesting that IL-6 inhibitors should be given only to patients with high IL-6. Indeed, a retrospective analysis of tocilizumab therapy as a function of baseline IL-6 concentrations showed a large reduction in mortality (from 36% to 16%) in patients with high-baseline IL-6, but no reduction in mortality in low-baseline IL-6 patients.<sup>5</sup>

In conclusion, clinical trials of IL-6 antagonist therapy, such as RECOVERY<sup>1</sup> and sarilumab COVID-19 global studies,<sup>2</sup> should consider reanalysis of their results as a function of IL-6 baseline concentrations. More generally, clinical trials of personalised precision medicine, based on cytokine profiling, are needed for optimisation of COVID-19 therapy.

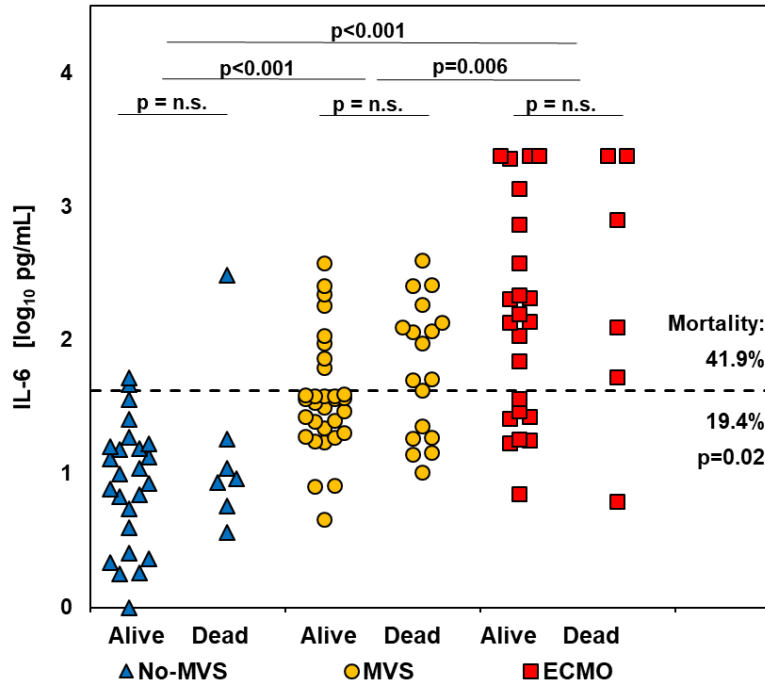
We declare no competing interests.

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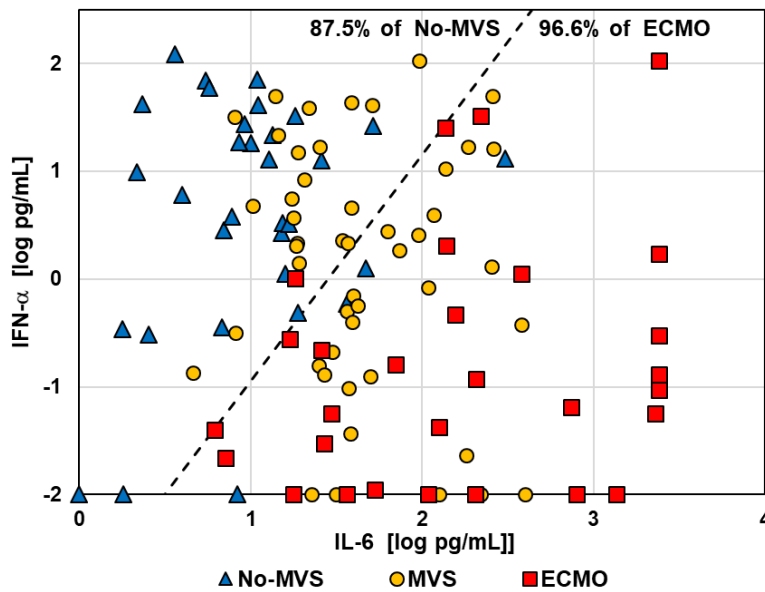
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Supplementary appendix:

A



B



**Figure 1: IL-6 association with COVID-19 severity and mortality.** IL-6 serum concentrations at day of hospitalization of COVID-19 patients (N=110) are significantly associated with respiratory severity (A), but better classification of severity is obtained by comparison of IL-6 and IFN- $\alpha$  concentrations (B) and even better by the combination of IL-6, IL-8, IL-10, and TNF- $\alpha$  concentrations in comparison to IFN- $\alpha$  and IFN- $\beta$ .<sup>4</sup> Mortality one month after admission is significantly higher if IL-6 admission concentrations are above the mean (40 pg/mL, dashed line in A), but within each respiratory severity group mortality is not significantly associated with IL-6 (A).

Study design, methods, patients' characteristics and ethical approval are given in Dorgham et al.<sup>4</sup>

MVS and No-MVS: Patients requiring mechanical ventilatory support or not. ECMO: Patients requiring extracorporeal membrane oxygenation. n.s.: not statistically significant.