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.

and those in the control group, in the TESEO Modena cohort are shown in the appendix. Our results are similar to the findings of Piano and colleagues, but we also showed a few outliers. The overall difference in mean alanine aminotransferase (ALT) concentration between the tocilizumab group and standard of care group was significant by ANOVA Fisher test (p<0·0001). Of note, given the quadratic nature of the relationship, the mixed linear model originally done failed to detect this difference in the ALT trend over time between treatment groups. Nevertheless, the increase of ALT in these patients might reflect multiple mechanisms of liver injury beyond tocilizumab toxicity, such as microthrombosis or reactivation of herpes viruses (HSV1 in particular), variables that were not accounted for in this simple unadjusted analysis.

Brian Lipworth and colleagues advocate for a personalised endotype-driven approach to facilitate earlier identification of patients with COVID-19 who might benefit from treatment with tocilizumab or glucocorticoids. We have developed a data-driven predictive model that provides a reliable 48 h prediction of severe respiratory failure, with an accuracy of 84%, which also minimises the false-negative rate.[4] The best performing model required approximately 20 variables, which included interleukin-6, C-reactive protein, and blood gas analyses. Of note, the identification of sick patients (relating to prediction) cannot be confused with the identification of patients who will benefit from the use of tocilizumab, or with questions regarding what intervention is needed to prevent severe complications of COVID-19, which need to be evaluated in the context of counterfactual predictions.[5] Lipworth and colleagues also suggest that the effect of tocilizumab in our analysis could have been due to more prevalent concomitant use of glucocorticoids in these patients, compared with those treated with standard of care; however, our estimates were adjusted for post-baseline use of glucocorticoids. It should also be noted that the optimal time for tocilizumab use in the clinical course of COVID-19 remains to be elucidated.

We declare no competing interests.

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Mavrilimumab for severe COVID-19

We read with interest the Article by Giacomo De Luca and colleagues[1] in *The Lancet Rheumatology*, in which the authors showed that mavrilimumab treatment was associated with improved clinical outcomes compared with standard care in non-mechanically ventilated patients with severe COVID-19 pneumonia and systemic hyperinflammation. However, we would like to highlight important limitations of the study

First, the authors used arbitrary cut-off points in continuous variables (serum C-reactive protein, ferritin, and lactate dehydrogenase) for selecting patients with hyperinflammation.[2] Such cut-offs were not derived from or validated in any predictive or prognostic studies in patients with COVID-19 that we are aware of.[3]

Second, the authors have not provided any confidence limits for their test statistics, which hinders us from drawing any conclusions from the study (given the lack of analysing uncertainty in effect estimates).

Third, the median duration of illness or fever was shorter in the control group than in the intervention group despite similar inflammatory markers and respiratory support in each group, suggesting that patients in the control group were in a more advanced stage of illness.

Finally, median IL-6 concentrations in both groups were substantially lower than those seen in patients even with the so-called hypoinflammatory phenotype of non-COVID-19 acute respiratory distress syndrome,[4] thereby casting doubt on whether IL-6 (and granulocyte–macrophage colony-stimulating factor as an upstream molecule) is the main driver of inflammation in COVID-19, and whether in future we should be more cautious when using further immunomodulation in this patient population, targeting single cytokines.[4]

We declare no competing interests.

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See **Online** for appendix

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In *The Lancet Rheumatology*, Giacomo De Luca and colleagues[1] examined whether mavrilimumab added to standard care could improve the clinical outcomes in patients with COVID-19 pneumonia and systemic hyperinflammation in a single-centre prospective cohort study. They compared 13 patients treated with mavrilimumab to 26 patients who received standard care. The analysis showed earlier clinical improvement in the intervention group than in the control group. However, the power of study was low due to the small sample size, and no statistical difference in mortality was found between the two groups (no patients died in the mavrilimumab group *vs* seven [27%] patients in the control group; p=0·086). The challenges of doing clinical studies to find safe and effective therapies during the COVID-19 pandemic are understandable, with shortfalls of adequate actions against the unknown disease and its complication in resource-limited conditions and given concerns over a potentially high case–fatality rates. However, as Cheung and colleagues caution,[2] underpowered studies that are susceptible to type II error could discourage clinicians from using potentially effective treatments against COVID-19 and lead to premature rejection of promising drugs.

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Although a prospective cohort, De Luca and colleagues' study[1] was done at a single centre, and patients were matched with a control group. As they mentioned in their limitations section, the absence of a pre-established randomisation process can introduce risks for selection bias. Although the distribution of demographic variables for both groups indicated no significant differences, one should note that this lack of difference might be due to low sample size, because a small sample size is more likely to show no difference according to type II error. In this case, the authors could use multivariate analysis (including a Cox regression model) to control for the potential confounders (eg, the predominance of male participants and longer fever duration in the intervention group than in the control group).

In summary, no strong conclusions about the effects of mavrilimumab in COVID-19 can be made until an appropriately powered trial has been done with appropriate statistical analysis to avoid potential bias.

We declare no competing interests.

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Authors' reply

We thank Mohamad Amin Pourhoseingholi and colleagues and Manish Soneja and colleagues for their interest in our Article.[1] As we stated in our manuscript, we agree that the small number of enrolled patients does not allow us to draw definitive conclusions on the effect of mavrilimumab on mortality in patients with COVID-19, and that randomised controlled trials are needed to unequivocally assess the efficacy and safety of this therapeutic strategy. However, we feel that the clinical data on clinical improvement emerging even in our small cohort support the strength of our results. Indeed, in our single-centre, prospective cohort study, we showed that single-dose mavrilimumab, administered in 13 patients with severe COVID-19 pneumonia and hyperinflammation, was associated with significantly greater and faster clinical improvement than standard management alone in a cohort of 26 patients.

As we stated in our Article, we are aware that the study design and the absence of a pre-established randomisation process can introduce risks for selection bias, treatment bias, and hence type II error. The same study design (prospective cohort study) has been adopted in many recent anti-cytokine therapies studies in this novel and unfamiliar clinical scenario[2–4] and these studies have contributed to the development of subsequent randomised controlled trials, most of which are still ongoing.

Additionally, in a pre-planned analysis, we used a Cox proportional-hazards model with treatment and a 7-point scale of clinical status at baseline as covariates to identify whether these variables were mutually independent factors associated with time to improvement in clinical status, and we found that both variables were independent predictors of clinical improvement at multivariate analysis (treatment: relative risk 5·84 [95% CI 2·5–13·6; p<0·001]; clinical status: 2·9 [1·3–6·5; p=0·011]). These data were not included in the Article because the final statistical model was considered appropriate for a non-randomised setting.

We agree that our definition of hyperinflammation might be considered somehow arbitrary, but we believe that any cut-off determined in pioneering studies is unavoidably arbitrary, and this was the case while dealing with the truly unprecedented condition that is COVID-19 pneumonia. Furthermore, similar cut-off values for C-reactive protein (CRP), ferritin, interleukin (IL)-6, and lactate dehydrogenase