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.

Response

To the Editor:

Thank you to Dr Thille and colleagues for their letter and comments.[1] We appreciate the additional analysis they were able to perform with these new trial-level data. We agree that there is a considerable gap in knowledge regarding the use of high-flow nasal cannula (HFNC) in the postoperative setting and that additional clinical trials are needed to inform clinical practice and future clinical practice guidelines for this indication in different patient populations.

In our initial analysis, despite results that had appeared statistically significant, and in keeping with Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methods, we had lowered our certainty in the pooled intubation outcome data for imprecision. We had done this because the optimal information size was not met (there were only 23 events [intubations] between arms). Our stated conclusion was that HFNC decreases the need for reintubation (based on moderate certainty evidence) and escalation of respiratory support (based on very low certainty evidence) compared with COT, but there was an element of ongoing uncertainty. How does the addition of the Futier data for the intubation outcome change our results?

Incorporating these new data, the overall pooled estimate remains dramatically on the side of benefit (relative risk [RR], 0.50, a 50% relative reduction in intubation with HFNC); however, the 95%CI does not rule out the possibility of important harm (upper end RR, 1.38). Even with the addition of data from the trial by Futier et al,[2] the optimal information size is still not met (now 34 events [intubations] between arms). Given this new information, one could argue that we should now lower our certainty further (to low certainty) in the pooled estimate by two levels for imprecision, given the wide CI and the small number of events. With the addition of this trial, our conclusion would remain similar—our best estimate would be that HFNC reduces the need for intubation (RR, 0.50); however, data are now based on low (as opposed to moderate) certainty evidence. The analysis for "escalation of respiratory support" would not change, because we had included data from the Futier trial in this outcome already, supporting very low certainty of a reduction using HFNC.

To summarize, we do not believe that new data from this trial changes the overall conclusion or interpretation of our meta-analysis.[3] It does, however, introduce more uncertainty in the intubation outcome (going from moderate to low certainty), underscoring the need for ongoing well-done clinical trials in the postoperative setting.

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Questioning Tocilizumab Use in Hospitalized Patients With Coronavirus Disease 2019

To the Editor:

We read with great interest the article by Price and colleagues[1] in *CHEST* (October 2020) reporting tocilizumab use in coronavirus disease 2019 (COVID-19) patients with suspected cytokine release syndrome (CRS). Despite the large number of patients and the results reported, we would like to raise some concerns about their conclusions.

First, the definition of CRS in their study is unclear. A classification of CRS' severity according to Lee and

colleagues[2] would have made it possible to classify subjects by severity more finely, thus identifying subgroups more likely to benefit from treatment. Indeed, the presence of other organ failure in patients was not detailed except for mechanical ventilation, suggesting low-grade CRS.

Second, two findings highlighted by the authors are the decrease in C-reactive protein (CRP) and the disappearance of fever, features also reported in another study of tocilizumab in COVID-19 by Hermine and colleagues.[3] Tocilizumab use is associated with an expected decrease in CRP because of its pharmacological effect. Hence the biological results suggest only tocilizumab usage, and considering the decrease of CRP as efficiency in COVID-19 treatment could be an overstatement.

Third, supplementary material shows that the standard-of-care consisted of atazanavir and hydroxychloroquine, two off-label treatments for COVID-19, further reducing the external validity of the study. In addition, up to 38% of patients in the severe group received corticosteroids, a treatment now recommended by the World Health Organization for severe COVID-19.[4] Overall, isolating the individual effect of tocilizumab among these therapies is difficult, particularly in an observational study, because we do not have the results of the control group.

These limitations call into question the authors' conclusion that tocilizumab may reduce mortality in COVID-19, especially since the publication of randomized clinical trials with negative results on mortality (Hermine and colleagues[3] and Stone and colleagues[5]). Further prospective studies are mandatory to define tocilizumab's place in the therapeutic arsenal for COVID-19.

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Response

To the Editor:

We reported our real-world experience with the coronavirus disease 2019 (COVID-19) during the beginning of the global pandemic as it affected the Northeastern part of the United States when there were no Food and Drug Administration-approved medications to treat COVID-19.[1] Our study reflected clinical practice based on available data during that time period. In the absence of proven therapies, tocilizumab was considered a good candidate for immunomodulatory therapy, based on experience with treatment of the cytokine-release syndrome in other disease conditions. To deploy the medication to those who would likely derive the greatest benefit, we selected patients with an oxygenation requirement and an elevated C reactive protein level. Though using a standard definition of cytokine-release syndrome may have been useful, our study definitions reflected real-world clinical decision-making rather than a preplanned intervention.

As the letter writers point out, our findings of decreased C reactive protein and disappearance of fever in those treated with tocilizumab suggest a biologic impact from tocilizumab use. In addition, we suggest that tocilizumab may impact survival and mechanical ventilation rates, as reported in our results. Regarding the external validity of the study, protease inhibitors and hydroxychloroquine have now been demonstrated to not be effective in randomized controlled trials for COVID-19 treatment. Therefore, we believe it is unlikely for these agents to have impacted study outcomes significantly, particularly that of mechanical ventilation. Furthermore, though it is certainly a limitation, treatment with additional agents has been a common occurrence with COVID-19 treatment-related trials and is by no means unique to our study.