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.

0.47-1.32), both compared with standard of care in patients with COVID-19. The outcomes of the study replicated the findings in the clinical trials[2,3] of corticosteroids and tocilizumab respectively which demonstrated opposing results for the two immunotherapies.

Perhaps the most surprising finding from the study was the reduced risk of death with the administration of both corticosteroids and tocilizumab.[1] Such findings cannot be treated as if the beneficial effects are arising solely from the corticosteroids because the observed risk reduction was even greater than the risk reduction with corticosteroid alone (HR, 0.44; 95% CI, 0.35-0.55); it implied that there must be some forms of synergism that exist between corticosteroids and tocilizumab in patients with COVID-19. Similarly, this synergism had also been suggested in a randomized controlled trial[3] of tocilizumab in patients with COVID-19, in which the primary analysis observed no difference on day 28 mortality rate with tocilizumab compared with usual care (HR, 0.92; 95% CI, 0.33-2.53), but the subgroup analysis revealed a reduced risk of death in patients who receive tocilizumab plus dexamethasone compared with those who receive usual care plus dexamethasone (HR, 0.13; 95% CI, 0.021-0.78).

Narain et al[1] failed to highlight this finding that could have very significant clinical implications. The mechanism that underlies the synergism between corticosteroids and tocilizumab is unclear, but we postulate that reduced bioactivity to corticosteroids for some reason and in at least certain patients with COVID-19 could lead to failure of corticosteroids to retard the effects IL-6, because IL-6 has been shown to be inhibited by corticosteroids. This reduced bioactivity may or may not be related to polymorphisms in the IL-6 gene (IL-6 174GG genotype) that has been associated with resistance to corticosteroids.[4] In addition, administration of corticosteroids had also been shown to contribute to an enhanced IL-6-induced proinflammatory acute-phase response.[5] We believe that the routine combination of corticosteroids with tocilizumab is worthy of more evaluation of its clinical outcomes in patients with COVID-19.

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Response

To the Editor:

We thank Drs Kow and Hasan for their critique of our article.[1] Our study highlighted the benefit of corticosteroids in reducing hospital deaths of patients with coronavirus disease 2019 (COVID-19) cytokine storm compared with standard of care (which did not include any steroids). Further, our study suggests a decreased mortality rate associated with corticosteroids plus tocilizumab when compared with corticosteroids alone.

We agree with the authors that there may be a synergistic effect with the combination of corticosteroids and tocilizumab. Our study was not designed to evaluate this effect due to the lack of standardization of drug dose, frequency, and timing of drug administration that were not controlled for in the observational analysis. Despite our attempts to control rigorously for confounders, there may have been inherent patient or treatment differences that may have contributed to outcomes.

Although we did not have the data on the interval between initial COVID-19 symptoms and the onset of hyperinflammatory state, our analysis shows that, after the onset of "cytokine storm," steroids were given earlier than

tocilizumab, both when used alone and in combination therapy. We hypothesized that the reason for the survival difference between steroids alone vs tocilizumab alone was possibly the delayed onset of action of tocilizumab in addition to its later administration. On the contrary, we surmise that, in the steroids plus tocilizumab combination group, steroids provided an initial immunosuppressive effect that was enhanced and sustained by tocilizumab. The importance of the timing of drug administration on survival is also emphasized in the correspondence by Martinez-Urbistondo et al.[2]

Our study demonstrated increased survival with corticosteroid use in hospitalized patients with laboratory evidence of hyperinflammation, when compared with standard of care. This finding has been supported by published randomized controlled studies, although the studies did not particularly select patients with hyperinflammation. However, randomized controlled studies have failed to show benefit of anti-IL6 therapies in COVID-19. These studies did not include critically ill patients, had small sample sizes, and included worsening oxygenation in the composite primary outcome. In the study of Hermine et al,[3] the authors note very wide CIs and decreased need for mechanical ventilation and death in the tocilizumab arm. In the tocilizumab arm, 33% of the patients received concomitant corticosteroids, although the timing in relation to tocilizumab is not known. The mortality rate in these studies was also far lower than in our cohort, regardless of the treatment arm. Although a large observational study[4] that included critically ill patients reported increased survival with combination therapy, in our opinion, the questions of whether tocilizumab and steroid combination decreases mortality rates in patients with severe COVID-19 infection when compared with steroid therapy alone has not yet been answered.

The proposed postulate of genetic polymorphisms that contribute to corticosteroid resistance is indeed interesting and warrants further investigation. We agree that clinical trials must be designed to evaluate the benefit of combination therapy in patients with COVID-19, with timing being key to the trial design. We want to emphasize the increased risk of infections observed in patients who receive combination immunosuppressive therapies vs steroids or tocilizumab alone.

Although increased infection rate may have been due to factors such as central lines and other critical illness-related procedures, adverse drug effects and complications should be monitored carefully in the future randomized trials to access properly the risk-benefit ratio of immunosuppressive therapy in severe COVID-19 infection.

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Remarks About Retrospective Analysis of Ivermectin Effectiveness on Coronavirus Disease 2019 (ICON Study)

To the Editor:

We read with interest the article in *CHEST* (January 2021) by Rajter et al,[1] a retrospective study examining 280 hospitalized patients with coronavirus disease 2019 (COVID-19), which concluded that ivermectin was associated with lower overall mortality.

We think that the study did not report two important variables that would have influenced the outcome. The first is time of symptom onset. We cannot know what the patients' COVID-19 infection stage was at admission. We already know that corticosteroids are effective for mortality reduction only in the second week after