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.

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Response

To the Editor:

We thank Rotzinger and Qanadli for the interest in our article on the chest CT imaging signature of coronavirus disease 2019 (COVID-19) infection.[1] In our article, we reported a pooled prevalence of vascular thickening of 72.9% (95% CI, 64.4% to 81.4%) in patients with COVID-19.[1] At the time our article was published, there was a lack of scientific data that correlated chest CT imaging to postmortem pathologic findings in this disease. Recently, Henkel et al[2] published a series of 14 patients who died of COVID-19, in whom a morphologic comparison of antemortem chest CT scans with postmortem gross findings and histopathologic findings was performed. Five of 14 patients in their study also underwent contrast-enhanced CT imaging.[2] Both vascular thickening (vascular enlargement/vascular congestion) and pulmonary arterial enlargement (related to the corresponding bronchus) were present in 12 of 14 patients (86%) on chest CT imaging.[2] Based on their histopathologic correlation and previous autopsy studies,[3,4] Henkel et al[2] speculated that the observation of enlarged pulmonary arteries might be related to an increase of parenchymal and predominantly intravascular pressure, due to severe COVID-19 pulmonary microangiopathy that affected the alveolar capillary network. The high incidence of microthrombosis was also thought to be suggestive of a possible underestimation of the vascular alterations associated with COVID-19 with the use of imaging, especially on unenhanced scans.[2] Henkel et al[2] concluded that both severe acute lung injury and vascular complications contribute to fatal outcomes. These considerations largely resonate with the excellent remarks by Rotzinger and Qanadli.[1] Nevertheless, the scientific evidence on the pathophysiologic condition and clinical relevance of vascular changes on chest CT imaging in COVID-19, besides frank pulmonary embolism, is still limited, and the interpretation of this limited evidence remains somewhat speculative. Further studies are warranted to understand the nature of vascular abnormalities seen on chest CT scans and how this can help to improve patient management and outcome.

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FINANCIAL/NONFINANCIAL DISCLOSURES: None declared.

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DOI: https://doi.org/10.1016/j.chest.2021.01.002

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Corticosteroid Plus Tocilizumab in COVID-19

When Two Is Better Than One

To the Editor:

We compliment the retrospective study by Narain et al[1] in *CHEST* (March 2021) that analyzed and compared the risk of death with different immunotherapies in patients with coronavirus disease 2019 (COVID-19). The findings of the study had some implications for the use of immunotherapy in this patient population. Specifically, the study found that the use of corticosteroids reduced the risk of death (hazard ratio [HR], 0.66; 95% CI, 0.57-0.76), but no survival advantage was observed with the use of tocilizumab, an IL-6 receptor monoclonal antibody (HR, 0.79; 95% CI,

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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FINANCIAL/NONFINANCIAL DISCLOSURES: None declared.

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DOI: https://doi.org/10.1016/j.chest.2020.11.073

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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