We thank Kuindersma and Spronk for their thoughtful review of our study describing subgroups in coronavirus disease (COVID-19)–related acute respiratory distress syndrome (ARDS) (1). In their letter, they highlight the potential value of phenotyping based on latent class analysis for patients with COVID-19–related ARDS and discuss the potential for targeting corticosteroids to identifiable subgroups to optimize benefit and minimize harm. Given the heterogeneity of ARDS (including COVID-19–related ARDS), we agree that precision medicine should inform the selection of appropriate patient populations or subpopulations that may benefit from specific therapies, especially immunomodulatory agents (2).

At the same time, it is important to highlight certain limitations of our study. The first is that corticosteroid administration was not randomized in the cohort, so there is potential for confounding by indication. In addition, because the study took place before the publication of the RECOVERY (Randomized Evaluation of COVID-19 Therapy) dexamethasone trial, corticosteroid use was not protocolized, and the majority of patients did not receive dexamethasone (3). The cumulative dose and duration of corticosteroids was similar among patients in the hypoinflammatory and hyperinflammatory subgroups, adding validity to the findings of differential treatment effect, but these limitations should be considered.

A second limitation is that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral load, based on cycle threshold value, was not monitored longitudinally. Within the hypoinflammatory subphenotype, cycle threshold value was a predictor of mortality, and there was a trend toward worse outcomes with corticosteroid use in this group. We hypothesized that these findings may reflect the underlying biological characteristics of the hypoinflammatory subphenotype or, as Kuindersma and Spronk note, may be owing to impaired viral clearance associated with the use of corticosteroids, as is seen in other respiratory viral infections. Although it has been established that elevated early viral loads and prolonged shedding periods are associated with increased disease severity in COVID-19, the impact of corticosteroids on SARS-CoV-2 viral clearance is unclear and warrants further evaluation (4, 5).

Despite these limitations, we agree with Kuindersma and Spronk that the results of our analysis merit consideration of how best to personalize care for patients with COVID-19–related ARDS. Given that prospective, randomized controlled trials have shown a benefit for corticosteroid therapy in severe COVID-19, there is a lack of equipoise to withhold its use for patients requiring invasive mechanical ventilation. Nevertheless, a more sophisticated approach to identifying patient populations with differential response to immunomodulatory therapy is appealing, particularly as ongoing studies reveal heterogeneous efficacy of corticosteroids in COVID-19 depending on disease severity, timing of administration, and underlying patient characteristics (6). Although our study provides one possibility to identifying subgroups with differential treatment response, the best approach to identifying such patients remains uncertain and requires further evaluation. Kuindersma and Spronk’s proposed method of incorporating a parsimonious classifier model and SARS-CoV-2 viral load into the decision to initiate corticosteroid therapy may ultimately be an effective strategy pending rigorous prospective studies to validate the process.

To achieve a more precise utilization of corticosteroid therapy in COVID-19–related ARDS, further steps are needed. The first step would be to validate the subgroups we identified in other populations of patients with COVID-19–related ARDS across wider geographic regions, as well as cohorts treated later in the pandemic. If these subphenotypes are ultimately validated, a classification model could be applied to previously published clinical trial data of corticosteroids and other immunomodulators in COVID-19 to identify clinically relevant subgroups. These insights could then be incorporated into future clinical trial design to guide treatment strategies for severe COVID-19 across heterogeneous populations. Until these studies are completed, however, corticosteroids remain the standard of care for mechanically ventilated patients with COVID-19.

From the Authors:

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