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Time to Tailor the One-Size-Fits-All Approach?

To the Editor:

We read with interest the study by Sinha and colleagues in a recent issue of the Journal (1) examining the latent classes of coronavirus disease (COVID-19)–associated acute respiratory distress syndrome (ARDS). The authors concluded that COVID-19–associated ARDS can be classified, like other causes of ARDS, into a hypoinflammatory and hyperinflammatory subphenotype. Both subphenotypes appear to have distinct outcomes, with increased mortality in the hyperinflammatory subgroup. In addition to these more generalizable effects in ARDS, this study also reveals more COVID-19–associated ARDS-specific findings. In particular, the viral load at the start of treatment influences the outcome, especially in patients with a hypoinflammatory subphenotype treated with corticosteroids with a high viral load, expressed as a low cycle threshold (CT) value. A delayed viral clearance was suggested as the underlying cause of the negative effects of corticosteroids in this group. Detrimental effects of corticosteroids on viral clearance are well known and have been described in multiple viral infections (i.e., severe acute respiratory syndrome coronavirus 1 and influenza). In addition, there is mounting evidence that secondary infections (e.g., COVID-19–associated pulmonary aspergillosis) are increased since the introduction of routinely starting corticosteroids in the treatment of COVID-19–associated ARDS (2, 3).

Given the many potential drawbacks of corticosteroids in the treatment of COVID-19–associated ARDS, there is an increased demand for personalized care in these patients, because one size may not fit all (4). Personalized or tailored medicine targeting the different ARDS phenotypes was suggested several years ago as an option to improve survival. Further understanding of the heterogeneity in the molecular, mechanical, and inflammatory response underlying the ARDS pathogenesis is an essential step to enable this personalized therapy.

How can we use the study of Sinha and colleagues to further personalize the therapy in daily care? First, we will have to be able to identify the two subphenotypes of ARDS. Ideally, we would apply classes from the latent class analysis to our patients. However, several of the parameters used are only available in a research setting and not readily available in daily practice. A suitable alternative may be to use a clinical classifier model that has also been studied and has a good correlation with the latent class analysis in ARDS of COVID-19 and non–COVID-19 origin (5). The top 10 criteria from this model (bicarbonate, vasopressor use, creatine, bilirubin, and albumin levels, heart rate, V̇e, platelet count, systolic blood pressure, and white blood cell count) are readily available and adequately differentiate between subphenotypes. Once this distinction in subphenotypes is established, a decision may be made regarding the initiation of corticosteroid therapy if the viral load is additionally factored in the decision. Readily available CT values of RT-PCR seem to be a reasonable derivative in this respect, although absolute values cannot be given because the quantified degrees of PCR-CT and viral loads are inconsistently defined across assays (6).

With parameters available almost everywhere, we may distinguish ARDS subphenotypes in COVID-19. Let us look carefully at the individual patient with COVID-19 in the ICU and prepare a tailored therapeutic strategy that may or may not include the use of steroids.

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Reply to Kuindersma and Spronk

From the Authors:

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.

Author disclosures are available with the text of this letter at www.atsjournals.org.

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