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CHEST

Clinical Subphenotypes in Critically Ill Patients With COVID-19

Now Looking for Different Treatment Responses!

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Patients with no COVID-19-associated ARDS form a highly heterogeneous group and secondary analyses of five randomized controlled trials that included such patients have consistently identified two phenotypes, termed "hyperinflammatory" and "hypoinflammatory."[1] Not only did the hyperinflammatory phenotype lead to a 20% higher mortality rate than its counterpart; however, most importantly, in three of these analyses, differential treatment responses to randomized interventions were observed between the two phenotypes.[1] Such prognostic and predictive enrichments could enable stratified and/or precision medicine strategies and thus be valuable for treating patients with ARDS.

In contrast, ARDS related to COVID-19 should show less heterogeneity because the causal injury (ie, SARS-CoV-2 infection) is identical in all patients.[2] Yet, critically ill patients with COVID-19 exhibit differences in respiratory system mechanics impairment, associated thrombosis and organ failures, viral load, and systemic inflammation and immune response that delineate a wide constellation of clinical pictures. Nevertheless, only 18 months after the first cases of COVID-19 had been reported in Wuhan, risk factors for death have been explored extensively in large patient cohorts, and the main clinical determinants have been identified, including mainly age, male sex, obesity and associated comorbidities, and clinical severity at admission.[3,4] Numerous randomized controlled trials have been conducted (or are still in progress), but only a few have demonstrated the positive effect of therapeutic interventions. Among these, dexamethasone[5] and tocilizumab[6] have shown a reduction in day-28 mortality rate. Interestingly, the effect of dexamethasone was significantly beneficial only in patients who received either invasive mechanical ventilation or oxygen at randomization (but not in patients who did not receive any respiratory support at randomization).[5] On the contrary, tocilizumab appeared to be beneficial in both patients not being treated with oxygen and patients being treated with noninvasive ventilation but appeared to not be beneficial in those who received mechanical ventilation.[6] These results illustrate the different responses of well-identified subgroups of patients (ie, receiving oxygen, noninvasive or invasive ventilation support) with severe COVID-19 pneumonia to therapeutic interventions.

In this issue of *CHEST*, Vasquez et al[7] hypothesized that latent subphenotypes exist within critically ill patients with COVID-19 and tested whether these would be associated with differences in the risk of important clinical outcomes using data from patients (n = 3,300) who were enrolled in the multicenter (n = 67) study of the treatment and outcomes in critically il patients with COVID-19.[4] The cohort was split into a discovery (n = 2,188 patients) and a replication (n = 1,112) cohort. Twenty-five acute clinical and laboratory class-defining variables that were selected a priori and obtained during the first day of ICU admission were included in latent class analysis models. Authors identified four homogeneous subphenotypes within a heterogeneous population: patients with the subphenotype 1 (12%) presented with shock, acidemia, and multiorgan dysfunction; patients with subphenotype 2 (29%)

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required early invasive mechanical ventilation and displayed the highest rate of ARDS; patients with subphenotype 3 (22%) had the highest rate of associated comorbidities, as opposed to those with subphenotype 4 (37%), who had fewer chronic medical conditions and showed milder physiologic abnormalities. Mortality rates at day 28 increased from subphenotype 1 (20.6% in the discovery cohort) to subphenotype 4 (52.9%) and remained significantly different across subphenotype classes after adjustment for confounders that included notably, but not exclusively, underlying comorbidities and organ dysfunction. All findings were similar in the replication cohort.

The authors showed a nice picture of subphenotypes in critically ill patients with COVID-19 and opened the door for an exciting research agenda. These results are strong and clean and make a lot of sense, but their clinical implications still have to be determined. Now, let's push research on this topic forward!

First, their approach requires external validation to assess generalizability. Vasquez et al[7] wisely chose 25 relevant and broadly available class-identifying variables, and it seems quite feasible to test reproducibility on existing observational or interventional cohorts of critically ill patients with COVID-19 to confirm their findings. Because the patients included in the study of Vasquez et al[7] were all admitted during the pandemics' first wave, one important question is whether the same four subphenotypes will be identified in patients from the second and third waves of the pandemic, comprising those infected with SARS-CoV-2 variants, patients from different health care systems, and patients who received different treatment strategies. Patients admitted in the ICU after the study inclusion period (ie, after mid-April 2020) likely received more corticosteroids, more antithrombotic medications, and more monoclonal antibodies directed against interleukins to limit inflammation. They also might have been treated with different airway treatment and oxygen delivery modalities.

Second and maybe more importantly, mirroring previous work on non-COVID ARDS hyperinflammatory and hypoinflammatory phenotypes,[2,8] we highly encourage researchers in this field to determine the difference of response to specific treatments on the four subphenotypes identified. In a recent issue of the *CHEST*, Chen et al[9] applied this approach in a monocentric cohort of critically ill patients with COVID-19. They showed that corticosteroid treatment was associated with increased survival in patients with the hyperinflammatory phenotype, representing 47.9% of their cohort, but had no effect on patients with the hypoinflammatory phenotype. Since the outbreak of the COVID-19 pandemics, so many randomized controlled trials have been conducted and so many observational cohorts have been followed worldwide that it would be a waste of resources not to build collaborations aimed at better identification of patients who could benefit more from each of the potential treatments that have been considered to date (eg, steroids, prone position, convalescent plasma, monoclonal antibodies).

Collaboration, precision medicine, and personalized treatment are a few keys that will open the door to a brighter future.[10]

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