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## COVID-19-related ARDS Subphenotypes and Differential Response to Corticosteroids: Time for More Precision?

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Immunomodulation is now standard of care for critically ill patients with COVID-19.<sup>1-4</sup> However, despite its singular causative pathogen, COVID-19-associated ARDS is a heterogeneous condition. Subphenotypes previously identified in ARDS have been identified in COVID-19.<sup>5</sup> Where distinct subphenotypes exist, the possibility of heterogeneity of treatment effect (HTE) exists as well.

Here, Sinha et al. present the interesting findings of a retrospective single-center observational study identifying distinct subclasses of critically ill COVID-19 patients with ARDS,<sup>6</sup> which were substantially similar to previously identified hypoinflammatory and hyperinflammatory subphenotypes of ARDS not related to COVID-19.<sup>7</sup> In a population of 483 mechanically ventilated patients who were admitted to two intensive care units in New York between March and April 2020, latent class analysis (LCA) identified two subphenotypes of COVID-19-related ARDS with differing clinical features, pro-inflammatory markers and outcomes. Class 2 (23% prevalence) was characterized by a higher sequential organ failure assessment (SOFA) score, ventilatory ratio, lactate, ferritin, and IL-6 compared to Class 1 (77% prevalence). Mortality at 90 days was significantly higher in class 2 (75% vs. 48%). Further, mortality differences between subphenotypes remained when adjusted for confounders including sex, body mass index, and SOFA score.

When a machine learning classifier model using clinical data only<sup>8</sup> was applied to assign subgroups previously described in ARDS<sup>7</sup>, similarity was noted between Class 1 and the hypoinflammatory subphenotype, and Class 2 and the hyperinflammatory subphenotype. HTE was noted, with hyperinflammatory/Class 2 patients showing improved survival with corticosteroids in contrast to hypoinflammatory/Class 1 patients who had worse outcomes. To the extent that the

LCA reproduces subphenotypes previously identified in non-COVID-19 ARDS, these data are further confirmation of the substantial similarity between COVID-19 ARDS and ARDS of other etiologies.

Of note, some patients were not consistently classified into conceptually concordant phenotypes by LCA and the machine learning model. 86% of the COVID-19-related ARDS-Class 1 patients were classified to the hypoinflammatory subphenotype and 81% of the COVID-19-related ARDS-Class 2 were classified as hyperinflammatory, leaving 14% and 19% “misclassified” respectively. This could be within the error limits of the model, or it could be that these classifier methods are identifying similar, but not identical, subgroups. Perhaps in the future it may be of benefit to think of subphenotypes as continuous, rather than categorical variables, with overlapping continuums and multiple factors influencing an individual’s position on each scale (Figure 1).

The strengths of this work are evident. The data describes a large population of patients with a high severity of illness, having a median SOFA score of 10 and a 31% rate of renal replacement therapy (RRT). The majority of screened patients (483 of 558) were included in the final analysis. A broad range of data was collected during a time when health services were under considerable strain, and care was taken to ensure retrospectively measured IL-6 was comparable to IL-6 measured at the time of hospitalization. The LCA method used is robust and is comparable to previous work in ARDS not due to COVID-19. The use of 90-day mortality as a primary endpoint is both rational and patient-centered.

There are some limitations that should be acknowledged. Most importantly, the study cohort may not be generalizable, evidenced by the very high mortality in early

pandemic New York. A trend of declining mortality due to COVID-19 over time has now been widely reported.<sup>9</sup> It will therefore be important to determine whether these findings can be replicated, particularly with respect to the relative subphenotypic proportions. Further, corticosteroid administration in this study was not randomized, meaning that the observed HTE may be confounded by unmeasured bias. Notwithstanding these concerns, the similarities between Class 1 and the hypoinflammatory phenotype and Class 2 and the hyperinflammatory phenotype support the face validity of these current data.

How do we resolve the differential response to corticosteroids noted in this study with the results of recent large trials? Benefit for dexamethasone in critically ill patients with COVID-19 has been demonstrated in two large clinical trials, with the strongest signal for benefit in mechanically ventilated patients.<sup>1,2</sup> If Class 1 and the hypoinflammatory subphenotype make up over 70% of the COVID-19-related ARDS population and this population may experience harm from corticosteroids, it is unlikely that these trials would have identified benefit with corticosteroids. There are a few potential explanations for this disparity. It is unlikely that the subphenotype proportions in this population of severely ill patients admitted to a tertiary center in a crisis scenario are representative of larger multicenter cohorts, highlighting the limitations of a single-center study design. Additionally, corticosteroids in this cohort were given ad hoc and varied in timing and duration. Corticosteroids are harmful when given later in the course of ARDS,<sup>10</sup> and indeed in RECOVERY a signal towards harm was seen in those patients not receiving supplemental oxygen.<sup>2</sup>

While the results presented by Sinha et al. are thought-provoking, data from large, randomized trials provide the best evidence we have regarding corticosteroids

in COVID-19, and their routine administration to hospitalized patients on supplemental oxygen should remain standard of care. At the peak of the COVID-19 pandemic, finding global treatment effects was of utmost priority. However, as in most critical care trials, non-responders will exist, and there is potential for harm in specific subgroups.

Once large trials establish standard of care, it becomes ethically challenging to prospectively study heterogeneity of treatment effect. This highlights the importance of collecting blood or tissue samples in clinical trials to aid future understanding of responders and non-responders. This has been accomplished in previous studies of ARDS not related to COVID-19<sup>11-13</sup> fueling a better understanding of HTE.<sup>7,14</sup> Such data was understandably not always collected during the peak of the COVID-19 pandemic, but where possible this should be undertaken. As stratification can be achieved with relatively limited data<sup>15</sup> this should be achievable in many settings.

Well-conducted retrospective studies such as the work of Sinha et al. provide important data to inform the need for a precision medicine approach embedded in clinical trials to address questions regarding treatment effects in specific subgroups.

## Declaration of Interest

KR reports grants from Wellcome Trust, outside the submitted work.

CCH reports his institution has received funding from Bayer to support his research outside the submitted work.

Outside the submitted work, DFM reports personal fees from consultancy for GlaxoSmithKline, Boehringer Ingelheim, Bayer, Novartis, SOBI and Eli Lilly, and from sitting on DMECs for trials undertaken by Vir Biotechnology and Faron Pharmaceuticals. In addition, his institution has received funds from grants from several funders for studies in patients with ARDS and COVID-19. In addition, DFM has a patent (US8962032) issued to his institution for a treatment for inflammatory disease. DFM is the MRC/NIHR EME Programme Director.

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## Figure Captions

**Figure 1:** A conceptual framework representing critical illness subphenotypes as continuous, rather than categorical, variables. A given individual might strongly allocate to a subphenotype by one classification method but may be indeterminate (in the uncertain area) in another classification schema, thereby residing on multiple points along the two lines representing class membership to Class 1/Class 2 and hyperinflammatory/hypoinflammatory. Continuous scores rather than absolute class membership, may then be used to select patients most likely to benefit from intervention, perhaps taking into account multiple class membership scores. A number of intrinsic and extrinsic factors (represented on the scales in the middle of the diagram), such as transcriptomic changes, vaccination status, socioeconomic factors, and infection with a particular SARS-CoV-2 variant (in the examples of subphenotypes of COVID-19) influence the individual's position on multiple continuums. VILI = ventilator-induced lung injury. IL-6 = interleukin-6

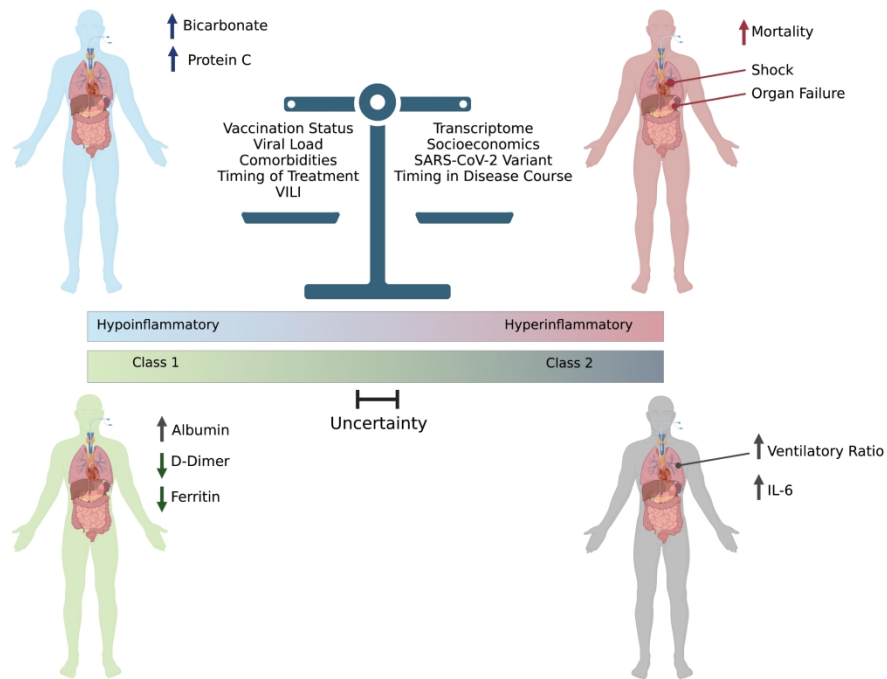


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