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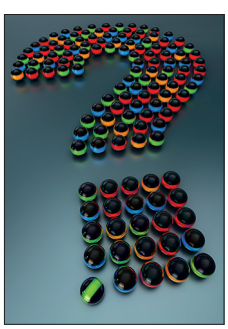
Physiological and biological heterogeneity in COVID-19-associated acute respiratory distress syndrome

One of the most common causes of hospital admission and death in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is acute respiratory distress syndrome (ARDS), a clinical syndrome characterised by acute lung inflammation and increased-permeability pulmonary oedema due to injury to the alveolar capillary barrier. As clinicians care for a surge of patients with ARDS due to COVID-19, two questions arise. First, is COVID-19-associated ARDS intrinsically different from ARDS unrelated to COVID-19? The answer to this question has implications for the use of evidence-based therapies such as lung-protective mechanical ventilation, proning, and conservative fluid management in COVID-19-associated ARDS. Second, is COVID-19-associated ARDS a uniform syndrome, or can phenotypes be identified? Recent clinical studies in so-called classical ARDS (a term used here to refer to ARDS unrelated to COVID-19, the causes and characteristics of which are heterogeneous) using latent class analysis have shown distinct hyperinflammatory and hypoinflammatory biological phenotypes of ARDS,[1] and emerging evidence indicates that these phenotypes respond differently to some clinical interventions.[2,3] Identification of similar, or new, distinct phenotypes within the scope of COVID-19-associated ARDS could shed light on mechanisms of lung injury in COVID-19 and have implications for clinical trial design.

In *The Lancet Respiratory Medicine*, two Articles begin to answer these questions. To address the first question, Giacomo Grasselli and colleagues[4] studied clinical and laboratory characteristics of 301 adults with COVID-19-associated ARDS admitted to intensive care units (ICUs) in seven Italian hospitals over a 2-week period in March, 2020. Lung mechanics were assessed in the first 24 h of ICU admission and compared with findings in historical cohorts of patients with classical ARDS. Similar to classical ARDS, the distribution of values for static compliance of the respiratory system was broad. Although patients with COVID-19-associated ARDS had higher median static compliance (41 mL/cm H_2O [IQR 33–52]) than those with classical ARDS (32 mL/cm H_2O [25–43]), this difference diminished in multivariable models controlling for other clinical characteristics. Furthermore, almost all of those with COVID-19-associated ARDS (280 [94%] of 297 patients) had static compliance values below the 95th percentile of reported values for classical ARDS, and the extent of pulmonary oedema in patients with COVID-19, measured by calculation of total lung weights from lung CT scans, was similar to that of patients with classical ARDS. D-dimers in 261 patients with COVID-19 were associated with ventilatory ratio, which is a surrogate for dead-space ventilation. A subgroup of patients with D-dimer concentrations greater than the median and static compliance equal to or less than the median (high D-dimers, low compliance [HDLC]) had markedly worse 28-day mortality than the others subgroups of high D-dimers, high compliance (HDHC); low D-dimers, low compliance (LDLC); and low D-dimers, high compliance (LDHC). 28-day mortality was 56% (40 of 71 patients) in the HDLC group, 27% (18 of 67 patients) in the LDHC group, 22% (13 of 60 patients) in the LDLC group, and 35% (22 of 63 patients) in



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the HDHC group. This worse survival in the HDLC group suggests that the intersection of more severe dysregulation of coagulation and fibrinolysis with more severe lung injury in COVID-19-associated ARDS is highly deleterious, supporting a pathophysiological role for pulmonary microvascular thrombosis in COVID-19-associated ARDS, as has been reported in classical ARDS. Overall, the findings of this large, systematic, multicentre study provide new evidence that lung physiology in COVID-19-associated ARDS is heterogeneous and not fundamentally different from that of classical ARDS, in contrast to previous single-centre reports in small groups of patients that suggested otherwise.[5] As such, these findings support recent calls for the application of evidence-based ARDS care, such as lung-protective mechanical ventilation and proning, in COVID-19-associated ARDS.[6]

The Article from Pratik Sinha and colleagues[7] addresses the question of whether the previously described hyperinflammatory and hypoinflammatory phenotypes of classical ARDS are present in COVID-19-associated ARDS. Validated models for phenotype classification[8] were applied to 39 patients with COVID-19-associated ARDS, using point-of-care biomarker measurements at the bedside. Patients could be classified into the two phenotypes with a high degree of certainty, suggesting that the previously identified ARDS phenotypes are robust in this new patient population. Overall mortality in COVID-19-associated ARDS was higher (17 [44%] of 39 patients had died by day 28 of the study) than in a matched cohort of patients with classical ARDS from the HARP-2 study (132 [24%] of 539). Consistent with classical ARDS, mortality in the hyperinflammatory phenotype (five [63%] of eight patients) was substantially higher than in the hypoinflammatory phenotype (12 [39%] of 31). Yet, in COVID-19-associated ARDS, only four (10%) to eight (21%), depending on cutoffs applied, were classified as hyperinflammatory, which was considerably lower than the proportion with this phenotype in the HARP-2 matched cohort (186 [35%] of 539). These findings are surprising, given the prevalent speculation in the literature that severe COVID-19 is characterised by an excessive inflammatory response or so-called cytokine storm. However, a report comparing interleukin-6 (IL-6) levels in patients with COVID-19-associated ARDS to levels measured in classical ARDS showed that IL-6 levels, on average, were lower in the patients with COVID-19 than in those with classical ARDS.[9] Taken together, these findings suggest that the pathophysiology of COVID-19-associated ARDS is more complex than a simple overproduction of cytokines, and that there is heterogeneity within COVID-19 that is similar to that of classical ARDS, albeit with different distributions.

Although both of these studies provide new information about COVID-19-associated ARDS, there are some limitations. The study by Grasselli and colleagues[4] was done over a 2-week period during a rapid spike in COVID-19 cases, which might have affected clinical care; and it reflects cases in only one country. The study by Sinha and colleagues[7] is also geographically limited and had a very small sample size. Both studies assessed patients at a single timepoint, which might not be reflective of the protracted course of critical illness in many patients with COVID-19-associated ARDS. A report of deep immune profiling of patients with COVID-19 identified three immunophenotypes that were quite stable over 7 days, but some immunological signatures that were highly dynamic over time, underscoring the need for serial analyses.[10] Despite the limitations, the authors of both of these studies are to be commended for applying high-quality research methods during a surge of COVID-19 cases.

The ongoing COVID-19 pandemic reminds physicians daily of the importance of clinical investigation as a tool for improving the understanding and treatment of human disease. Like all good clinical investigations, the studies from Grasselli and colleagues[4] and Sinha and colleagues[7] provide answers that lead to new questions. The study by Grasselli and colleagues[4] prompts the question of whether identification of an HDLC group could be used to predictively enrich trials of empirical therapeutic anticoagulation to reduce sample size and improve the ratio of benefit to risk. The fact that only a small minority of the patients in the study by Sinha and colleagues[7] had a hyperinflammatory phenotype raises the question of whether dexamethasone treatment, which has been shown to be effective in patients with severe COVID-19 disease, will be uniformly beneficial across both phenotypes of COVID-19-associated ARDS. To answer these questions and the many others that

arise during the daily care of patients with COVID-19-associated ARDS, it is imperative that high-quality clinical investigation proceeds, despite the inherent challenges of implementing research protocols in the uncertain and risky environment of a pandemic.

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Lorraine B Ware
lorraine.ware@vumc.org

Departments of Medicine and Pathology, Microbiology and Immunology, Vanderbilt University School of Medicine, Nashville, TN 37232-2650, USA

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Autopsy insights from the EVALI epidemic

The first recorded autopsy was that of Julius Caesar in 44 BCE to establish which knife wound had caused his death; the wound that ruptured his aorta was the culprit. Autopsies have been the foundation of medical advancement over the subsequent centuries, and were done in 40–60% of all hospital deaths as recently as the 1950s.[1,2] With increasingly sophisticated imaging and diagnostic advancements, autopsy rates have declined substantially to less than 1%.[3] Despite these advancements, clinically missed diagnoses involving a primary cause of death are found at autopsy about 8–24% of the time.[4]

Given the frequency of misclassification when clinicians diagnose familiar diseases; e-cigarette, or vaping, product use-associated lung injury (EVALI), a new syndrome whose definition is evolving, is expected to result in similar or even greater diagnostic error. Initial reports were based on a non-specific clinical case definition of vaping, imaging opacities, and exclusion of alternative explanatory diagnoses.[5]

In *The Lancet Respiratory Medicine*, Sarah Reagan-Steiner and colleagues[6] present the first systematic characterisation of EVALI using autopsy and lung biopsy findings, which help to improve the understanding of what EVALI is, and is not. In addition to lung biopsy samples from 10 patients, the report includes autopsy findings from 13 individuals, representing a quarter of patients who were reported to have died from EVALI (52 as of Dec 10, 2019).[7] Three (23%) of 13 individuals who died from suspected EVALI had pulmonary pathology suggesting an alternative or concomitant disease. In retrospect, given the pathological findings of bronchopneumonia, bronchoaspiration, or interstitial lung disease, these patients would not have met the definition of EVALI that required exclusion of alternative diagnoses. Clinicians face this diagnostic challenge daily, with inadequate data, and they need to decide how invasive an evaluation should be to exclude alternative causes of respiratory failure.

The findings generated from this pathological case series reveal how heterogenous a lethal syndrome such as EVALI can be. Severe diseases often manifest with multiple organ dysfunction regardless of the original injury. Some patients with EVALI had microthrombi in the renal glomeruli, and other studies have characterised patients with gastrointestinal symptoms.[5,8] Additionally, the presence of fibrosis, aspiration, infection, heart failure, and asthma all suggest alternative or additional diagnoses in up to


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