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COVID-19 and Interstitial Lung Disease: Keep Them Separate

Since the emergence of the novel coronavirus now known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019, there have been more than 50 million documented infections and 1.2 million deaths worldwide (1). Our understanding of SARS-CoV-2 transmission and pathogenicity and the mechanism by which it causes coronavirus disease (COVID-19) has evolved rapidly, as have the recommendations on treatment and risk mitigation strategies. The clinical spectrum of SARS-CoV-2 infection ranges from asymptomatic to severe disease necessitating ICU admission and mechanical ventilation (2). Up to 45% of those infected are asymptomatic, whereas approximately 3–10% require hospitalization (3–5). Severe disease, defined by dyspnea, hypoxemia, and pulmonary infiltrates, occurs in up to 20% of hospitalized patients and is associated with a high mortality rate (6). However, these estimates vary widely depending on the population being studied. Advanced age, male sex, and multiple comorbidities all increase the risk of death from COVID-19 (7). A key component of the public health response to COVID-19 has been a focus on identifying groups at increased risk for complications and death from COVID-19 and reducing their risk of exposure to SARS-CoV-2.

Interstitial lung disease (ILD) is characterized by injury to the alveolar epithelium and abnormal wound healing (8). Patients with ILD have diminished pulmonary reserve and impaired gas exchange. Viral infections can trigger acute exacerbations, which are associated with poor outcomes (9). Many patients with ILD are on immunosuppressive medications. It stands to reason that patients with ILD would have an increased rate of complications and death from COVID-19. However, until now, no studies have examined the impact of COVID-19 on these patients.

In the current issue of the *Journal*, two manuscripts report on the outcomes of adults with COVID-19 and preexisting ILD. Drake and colleagues (pp. 1656–1665) assess in-hospital mortality of 161 patients with ILD hospitalized with COVID-19 across multiple centers in Europe and compare it with a control group of patients with COVID-19 without underlying lung disease, matched on age, sex, and nonpulmonary comorbidities using a propensity score (10). They find that patients with ILD have significantly higher in-hospital mortality compared with those without ILD (49% vs. 35%). The risk of mortality increases with older age and male sex. For instance, for males over the age of 75, mortality is 62%. The presence of obesity, idiopathic pulmonary fibrosis, and FVC below 80% predicted are also associated with greater risk of death.

Esposito and colleagues (pp. 1710–1713) examine mortality among 46 patients with preexisting ILD diagnosed with COVID-19 at six Boston medical centers and compare it with age-, sex-, and race-matched controls without ILD evaluated at the same hospitals (11). Mortality in this study is 33% for patients with ILD, compared with 13% for controls. After adjustment for age, sex, race, smoking status, comorbid cardiovascular disease, and use of immunosuppression, patients with ILD were found to have a more than fourfold higher risk of dying compared with controls. In contrast to Drake and colleagues, this study included both hospitalized and nonhospitalized patients. Adults with ILD were more likely to be admitted to the hospital (74% vs. 58%) and require ICU care (47% vs. 23%) and less likely to be discharged

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home. Those who died were older, had lower D_{LCO}, and had an increased proportion of a usual interstitial pneumonia pattern on computed tomography scan. The small sample size of this study limits any conclusions regarding clinical and demographic factors associated with mortality.

Taken together, these two studies show that patients with a broad range of ILDs across multiple international healthcare settings have an increased risk of death from COVID-19 compared with adults without ILD, even after controlling for age, sex, and comorbidities. Most of the patients included in both studies had disease severe enough to require hospitalization. Many were admitted to the ICU. Patients with mild or asymptomatic disease were unlikely to have been tested or evaluated at the hospitals included in these studies and were not captured in the analyses. This limits any inferences about the risk of severe SARS-CoV-2 infection in patients with ILD. Neither study reported in detail on the clinical events that preceded death. Autopsy data are not available. It is therefore unknown if patients with ILD have increased rates of thrombotic or infectious complications that may contribute to increased mortality. The studies were also not designed to examine any treatment effects of steroids or antifibrotics in this patient population, and the number of patients on these medications was small. The low number of patients on mechanical ventilation also limits conclusions about this modality in patients with ILD and COVID-19. However, those on mechanical ventilation had very high mortality, suggesting that the use of mechanical ventilation in this population should be reserved for carefully selected patients. Given the high mortality rate of patients with acute exacerbations of ILD, establishing advanced care directives remains critically important for this group of patients, and the findings by both Drake and Esposito should inform these discussions (12).

These findings have practical implications for the care of patients with ILD during the COVID-19 pandemic. Both studies identify patients with ILD as a group at high risk for morbidity and mortality from SARS-CoV-2 infection. Healthcare providers should appropriately advise patients with ILD on self-isolation, mask use, and other strategies to reduce the risk of SARS-CoV-2 infection. However, these recommendations must be balanced with the need for disease and treatment monitoring (13). Idiopathic pulmonary fibrosis and other fibrotic ILDs are chronic, progressive, and highly morbid conditions. Patients with ILD are often older, with multiple comorbidities and impaired quality of life. Depression and anxiety are common and may be exacerbated by the stress of the pandemic and the need for social distancing (14). The loss of access to pulmonary rehabilitation programs and concern about leaving the house may lead to inactivity, deconditioning, and weight gain. Given the increased risk of mortality associated with obesity in this patient population, and reported by Drake and colleagues, it remains important to continue to encourage patients to remain active and exercise while maintaining appropriate physical distancing (10, 15). Providers caring for patients with ILD need to be aware of these issues and implement initiatives that mitigate the adverse impact of the pandemic on patient outcomes.

The COVID-19 pandemic has also resulted in an opportunity for more widespread use of novel technology for remote disease monitoring, including video visits, telemedicine, home spirometry, and other eHealth interventions. The available technology is rapidly improving and gaining acceptance among patients and healthcare providers as a feasible alternative to deliver care to patients at high risk for complications due to SARS-CoV-2 infection. eHealth resources can be incorporated into the care of patients with ILD and have been shown to improve psychological well-being (16). Remote monitoring should not fully replace in-person evaluations, but it can individualize care and maximize patient–provider interactions while minimizing the risk of exposure.

The two papers in this issue of the *Journal* add to the body of work on increased risk of death from COVID-19 in patients with underlying lung disease. However, the additional consequences of the COVID-19 pandemic in this patient population will include long-term disability in those who survive; excess morbidity and mortality owing to limited access to timely diagnosis, treatment, and follow-up care; and decreased rates of lung transplantation, all adding to the burden of an already high-burden disease. The long-term impact of COVID-19 on patients with ILD remains undefined. As we near 1 year since the emergence of SARS-CoV-2, we must continue to adapt our practice based on new data and evolving knowledge of this disease while continuing to ensure that patients with ILD receive optimal and evidence-based care focused on improving outcomes and quality of life. ■

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In Pursuit of Microbiome-based Therapies for Acute Respiratory Failure

A presumably overly robust inflammatory response has been associated with poor clinical outcomes in patients with acute respiratory failure, including patients with acute respiratory distress syndrome (ARDS) and sepsis (1). Likewise, both abnormal gut and respiratory microbiota patterns (termed "dysbiosis") are also predictive of increased mortality among critically ill patients (2). The ambitious aim of the study by Kitsios and colleagues (pp. 1666–1677) in this issue of the *Journal* is to better define the interplay between the host inflammatory response and the lung microbiome and the impact of this relationship on clinical outcomes in a heterogenous population of critically ill patients with acute respiratory failure (3). The results of this investigation represent an important step in the process of developing a microbiome-guided or microbiome-based treatment for critically ill patients with acute respiratory failure.

The cohort characteristics in the study by Kitsios and colleagues were typical of an ICU population of patients with acute respiratory failure requiring mechanical ventilation: extrapulmonary sepsis (18%), ARDS (24%), and pneumonia (40%) were common diagnoses, and 32% of the patients received antibiotics before admission to the ICU. At the time of enrollment (<72 h postintubation), posterior oropharyngeal swab and endotracheal aspirate (ETA) samples were collected and analyzed with 16s ribosomal RNA gene sequencing to characterize the microbiota of these respective environments. Simultaneously, the following plasma inflammation–related biomarkers were measured: receptor of advance glycation end-products, soluble tumor necrosis factor receptor 1, IL-10 fractalkine, and angiopoietin 2. This biomarker data was used in conjunction with clinical variables to dichotomize the patients into either hyper- (23%) or hypoinflammatory (77%) phenotypes. Similar to prior, albeit smaller, microbiome studies of the critically ill, the upper and lower respiratory microbiota demonstrated reduced α and β diversity when compared with samples from healthy control subjects (4). Nonetheless, there was substantial heterogeneity in bacterial composition across samples from study patients, which was addressed by using Dirichlet-multinomial models and Laplace approximation of model fitting to identify distinct microbial clusters among the upper and lower respiratory samples. Common to both the upper and lower respiratory sampling was a particular cluster ("cluster 2") that was notable for having a lower α diversity and a high abundance of respiratory pathogens. In particular, cluster 2 samples found in lower respiratory samples demonstrated a high abundance of *Staphylococcus*, *Stenotrophomonas*, *Enterobacteriaceae*, and *Pseudomonadaceae* and a low abundance of oral-origin organisms associated with a healthy lung microbiome. In addition, cluster 2, especially in ETA samples, was noted to have a number of clinical associations, most of which were unfavorable. Patients with ETA cluster 2 were more likely to have chronic obstructive pulmonary disease at baseline, were more likely to have been treated with antibiotics before being admitted to the ICU, and were more likely to be diagnosed with ARDS and extrapulmonary sepsis. The hyperinflammatory subphenotype was also more prevalent among patients with cluster 2–enriched ETA samples (odds ratio, 1.2 [1.1–1.9]; $P = 0.03$, adjusted for antibiotic exposures). Unsurprisingly, patients afflicted within cluster 2 microbiota suffered comparatively worse outcomes, including a higher 30-day mortality. The authors then used these results to construct a dysbiosis index based on the relative abundance of protective microbiota (≥30%) and α diversity (Shannon index ≥ 1.98) that was predictive of both a hyperinflammatory state and an increased mortality rate.

The limitations of this study are worth noting but do not detract significantly from the overall results. It was a single-center trial (microbiomes are known to vary based on geography), convenience sampling was employed, and enrollment was

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