Double Jeopardy: Precapillary Pulmonary Hypertension Increases the Risk of Hospitalization and Death from COVID-19

Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in more than 6.2 million deaths globally. Despite the expeditious development of effective vaccinations and treatments, vulnerable individuals remain susceptible to complications from COVID-19, especially patients with cardiopulmonary disease (1).

The lungs are the prime target of SARS-CoV-2 infection, and a primary cause of death is severe pneumonia resulting in respiratory failure (2). In autopsy studies of COVID-19 decedents, investigators identified pulmonary histopathologic abnormalities frequently observed in patients with acute respiratory distress syndrome (ARDS), including diffuse alveolar damage and pulmonary vascular microthrombi (3). Pulmonary vascular complications have long been a pathological hallmark of ARDS (4, 5), and patients with ARDS who develop pulmonary hypertension (PH) and right ventricular dysfunction are at increased risk of death (6, 7). Mounting evidence suggests that severe COVID-19 causes prominent pulmonary vascular dysfunction, including endotheliopathy (8, 9), pulmonary vascular microthrombi (10, 11), and increased estimated dead space fraction (11, 12).

These observations led investigators to hypothesize that PH is a risk factor for adverse outcomes from COVID-19 and, conversely, that pulmonary arterial hypertension (PAH) therapies, which ameliorate pulmonary endothelial function, could protect patients from the pulmonary vascular effects of COVID-19. However, observational data were conflicting, with some studies reporting paradoxically favorable outcomes (13, 14) and others poor outcomes (15, 16). To date, the clinical trajectory of patients with COVID-19 with precapillary PH has not been adequately described.

In this issue of the Journal, Montani and colleagues (pp. 573–583) report the largest prospective study to describe the baseline characteristics and clinical outcomes of patients with precapillary PH who received diagnoses of COVID-19 (17). In the national French PH registry, 211 of 7,678 patients (2.7%) received diagnoses of COVID-19 (Figure 1). Investigators observed a high rate of hospitalization (60%) and in-hospital mortality (41.3%), which they highlight is well above the COVID-19 mortality cited for France during the study period (~19%). Those at highest risk of dying were male, older, had more severe baseline PH, and were more medically comorbid.

A key strength of this study is its cohort design: given the centralized nature of the PH referral network in France, the investigators assembled the largest prospective cohort study of patients with PH with comprehensive baseline phenotyping and longitudinal follow-up. Patients underwent right heart catheterization within a median of 12 months before COVID-19 diagnosis, demonstrating definitive precapillary PH. A slight majority (56.9%) were in New York Heart Association functional class I or II; elevated natriuretic peptide concentrations were present in half (49.5%) before their diagnoses; most (84%) were on at least one PAH therapy, with monotherapy, dual therapy, and triple therapy observed in 31.8%, 38.9%, and 13.3%, respectively; and just over half (55%) were on therapeutic anticoagulation.

In addition, because the data collection spanned from the onset of the pandemic (when treatment options were limited) to the spring of 2021 (when corticosteroids were more widely used), the investigators were positioned to capture national secular trends in COVID-19 management. For example, comparing the period before and after September 2020, the proportion of patients treated with corticosteroids and high-flow oxygen increased from 9.8% and 14.6% to 75.3% and 48.2% (\(P < 0.001\)), respectively, with no change in the observed rate of mechanical ventilation (12.2% vs. 10.6%; \(P = 0.97\)) or survival (46.3% vs. 38.3%; \(P = 0.54\)). Unfortunately, the impact of vaccination on this population could not be addressed during the present study period, but ongoing longitudinal follow-up will help clarify this question.

There are several observations regarding prognosis worth emphasizing. First, the investigators identified anticipated risk factors for poor clinical outcomes in addition to the sex dimorphism characteristic of prognosis in both COVID-19 and PH: men are at increased risk of in-hospital mortality, with ~2.5 times increased odds of death (95% confidence interval, 1.12–5.40; \(P = 0.025\)). Sex-based differences in pulmonary vascular–right ventricular response to acute illness with COVID-19 warrant further study. Second, although most patients (60%) required hospitalization, only a quarter (27.5%) required ICU admission, and although natriuretic peptide elevation was observed in 54.5% of hospitalized patients, only 11% of patients developed right ventricular failure requiring inotropic support, and two received extracorporeal membrane oxygenation. Few patients (11.1%) received mechanical ventilation—a therapy generally avoided in patients with right ventricular dysfunction—but if intubated, one-third survived, and of those who received high-flow oxygen, half survived. Finally, among the 74 patients discharged alive, only 5.4% died in the subsequent year. COVID-19 is definitively morbid if patients with PH develop respiratory and/or right ventricular
Figure 1. Patients with precapillary pulmonary hypertension (PH) are at increased risk of hospitalization and in-hospital mortality from coronavirus disease (COVID-19). Patients with underlying cardiopulmonary disease are at increased risk of adverse clinical outcomes from COVID-19, but observational data are conflicting regarding the risk posed to patients with PH. In this issue of the *Journal*, Montani and colleagues report results from the largest national prospective cohort study of patients with PH who received diagnoses of COVID-19, wherein they observed high rates of hospitalization (60%) and in-hospital mortality (41.3%). Patients at highest risk of dying were male, older, had more severe baseline PH, and were more medically comorbid. Pulmonary vasodilator therapies did not protect against in-hospital death, but patients on baseline anticoagulation were more likely to survive their hospitalization. This study establishes that patients with precapillary PH are at increased risk of adverse clinical outcomes from COVID-19, underscoring the public health importance of preventive measures in this high-risk population. CTEPH = chronic thromboembolic pulmonary hypertension; PAH = pulmonary arterial hypertension. Illustration by Jill Gregory.
Calcineurin Inhibitors in Lung Donors to Attenuate Ischemia–Reperfusion Injury in Recipients

Next Steps?

Lung transplantation is a life-saving procedure for patients with advanced lung disease. However, a major challenge in lung transplantation has been the low use of donor lungs, with rates estimated at 20%, internationally (1). The early post-transplant period can be complex, and ischemia-reperfusion (IR) injury of the lung graft is one of the most common risk factors for primary graft dysfunction (2), observed in approximately 30% of lung transplants (3). Primary graft dysfunction can lead to significant early morbidity (prolonged length of mechanical ventilation and hospital stay) (4) and also increase the risk of premature graft loss, chronic allograft dysfunction, and mortality (5).

Donor shortage is more common in lung transplantation than in other solid-organ transplants (6). Organ donation after circulatory death, chronic allograft dysfunction, and mortality (5).

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