



COVID-19 Experience and Pulmonary Arterial Hypertension: Do Earlier Theses and New Data Still Match?

To the Editor:

We read with interest the survey estimating the incidence and outcomes of coronavirus disease (COVID-19) in patients with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) (1) and its associated editorial (2).

It is indeed valuable knowledge regarding the impact of this pandemic on the PAH/CTEPH population in the United States, estimating a higher COVID-19–related mortality compared with the general population. Data are consistent with the survey recently published in the *European Respiratory Journal*, in which most of the information was collected from European countries (3). Nevertheless, it is our opinion that this information needs to be cautiously read in view of the number of patients included (70 and 50 in *European Respiratory Society* and *AnnalsATS*, respectively), the high variability between patients' age, collection methods, and mortality figures across the countries. Although the PAH/CTEPH fatality rate is inevitably higher than in the general population, it is important to keep in mind that initial case-reports published at the beginning of this pandemic emphasized the surprisingly uneventful course of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in these patients, and efforts were made trying to explain these observations (4, 5). We still have the impression, based on our own updated data with 38 confirmed COVID-19 cases in a cohort of 770 patients under follow-up, that their COVID-19–associated risk continues to be lower than expected back in March 2020. In fact, only 3 of these 38 (8%) patients died, all of them belonging to low-risk PAH/CTEPH scores but with significant advanced age and comorbidities. On the contrary, younger patients with higher-risk PAH score hospitalized with bilateral pneumonia performed surprisingly well and could be discharged, whereas their usual mortality risk from respiratory failure processes reaches 20%.

We enjoyed the editorial reviewing how the substrates inherent to the vascular remodeling that characterizes both PAH and CTEPH could modify COVID-19 course by various mechanisms. In a recent review of this topic, it was indeed pointed out how difficult it was to estimate the net effect of this PAH/CTEPH–underlying histopathology (6). Many theories in different directions have been formulated about the role of ACE2 receptor, the ventilation–perfusion mismatch, or the tertiary lymphoid tissue that characterizes PAH. The same is true for the impact of PAH-targeted treatments. Although this net effect might be difficult to estimate, we should not forget that it has drawn the attention of the scientific community, and several trials are ongoing exploring the effectiveness of PAH-specific therapies in COVID-19 (6). We are awaiting with particular interest the results of the randomized clinical trial evaluating ambrisentan.

We would also like to stress the importance of the prothrombotic status that accompanies COVID-19 and the current consensus on the use of prophylactic heparin in COVID-19 pneumonia. Notably, no thromboembolic events were reported in the *European Respiratory Journal* survey despite thromboembolism being a well-recognized complication of COVID-19 (3). This endorses our theory of chronic anticoagulation being another potential gamechanger in the course of COVID-19 in patients with CTEPH, in whom it may offset this thrombogenic environment. In this line, ongoing clinical trials are evaluating the use of different anticoagulant drugs in COVID-19 (6).

In conclusion, large international surveys are indeed necessary to better estimate the impact of COVID-19 in patients with PAH/CTEPH. However, collection methods and baseline characteristics of patients among countries make still difficult to draw conclusions. Although their overall risk related to COVID-19 might be understandably higher than that for the general population, it is our experience that is not as catastrophic as we initially expected. Moreover, some of the observations made in the field of COVID-19–PAH/CTEPH have prompted the design of clinical trials that may allow us to broaden the knowledge of this disease and hopefully to improve its management.

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Reply: COVID-19 Experience and Pulmonary Arterial Hypertension: Do Earlier Theses and New Data Still Match?

From the Authors:

We would like to thank Dr. Segura de la Cal and colleagues for their interest in our work (1) and dedication to these important questions. We share their wish that patients with pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH) might ultimately be found to have a lower-than-expected risk for poor outcomes from coronavirus disease (COVID-19). Nevertheless, we would like to caution against early speculation that pulmonary vascular disease or its treatments may be protective in the setting of COVID-19 infection.

Although case fatality rates for COVID-19 have been hard to estimate (2), overall and age-specific case fatality rates have been reported in the general population of New York and may be reasonable benchmarks (3). The overall case fatality rate in New York was 1.4%. For individuals <64 years old, the case fatality rate was <1%. The case fatality rate then rose dramatically with age. Those aged 65–74 had a case fatality rate of 4.9% and those aged ≥75 had a case fatality rate of 14.2%. We believe these numbers are important to keep in mind when interpreting available data in patients with PAH/CTEPH.

For example, case fatality rates in our United States–based survey (12%) and the international survey of PAH/CTEPH centers (4) (19%) approach or exceed case fatality rates expected for the oldest members of the population (≥75 yr old) in New York. In fact, most patients with COVID-19 in the international survey were <65 years old, making the reported case fatality rate of 19% even more concerning. Dr. Segura de la Cal and colleagues note that their data

describing patients with PAH and COVID-19 show an 8% overall case fatality rate. All three deaths (among 39 total cases) were in patients with “significant advanced age.” If we presume that some patients with recognized COVID-19 were <65 years old, the case fatality rate in their older patients must have been over 8% and could possibly be significantly higher depending on the age of the other patients. As such, their data also do not appear to suggest clear protection in the older age group. Published case series include fewer than 100 patients; therefore, we do not yet have sufficient data to suggest or refute the likelihood for protection in younger patients with PAH/CTEPH relative to the general population of the same age (in which case fatality is <1%). Although we acknowledge age-related differences in pulmonary hypertension phenotypes, it seems unlikely that PAH/CTEPH or its treatments would exert a protective effect against COVID-19 in younger patients and a detrimental effect in older patients.

To the broader point, we emphatically agree that these interesting issues are worthy of further study. The respondents are correct to highlight limitations in available population data and to temper any rush to definitive conclusions. Current studies involve small numbers of patients and comparison with the broader population must be done with caution. Differences in confounders, health behaviors, and access to COVID-19 testing (especially early in the pandemic) among patients with PAH/CTEPH might make independent associations of COVID-19 and case fatality either more or less pronounced with respect to the general population than initially reported.

In summary, existing population studies consistently suggest the same or a higher risk for poor outcomes with COVID-19 in patients with PAH/CTEPH relative to the general population. There are deficiencies in available population data, and the results contrast with hypotheses at the bench that may suggest protection (5). We would enthusiastically welcome population data that support better outcomes for these patients; however, barring this evidence, we worry that a premature impression of disease-specific protection might lead some patients with PAH/CTEPH to avoid taking life-saving precautions against contracting COVID-19.

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