entirely explain lower D_{LCO}. Therefore, it is conceivable to conclude that structural lung lesions, not precapillary PH, contributed to mortality.

The majority of patients in this study received pulmonary vasodilator therapy. Considering the patient population in this study, many patients could have PH due to left heart disease (4). The authors refuted this hypothesis and contended that pulmonary arterial hypertension (PAH)–specific medications may not be protective during COVID-19. Pulmonary vasodilator therapy has not been shown to improve outcomes in PH due to left heart disease. Therefore, it may not be logical to refute the hypothesis, as the beneficial effects of PAH-specific medications could have been counteracted by possible harmful effects in PH due to left heart disease. Moreover, the nonsurvivors had poor D_{LCO}, and patients with poor D_{LCO} have a different kind of vasculopathy and are less responsive to PAH therapy (5). Furthermore, the investigators should have also aimed to provide echocardiographic data and medications used to treat comorbidities.

In conclusion, symptomatology and cardiac catheterization data of PH and heart failure are often indistinguishable in older populations with multiple comorbidities. Isolated precapillary PH should be clearly differentiated from IpcPH and CpcPH, as PAH-directed therapy may not be appropriate for all three phenotypes of PH. The impact of PAH-directed therapy in a mixed population of individuals with PH and COVID-19 may not be assessed distinctly. ■

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Ajay Kumar Jha, M.D., D.M.*
Jawaharlal Institute of Postgraduate Medical Education and Research Pondicherry, India

ORCID ID: 0000-0002-8968-9216 (A.K.J.).

*Corresponding author (e-mail: drajaykjha@rediffmail.com).

References

1. Montani D, Certain MC, Weatherald J, Jaïs X, Bulifon S, Noel-Savina E, *et al.*; French PH Network PULMOTENSION Investigators. COVID-19 in patients with pulmonary hypertension: a national prospective cohort study. *Am J Respir Crit Care Med* 2022;206: 573–583.
2. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, *et al.* 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2022;145:e895–e1032.
3. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, *et al.* Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J* 2019;53: 1801913.
4. Al-Omary MS, Sugito S, Boyle AJ, Sverdlov AL, Collins NJ. Pulmonary hypertension due to left heart disease: diagnosis, pathophysiology, and therapy. *Hypertension* 2020;75:1397–1408.
5. Souza R, Fernandes CJ, Hoeper MM. Carbon monoxide diffusing capacity and the complexity of diagnosis in pulmonary arterial hypertension. *Eur Respir J* 2014;43:963–965.

Reply to Jha

From the Authors:

We thank the author for their interest in our recent article on the French prospective cohort of coronavirus disease (COVID-19) in patients with pulmonary hypertension (PH) (1). First of all, the author wondered if all patients in our study truly had precapillary PH. As stated in the methods, all patients' data were extracted from the French registry, which includes well-phenotyped patients with PH, all having undergone complete hemodynamic evaluation, and has led to many publications in recent decades (2, 3). All patients included in this analysis had precapillary PH at the time of diagnosis, in accordance with the current definition during the inclusion period (i.e., a mean pulmonary arterial pressure of ⩽25 mm Hg, a normal pulmonary arterial wedge pressure [PAWP] of ⩽15 mm Hg, and pulmonary vascular resistance of >3 Woods units) (4). According to international definitions, this excluded the presence of PH due to left heart diseases (group 2 PH) as the main cause of PH in this population. The most recent right heart catheterization data for these patients yielded a median PAWP of 10 (interquartile range, 7–13) mm Hg. At the last hemodynamic evaluation before COVID-19, a small subgroup of 14 patients (6.6% of the overall 213 patients) had combined pre- and postcapillary PH with PAWP >15 mm Hg, which is in accordance with the age and comorbidities reported in this population as well as the possibility of ventricular interdependence. The etiologies of PH among these patients were PH associated with chronic respiratory diseases ($n = 6$), idiopathic pulmonary arterial hypertension (PAH) ($n = 4$), anorexigen-associated PAH ($n = 2$), and chronic thromboembolic PH ($n = 2$). We disagree with the assumption that the high prevalence of comorbidities is, on its own, indicative of postcapillary PH and also wish to correct the author's statement that all patients were >60 years of age, as the interquartile ranges for age in the groups presented in our Table 1 include patients in their 40s and 50s. Recent national registries highlight frequent pulmonary and cardiovascular comorbidities in patients with PAH (3, 5, 6). In the French PH Registry, systemic hypertension, obesity, diabetes, coronary heart disease, and atrial fibrillation were recorded in 50%, 32%, 25%, 14%, and 11%, respectively, in a large population ($n = 1{,}611$) of subjects with idiopathic, heritable and anorexigen-associated PAH (3). The prevalence of comorbidities was broadly similar in the present study, especially if we put in perspective that our cohort included patients with groups 3 and 4 PH, classically associated with older age and more frequent comorbidities. Indeed, the assumption that normal right atrial pressure in the presence of high brain natriuretic peptide or N-terminal pro–brain natriuretic peptide indicates left ventricular failure with normal right ventricular function has no meaning in a population with precapillary PH

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confirmed by cardiac catheterization with increased pulmonary vascular resistance and decreased cardiac index (1). Of the 14 patients with precapillary PH with increased PAWP diagnosed during hemodynamic follow-up, 3 patients died during hospitalization for COVID-19, representing a mortality rate of 21.4% that is in accordance with the overall mortality of the entire cohort (24.6%; 95% confidence interval, 18.8–30.5%). It is likely that some patients with precapillary PH had associated heart failure with preserved ejection fraction (HFpEF), as evidenced by the occurrence of increased PAWP in a subset of patients undergoing hemodynamic monitoring. However, the increase in PAWP in patients with precapillary PH was not associated with excess mortality in our cohort. It is nevertheless likely that HFpEF was probably underestimated in patients with precapillary PH, as fluid challenge was not systematically performed during right cardiac catheterization to diagnose HFpEF.

Similarly, the D_{LCO} of 53.5% (95% confidence interval, 35–66%) reported in our cohort is in accordance with the etiologies of precapillary PH, including mainly PAH and chronic thromboembolic PH but also pulmonary venoocclusive disease and chronic respiratory disease–associated PH, which are all typically associated with major decreases in D_{LCO}. Indeed, Hoeper and colleagues recently reported that low D_{LCO} (<45%) was frequently observed in patients with diagnoses of idiopathic PAH, and this may represent a specific phenotype close to group 3 PH (6). In our cohort, we observed an increased risk of mortality in patients with chronic respiratory diseases, giving an obvious explanation for the lower D_{LCO} in deceased patients. The recent 2022 European Society of Cardiology/European Respiratory Society guidelines highlight that comorbidities, including decrease in D_{LCO}, were associated with worse response to PAH-approved drugs in patients with PAH (7).

In conclusion, the prevalence of cardiovascular and pulmonary comorbidities reported in our cohort is in accordance with the epidemiology of patients with precapillary PH in large national registries. Although it is possible that some patients had occult HFpEF, a small number had elevated PAWP during follow-up, and this was not associated with outcomes. Univariate and multivariate models demonstrated significant associations between chronic respiratory and cardiovascular diseases and the risk of in-hospital mortality in patients with precapillary PH. This is not surprising given that cardiopulmonary comorbidities are considered poor prognostic factors for PH and COVID-19. ■

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David Montani*
Université Paris-Saclay
Le Kremlin-Bicêtre, France

Hôpital Marie Lannelongue
Le Plessis Robinson, France

and

Hôpital Bicêtre
Le Kremlin-Bicêtre, France

Jason Weatherald
University of Calgary
Calgary, Alberta, Canada

Marc Humbert
Olivier Sitbon
Université Paris-Saclay
Le Kremlin-Bicêtre, France

Hôpital Marie Lannelongue
Le Plessis Robinson, France

and

Hôpital Bicêtre
Le Kremlin-Bicêtre, France

ORCID IDs: 0000-0002-9358-6922 (D.M.); 0000-0002-0615-4575 (J.W.); 0000-0003-0703-2892 (M.H.); 0000-0002-1942-1951 (O.S.).

*Corresponding author (e-mail: david.montani@aphp.fr).

References

1. Montani D, Certain MC, Weatherald J, Jaïs X, Bulifon S, Noel-Savina E, *et al.*; French PH Network PULMOTENSION Investigators. COVID-19 in patients with pulmonary hypertension: a national prospective cohort study. *Am J Respir Crit Care Med* 2022;206:573–583.
2. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, *et al.* Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med* 2006;173:1023–1030.
3. Boucly A, Savale L, Jaïs X, Bauer F, Bergot E, Bertoletti L, *et al.* Association between initial treatment strategy and long-term survival in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2021;204: 842–854.
4. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, *et al.* Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J* 2019;53:1801913.
5. Hoeper MM, Pausch C, Grünig E, Klose H, Staehler G, Huscher D, *et al.* Idiopathic pulmonary arterial hypertension phenotypes determined by cluster analysis from the COMPERA registry. *J Heart Lung Transplant* 2020;39:1435–1444.
6. Hoeper MM, Dwivedi K, Pausch C, Lewis RA, Olsson KM, Huscher D, *et al.* Phenotyping of idiopathic pulmonary arterial hypertension: a registry analysis. *Lancet Respir Med* 2022;10:937–948.
7. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, *et al.*; ESC/ERS Scientific Document Group. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2022;43:3618–3731.

Resolving the Microbial Burden with Tailored Immune Modulation in COVID-19 Acute Respiratory Distress Syndrome?

To the Editor:

Nonresolving acute respiratory distress syndrome (ARDS) with prolonged mechanical ventilation has been common during the previous severe acute respiratory syndrome coronavirus 2

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