The COVID-19 pandemic and pulmonary arterial hypertension in Italy: adaptation, outcomes and valuable lessons learned

Claudia Mickael[1], Michael H. Lee[2] and Brian B. Graham[2]

[1]Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO, USA. [2]Department of Medicine, University of California San Francisco, San Francisco, CA, USA.

Corresponding author: Brian B. Graham (Brian.Graham@ucsf.edu)

Shareable abstract (@ERSpublications)
This editorial summarises the key findings of R. Badagliacca and co-workers regarding the changes in care and clinical outcomes of PAH patients during the initial COVID-19 pandemic in Italy
https://bit.ly/3ytgljk

Cite this article as: Mickael C, Lee MH, Graham BB. The COVID-19 pandemic and pulmonary arterial hypertension in Italy: adaptation, outcomes and valuable lessons learned. *Eur Respir J* 2022; 60: 2200796 [DOI: 10.1183/13993003.00796-2022].

Received: 21 April 2022
Accepted: 29 April 2022

The ongoing coronavirus disease 2019 (COVID-19) pandemic caused by widespread infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused immense morbidity and mortality worldwide. While COVID-19 has affected many patients with chronic comorbidities, its potential impact on patients with chronic diseases is of great concern, and particularly those with pulmonary arterial hypertension (PAH), as the viral infection also causes pulmonary vascular pathology [1]. PAH patients are prone to decompensated right heart failure resulting in hospitalisations and even deaths [2], with infections representing a common triggering factor [3]. Furthermore, even patients without underlying PAH can secondarily develop pulmonary hypertension due to acute respiratory distress syndrome (ARDS) [4], and COVID-19-associated ARDS also appears to cause pulmonary hypertension [5–7], which can be long-lasting [8–10].

Despite the concern that PAH patients may be more susceptible to developing COVID-19 and suffering from its complications, observational studies have shown rather conflicting results, with some studies demonstrating anticipated high mortality [11–14] but others reporting surprisingly positive outcomes [15–18]. While many hypotheses have been raised around the underlying pathobiology of PAH and its targeted treatments in attempt to explain their overall effect on COVID-19 contraction and eventual outcomes [19–21], such as the potential protective role of endothelin receptor antagonists like ambrisentan (currently being studied in COVID-19, independent of PAH: NCT04771000), the true impact of COVID-19 in the PAH population remains undefined.

Aside from the pathophysiology of COVID-19 in PAH, the global response to the pandemic raises structural issues in the PAH community, related to limited in-person clinical access and adverse psychosocial consequences. For example, the enforcement of social distancing and prioritisation of healthcare resources toward COVID-19 patients have led to more telehealth visits and fewer semi-elective procedures, such as echocardiograms and right heart catheterisations [11, 14]. Moreover, studies have suggested a negative impact of pandemic-associated behavioural changes on the mental and physical health of PAH patients [22, 23]. Although it is clear that the COVID-19 pandemic has influenced the care of PAH patients, its collective and long-term effects on PAH-related outcomes are unclear.

The study presented in this issue of the *European Respiratory Journal* by Badagliacca *et al.* [24], on behalf of the Italian Pulmonary Hypertension NETwork (iPHNET), investigates the consequences of COVID-19 social distancing measures on PAH management and outcomes, and the risk of poor outcomes in SARS-CoV-2-infected PAH patients (figure 1). This is a commendable multicentre, nationwide study, conducted during the period of 1 March to 1 May 2020, coinciding with the peak of the initial COVID-19 outbreak in Italy.

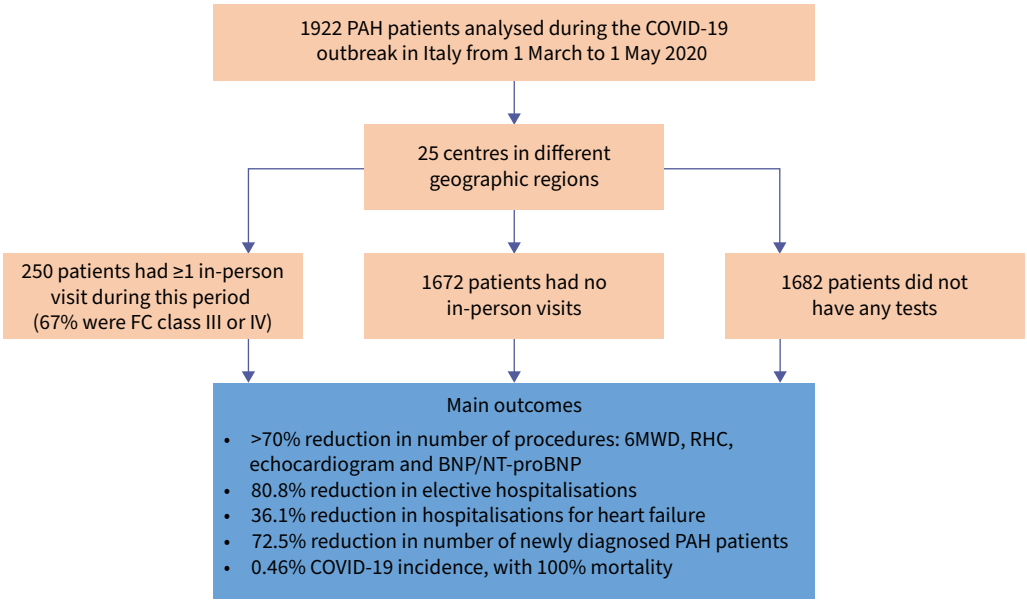

FIGURE 1 Summary of the primary findings. PAH: pulmonary arterial hypertension; FC: functional class; 6MWD: 6-min walk distance; RHC: right heart catheterisation; BNP: brain natriuretic peptide; NT-proBNP: N-terminal prohormone of brain natriuretic peptide.

During the outbreak, only severe PAH cases were seen in person (most in functional class III and IV), while the remaining patients were seen by telehealth systems. There was a significant decrease in elective procedures and testing. These programmes were rapidly implemented at the local level, with concurrent professional networking and sharing of experiences across the national system. In this observational study, 1922 PAH patients were treated and managed in 25 participant centres of iPHNET, located in different parts of Italy. The data obtained was compared with 1967 individuals from the same period in the prior calendar year as a control group.

The authors found that, despite a significant decrease in the number of PAH outpatient visits and PAH-related tests (for example, 70% fewer echocardiograms) during the COVID-19 outbreak, there was in fact a 36.1% reduction in hospitalisations and a lower proportion of PAH patients' deaths compared to the previous year, along with decreased PAH progression. During this time period, 20 patients were diagnosed with SARS-CoV-2 infection, and nine with COVID-19 (0.46% incidence), comparable to the 0.34% incidence across the entire Italian population during the same time. Unfortunately, all nine were hospitalised and ultimately succumbed to the infection: 100% mortality.

This study has several strengths, including that it is one of the first in the literature describing prevalence of COVID-19 in PAH subjects and clinical outcomes, and the largest to date to our knowledge [5, 9, 25]. Moreover, this investigation is unique as it has an impressively large scope, encompassing a large cohort with a wide geographic distribution, and includes almost all PAH patients from many centres across Italy during the first peak of the COVID-19 pandemic. Also noteworthy is the use of data from the same cohort 1 year prior as a reference group.

Despite the comprehensive nature of this study, there are some pitfalls that should be acknowledged, as was done so by the authors, including the retrospective nature of the study. Some of the investigation outcomes, such as slower disease progression, may be confounded by behavioural changes such as social distancing, as patients could have been afraid to seek medical care or may not have reported worsening signs of PAH to avoid breaking quarantine. Therefore, worse clinical outcomes could have increased in the period after the study, particularly as the time frame of 2 months is fairly short. During the peak pandemic, semi-elective hospitalisations may have been avoided due to bed shortages. Mortality could have been particularly high because it was the very beginning of the pandemic and treatment protocols were still being developed in the early days.

What are some lessons we can draw from this study? First, how many diagnostic studies do we really need to do to obtain the best outcomes for our patients? It is remarkable that in aggregate the patients did not apparently do worse despite the reduction in the number of echocardiograms performed, 81% fewer right heart catheterisations, 77% fewer BNP/NT-proBNP tests, and 84% fewer 6-min walk tests. As noted above, certainly many of these tests were delayed until the pandemic was under better control, but it is likely that some of these tests were ultimately not performed. It may be that prioritising testing of the sickest patients is appropriate and leads to non-inferior outcomes, an approach that could be considered in future prospective studies of optimal healthcare utilisation.

Second, how adequately telehealth visits substitute for in-person visits is something that the entire medical field is working out at this time. Again, existing patients did not apparently do worse. However, there was a 73% reduction in new PAH diagnoses (no doubt contributing to the well-acknowledged significant delay in PAH diagnosis [26]), as well as a significant reduction in the prescribing of sequential add-on therapy. It should be acknowledged that telehealth is rapidly evolving, and it would be of interest to see how the rates of diagnosis and prescribing are changing in telehealth *versus* in patient encounters, and if there are best practices that can be shared from the most successful telehealth programmes.

Third, was there something inadvertently beneficial that occurred during this otherwise horrible time, such as less exposure to environmental risk factors that drive hospitalisation or disease progression (salt intake, perhaps), or improved medication utilisation? This will be difficult to determine retrospectively, but should be considered for future studies.

Fourth, the high mortality rate among those with PAH who developed COVID-19 supports the concept of a shared pathophysiology of the pulmonary vascular system among these two disease processes. It may well be that the pre-existing vascular disease increases susceptibility to severe pathology from concurrent viral infection tropic to the pulmonary system. It would be of great interest to compare the outcomes of PAH patients with COVID-19 compared to those with ARDS caused by other respiratory viruses.

Lastly, the members of iPHNET should be congratulated on their success caring for PAH patients during this early stage of the pandemic: a time of great uncertainty and stress to the social fabric. If we unfortunately encounter future pandemics or other great disturbances to the healthcare system, we should remember the lessons of this group in their ability to quickly adapt healthcare delivery methods to achieve remarkable outcomes.

Conflicts of interest: B.B. Graham reports grants from NIH, outside the submitted work. All other authors have nothing further to disclose.

Support statement: Funding was provided by Actelion Pharmaceuticals Entelligence Early Investigator award (C. Mickael); and NIH grants P01HL152961 and R01HL135872 (B.B. Graham). Funding information for this article has been deposited with the Crossref Funder Registry.

References

1 Ackermann M, Verleden SE, Kuehnel M, *et al.* Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med* 2020; 383: 120–128.
2 Galie N, Channick RN, Frantz RP, *et al.* Risk stratification and medical therapy of pulmonary arterial hypertension. *Eur Respir J* 2019; 53: 1801889.
3 Sztrymf B, Souza R, Bertoletti L, *et al.* Prognostic factors of acute heart failure in patients with pulmonary arterial hypertension. *Eur Respir J* 2010; 35: 1286–1293.
4 Revercomb L, Hanmandlu A, Wareing N, *et al.* Mechanisms of pulmonary hypertension in acute respiratory distress syndrome (ARDS). *Front Mol Biosci* 2020; 7: 624093.
5 Pagnesi M, Baldetti L, Beneduce A, *et al.* Pulmonary hypertension and right ventricular involvement in hospitalised patients with COVID-19. *Heart* 2020; 106: 1324–1331.
6 Halawa S, Pullamsetti SS, Bangham CRM, *et al.* Potential long-term effects of SARS-CoV-2 infection on the pulmonary vasculature: a global perspective. *Nat Rev Cardiol* 2022; 19: 314–331.
7 Corica B, Marra AM, Basili S, *et al.* Prevalence of right ventricular dysfunction and impact on all-cause death in hospitalized patients with COVID-19: a systematic review and meta-analysis. *Sci Rep* 2021; 11: 17774.
8 Rossi R, Coppi F, Monopoli DE, *et al.* Pulmonary arterial hypertension and right ventricular systolic dysfunction in COVID-19 survivors. *Cardiol J* 2022; 29: 163–165.
9 Tudoran C, Tudoran M, Lazureanu VE, *et al.* Evidence of pulmonary hypertension after SARS-CoV-2 infection in subjects without previous significant cardiovascular pathology. *J Clin Med* 2021; 10: 199.

10 Tudoran C, Tudoran M, Lazureanu VE, *et al.* Factors influencing the evolution of pulmonary hypertension in previously healthy subjects recovering from a SARS-CoV-2 infection. *J Clin Med* 2021; 10: 5272.

11 Belge C, Quarck R, Godinas L, *et al.* COVID-19 in pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: a reference centre survey. *ERJ Open Res* 2020; 6: 00520-2020.

12 Farmakis IT, Karyofyllis P, Frantzeskaki F, *et al.* Incidence and outcomes of COVID-19 in patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: data from the Hellenic pulmOnary hyPertension rEgistry (HOPE). *Hellenic J Cardiol* 2022; 64: 93–96.

13 Sulica R, Cefali F, Motschwiller C, *et al.* COVID-19 in pulmonary artery hypertension (PAH) patients: observations from a large PAH center in New York City. *Diagnostics (Basel)* 2021; 11: 128.

14 Lee JD, Burger CD, Delossantos GB, *et al.* A survey-based estimate of COVID-19 incidence and outcomes among patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension and impact on the process of care. *Ann Am Thorac Soc* 2020; 17: 1576–1582.

15 Nuche J, Perez-Olivares C, Segura de la Cal T, *et al.* Clinical course of COVID-19 in pulmonary arterial hypertension patients. *Rev Esp Cardiol (Engl Ed)* 2020; 73: 775–778.

16 Scuri P, Iacovoni A, Abete R, *et al.* An unexpected recovery of patients with pulmonary arterial hypertension and SARS-CoV-2 pneumonia: a case series. *Pulm Circ* 2020; 10: 2045894020956581.

17 Horn EM, Chakinala M, Oudiz R, *et al.* Could pulmonary arterial hypertension patients be at a lower risk from severe COVID-19? *Pulm Circ* 2020; 10: 2045894020922799.

18 Segura de la Cal T, Nuche J, Jimenez Lopez-Guarch C, *et al.* COVID-19 experience and pulmonary arterial hypertension: do earlier theses and new data still match? *Ann Am Thorac Soc* 2021; 18: 1080–1081.

19 Franco V, Bradley EA, Badagliacca R, *et al.* Pulmonary vasodilators: beyond the bounds of pulmonary arterial hypertension therapy in COVID-19. *Pulm Circ* 2020; 10: 2045894020970369.

20 Farha S, Heresi GA. COVID-19 and pulmonary arterial hypertension: early data and many questions. *Ann Am Thorac Soc* 2020; 17: 1528–1530.

21 Nuche J, Segura de la Cal T, Jimenez Lopez Guarch C, *et al.* Effect of coronavirus disease 2019 in pulmonary circulation. the particular scenario of precapillary pulmonary hypertension. *Diagnostics (Basel)* 2020; 10: 548.

22 Wieteska-Milek M, Szmit S, Florczyk M, *et al.* Fear of COVID-19, anxiety and depression in patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension during the pandemic. *J Clin Med* 2021; 10: 4195.

23 Dobler CL, Kruger B, Strahler J, *et al.* Physical activity and mental health of patients with pulmonary hypertension during the COVID-19 pandemic. *J Clin Med* 2020; 9: 4023.

24 Badagliacca R, Papa S, D'Alto M, *et al.* The paradox of pulmonary arterial hypertension in Italy in the COVID-19 era: is risk of disease progression around the corner? *Eur Respir J* 2022; 60: 2102276.

25 Norderfeldt J, Liliequist A, Frostell C, *et al.* Acute pulmonary hypertension and short-term outcomes in severe Covid-19 patients needing intensive care. *Acta Anaesthesiol Scand* 2021; 65: 761–769.

26 Brown LM, Chen H, Halpern S, *et al.* Delay in recognition of pulmonary arterial hypertension: factors identified from the REVEAL registry. *Chest* 2011; 140: 19–26.