



# COVID-19 in pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: a reference centre survey

To the Editor:

There is currently limited data available regarding COVID-19 infection in patients with pulmonary hypertension (PH), resulting in poor evidence-based guidance to manage this specific patient population and to reliably predict the clinical course.

According to the US Centers for Disease Control and Prevention (CDC), patients with underlying health conditions, including all types of lung and cardiovascular diseases, have an increased risk of developing serious disease when infected by SARS-CoV-2 [1]. Based on prior publications on the effects of acute right heart failure superimposed on systemic infection [2–5], RYAN *et al.* [6] suggested that right heart failure and concomitant COVID-19 infection may result in increased mortality in pulmonary arterial hypertension (PAH) patients. Surprisingly, the number of hospitalised PAH-COVID-19 patients remained rather low in Italy and the USA so far [7]. In late March 2020, experts from over 32 US PH expert centres answered a query endorsed by the US Pulmonary Hypertension Association. COVID-19 infection was reported in 13 PAH patients, among whom three required intubation and one died. This is consequently raising the question whether and why PAH patients appear to be at lower risk of developing severe COVID-19 [7].

Considering that more evidence was needed, an international survey was launched from 17 April 2020 to 10 May 2020, in the middle of the pandemic surge in Europe, to evaluate the impact of COVID-19 infection in patients with rare forms of PH, *i.e.* PAH and chronic thromboembolic pulmonary hypertension (CTEPH).

The aim of the survey was to collect data on the clinical course, treatment, hospitalisations, intensive care unit (ICU) admissions and outcomes of COVID positive patients with PAH and CTEPH. The SurveyMonkey platform was used for data collection. Numbers of available data are listed in brackets.

47 PH centres, from 28 countries worldwide, responded to the survey (figure 1a). During the pandemic period, most consultations for patients with PAH and CTEPH occurred remotely (80%), either by tele- (68%) or video-consultation (12%), whereas 9% were followed live, with normal outpatient consultation, 8% exclusively when the patients called and 3% were not followed at all. In total, COVID-19 infections were reported in 70 PAH or CTEPH patients by 19 of the participating centres. 13 of these centres reported more than one case and 28 did not report any case.

Most patients had idiopathic or heritable PAH (31%), followed by PAH due to connective tissue diseases (23%), CTEPH (20%), PAH associated with congenital heart diseases (10%), porto-pulmonary hypertension (4%), and other causes (11%, including pulmonary veno-occlusive disease, PAH associated with HIV infection or with intake of drugs and toxic oil) (data available for 70 patients). Median age of the cohort was 50–59 years (n=70; figure 1b). Most of the patients were under specific PAH combination



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**This international survey highlights that a limited number of PAH and CTEPH patients suffered from severe #COVID19 infection** <https://bit.ly/3jGuBQq>

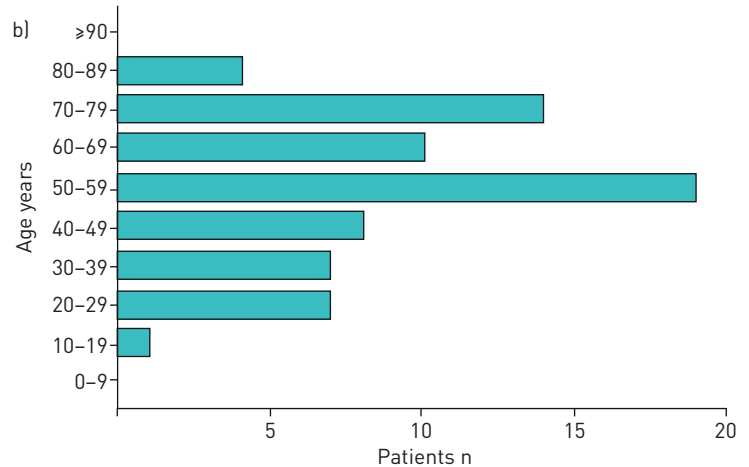
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a)

Country	Centres	COVID-19 infections	Deaths
Argentina	1	0	0
Australia	2	0	0
Austria	1	1	1
Belgium	2	7	0
Brazil	1	0	0
Canada	1	0	0
Czech Republic	1	0	0
Denmark	1	0	0
France	1	13	6
Germany	3	0	0
Greece	1	1	0
Iran	1	2	0
Ireland	1	0	0
Israel	1	0	0
Italy	1	2	2
Lithuania	2	0	0
Mexico	1	3	0
Poland	6	0	0
Portugal	2	0	0
Russian Federation	1	0	0
Serbia	1	0	0
Spain	3	19	0
Switzerland	1	1	0
The Netherlands	3	5	2
Turkey	2	1	0
UK	2	11	2
Ukraine	1	0	0
USA	3	4	0



**FIGURE 1** COVID-19 in pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension patients. a) Table showing number of participating centres, reported COVID-19 cases and COVID-19 related mortality per country in 47 centres from 28 countries worldwide. b) Age distribution of patients (n=70).

therapy (59%), followed by monotherapy (21%) and only a minority were on triple therapy (7% and 13% on oral and parenteral prostanoids, respectively) (n=56). Very few patients were on immunosuppressive therapy (4%). Regarding CTEPH patients, 73% were inoperable or with post-operative residual PH, 18% were waiting for balloon pulmonary angioplasty (BPA) and 9% for pulmonary endarterectomy (PEA); 9% had BPA, but none had PEA delayed, because of the pandemic logistic situation (n=11).

Pneumonia was the most frequent presentation at diagnosis (56%), followed by only fever (28%), then upper respiratory tract infection (13%), other symptoms including myalgia, dyspnoea or cough (13%), PH exacerbation and/or right heart failure (5%); anosmia and/or ageusia was observed in 3% of the patients and 3% were asymptomatic. Venous thromboembolism or haemoptysis were not reported at diagnosis (n=61). Nasopharyngeal swabs (74%) and a few low-dose computed tomography (CT) scans (15%) were used to confirm COVID-19 diagnosis, irrespective of the geographic location (n=66). The diagnosis was clinically suspected but unproven in 11% and no patient received a bronchoalveolar lavage. Most of the patients displayed typical COVID-19 CT (54%), 7% harboured atypical CT and 39% did not undergo a CT scan at diagnosis; normal CT was not reported (n=46). The majority of the patients were hospitalised on a general ward (46%), 17% needed ICU admission, 6% were in other healthcare facilities (including nursing homes, intermediate care unit and social-sanitary centre) and 30% were treated at home (n=63). The median duration of symptoms was 6.0 days (range: 1–36 days). The median duration of hospitalisation was 3.4 days (range: 2–32 days) and patients were mostly hospitalised in the hospital of the responding centre (47%), 31% in a local hospital and 22% in another expert centre. Most of the patients needed respiratory support, 57% received oxygen, 12% required high-flow nasal cannula, 2% received continuous positive airway pressure or bilevel positive airway pressure, 11% required invasive mechanical ventilation and no patient was reported on extracorporeal membrane oxygenation (ECMO) (n=65). COVID-19 treatment consisted in most of the cases of antibiotics (41%, including 20% azithromycin) followed by hydroxychloroquine or chloroquine (31%), lopinavir or ritonavir (14%), itraconazole (1%) and other treatments including tocilizumab, methylprednisolone, mycophenolate, favipiravir and rituximab (14%); none of them received remdesivir/GS-5734 (n=70). For all cases (n=70), mortality was 19%, 20% for PAH and 14% for CTEPH patients.

The results of this international survey show that few PAH and CTEPH patients required ICU admission or invasive ventilation and none were treated with ECMO, in contrast to expectations for patients with underlying respiratory or cardiovascular diseases [1]. The observed case-fatality rate, estimated as the number of deaths per 100 reported cases, was 19%, which is high in comparison with the rate observed in the general population (5.9% to 16.3%, in the USA and Belgium, respectively; data extracted on 25 May 2020 [8]), and with hospital mortality in the large series from New York City (9.7% [9]). However, comparing mortality to a general population is difficult; there was an important variability between countries (figure 1a), partially explained by age distribution (Pearson correlation between the number of deaths and the number of patients older than 60 years of age:  $r=0.93$ ,  $p=0.02$ ), and by disrupted systematic follow-up (correlation between the number of deaths and the proportion of patients without remote or live consultation:  $r=0.98$ ,  $p=0.02$ ), suggesting underestimation of benign cases.

Shielding at home could, in part, explain the low number of cases reported in this survey since the PAH and CTEPH population is medically educated, thereby better prepared to respect social distancing instructions, and sometimes socially isolated by the disease and its consequences. HORN *et al.* [7] also suggested a potential protective effect of PAH medication by different mechanisms involving pulmonary endothelial cells. In the current international survey, most patients actually benefited from combination therapy of endothelin receptor antagonists, phosphodiesterase 5 inhibitors and/or prostanoids (62%), showing a net progress in comparison with most recent registries (*i.e.* 41% in COMPERA) [10], in agreement with the most recent European Society of Cardiology/European Respiratory Society recommendations [11]. The use of anticoagulants was not queried in this survey; however, no case of venous thromboembolism was reported despite the increased prevalence of pulmonary embolism/thrombosis [12–15] and the presence of microthrombi within pulmonary capillaries [14, 15] reported in COVID-19 patients.

In summary, this survey, although incomplete, highlights that a limited number of PAH and CTEPH patients suffered from COVID-19, whereas the case-fatality rate related to COVID-19 was rather high in comparison with the general population. Further comprehensive investigation would be required to elucidate 1) whether underreporting of benign cases can explain the heterogeneity of outcome among different countries, and 2) whether tight adherence to social distancing is the main explanation or other physiopathological factors may prevent COVID-19 infection in severe PH.

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