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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)

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Coronavirus disease 2019 (COVID-19) is a novel, predominantly pulmonary, but also systemic, infectious disease that may severely affect patients with comorbidities. Patients with pulmonary arterial hypertension (PAH, group 1) and chronic thromboembolic pulmonary hypertension (CTEPH, group 4) are prone to complications from non-cardiovascular diseases, such as sepsis and respiratory failure.[1,2] Few reports on COVID-19 infection in patients with group 1 or group 4 pulmonary hypertension (PH) have been published, with a discrepancy in the incidence of the disease in this rare and heterogeneous population and also differences in the reported outcomes, such as hospitalization and mortality rates.[3–6] The present brief report aims to describe the case incidence of COVID-19 among Greek PH expert centers.

A total of 9 PH expert centers were studied in this report, cumulatively caring for 499 PH patients (372 patients with PAH and 127 patients with CTEPH) according to recent data retrieved from the prospective Hellenic pulmOnary hyPertension REgistry (HOPE) and personal communication with the expert centers.[7] Eighteen cases of COVID-19, confirmed with RT-PCR testing, were reported from the start of the pandemic in Greece (end February 2020) up until 14 August 2021, contributing to an estimated incidence of 36.1 (95% CI 21.5– 56.4) COVID-19 cases in 1,000 patients with group 1 and 4 PH (Fig. 1A). Two patients were fully vaccinated (11.1%). The median age of the affected patients was 54.5 years (range 25-86 years), and 77.8% of the patients were women. Twelve COVID-19 cases had PAH: four with idiopathic PAH, one with hereditary PAH, one with PAH due to Eisenmenger syndrome, and six with PAH associated with connective tissue disease (CTD). The six remaining cases were patients with CTEPH; three of them had persistent CTEPH post pulmonary endarterectomy and three had inoperable CTEPH. The baseline characteristics and data from the most recent follow-up in the PH outpatient clinic are presented in Table 1.

All patients reported a symptomatic course of COVID-19. Specifically, fever, cough, and fatigue were the most common symptoms (Fig. 1B). The median duration of the symptoms was 6 days (range 2–30 days). No case of incident venous thromboembolism was described. All patients resumed PAH-targeted therapies during the course of the infection. In total, eight patients (44.4%) were hospitalized and required oxygen therapy. COVID-19-specific therapy included dexamethasone, remdesivir, antibiotics, and low-molecular-weight heparin. Four patients (22.2%) died; three patients during hospitalization and the fourth one three days post-discharge due to COVID-19 complications. Three of them were elderly (≥70 years), while the others had significant comorbidities. The remaining four patients recovered and were discharged after a median of 11 days (range 8–30 days). All recovered patients, including those with a milder course of the disease, neither reported deterioration of their functional status after COVID-19 infection nor showed persistent symptoms.

Herein, we report a 3.6% incidence of COVID-19 in PH groups 1 and 4. Furthermore, we report a hospitalization rate of 44.4% and a mortality rate of 22.2% in the affected patients. In context, in the general Greek population, the incidence risk in the 25–80+ years age group is 4.8% and the mortality rate is nearly 3%. Multicenter surveys from the US and Europe report hospitalization rates of 30% and 70% and mortality rates of 12% and 19%, respectively.[5,6] To date, it is not evident whether the observed increased severity of COVID-19 among PAH and CTEPH patients is due to the characteristics inherent to the disease or due to the increased age and comorbidities of the patients, as the small number of cases in the studies does not allow a formal adjusted statistical analysis. On the other hand, there have been suggestions of a potential protective effect of the PAH targeted therapies in COVID-19, and notably, a randomized controlled trial is ongoing to test the efficacy of ambrisentan in severe COVID-19.[8,9] Moreover, anticoagulation in the context of CTEPH may alter the thrombogenic environment created by the virus and provide thrombotic protection. A major limitation of this, and other similar reports, is the potential unrecognized and underreported mild, or even asymptomatic, COVID-19 cases in the PH population that could artificially overestimate the hospitalization and mortality rates. However, in our opinion, the majority of the precapillary PH patients are well educated and informed about their disease and strongly attached to the attending PH centers; therefore, frequent testing and increased alertness for systemic

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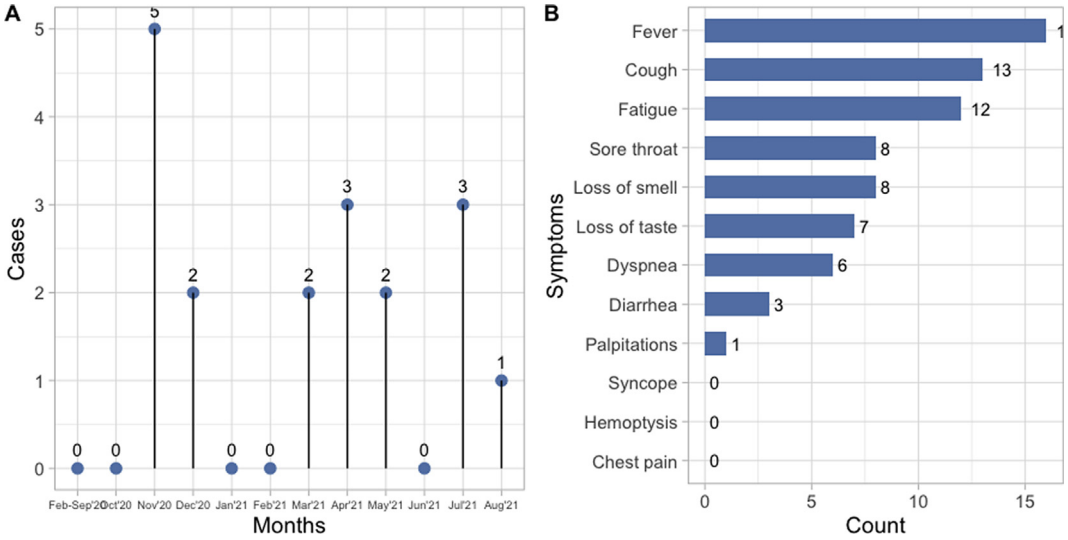

Figure 1. A. Distribution of case incidence across the pandemic period. B. Prevalence of COVID-19 symptoms among cases.

Table 1
Most recent assessment of the characteristics of patients with pre-capillary PH and outcomes

Patients (Sex, age, y)	PH diagnosis	Duration from PH diagnosis (years)	BMI (kg/m^2)	Comorbidities	NYHA class	NT-proBNP (pg/ml)	mPAP (mm Hg)	PVR (WU)	CI (l/min/m^2)	SvO2 (%)	Risk assessment (ESC/ERS classification)	PAH-targeted therapy	Hospital admission	Death
Case 1 M, 35	Eisenmenger syndrome (ASD and VSD)	16	23.1	None	II	108	140	NA	5.5	NA	Low	Bosentan	Yes	No
Case 2 F, 78	CTEPH (inoperable)	1	33.3	None	III	500	45	22.2	1.4	56	NA	Riociguat	Yes	Yes
Case 3 F, 62	Idiopathic PAH	10	22.4	None	II	29 (BNP)	26	4	2.7	75	Low	Macitentan	No	No
Case 4 F, 70	CTEPH (post PEA and BPA)	27	NA	AF, COPD, CKD, Hypertension	III	2946	34	3.6	2.1	67	NA	No	Yes	Yes
Case 5 M, 43	CTEPH (post PEA and two sessions of BPA)	6	26.9	None	II	331	36	3	3	75	NA	Riociguat	Yes	No
Case 6 F, 50	PAH associated with SLE	4	18.4	None	III	2734	46	13	2.5	74	Intermediate	Tadalafil, ambrisentan, selexipag	Yes	No
Case 7 F, 59	PAH associated with SSc	3	23.5	Smoking, Hypertension	II	279	30	4.8	2.7	72	Low	Tadalafil, ambrisentan	No	No
Case 8 F, 58	PAH associated with SSc	4	19.8	Hypothyroidism	III	77 (BNP)	26	3.2	3.5	74	Intermediate	Tadalafil, bosentan	No	No
Case 9 F, 39	Hereditary PAH	3	21	None	I	156	50	6.5	3.6	76	Low	Tadalafil, macitentan, selexipag	No	No
Case 10 F, 61	PAH associated with SSc	8	37.8	DM, Obesity, COPD, Hypertension	III	565	41	3.8	3.4	72	Intermediate	LTOT, riociguat, ambrisentan	Yes	Yes
Case 11 F, 78	PAH associated with MCTD	4	22.3	Cancer (breast, ovarian)	III	1911	51	17.7	1.7	69	High	LTOT, tadalafil, macitentan, selexipag	Yes	Yes
Case 12 F, 86	CTEPH (inoperable)	4	29.1	Parkinson's, pacemaker	III	212	21	4.3	2.2	73	NA	LTOT, riociguat	No	No
Case 13 M, 48	CTEPH (inoperable)	4	30	COPD, hypertension	II	115	35	4.8	2.4	78	NA	LTOT, riociguat	Yes	No
Case 14 F, 51	PAH associated with MCTD	5	22	None	II	879	53	10.5	2	65	Intermediate	Tadalafil, macitentan, selexipag	No	No
Case 15 M, 68	CTEPH (post PEA)	4	22	CAD	III	2521	62	10.7	2.2	56	NA	LTOT, riociguat	No	No

Table 1 (*continued*)

Patients (Sex, age, y)	PH diagnosis	Duration from PH diagnosis (years)	BMI (kg/m^2)	Comorbidities	NYHA class	NT-proBNP (pg/ml)	mPAP (mm Hg)	PVR (WU)	CI (l/min/m^2)	SvO2 (%)	Risk assessment (ESC/ERS classification)	PAH-targeted therapy	Hospital admission	Death
Case 16 F, 49	Idiopathic PAH	13	30.1	Dyslipidemia, thyroid disease, obesity, former smoker	II	161	53	7.9	2.5	74	Low	Tadalafil	No	No
Case 17 F, 48	Idiopathic PAH	17	27.5	None	II	NA	35	4.8	2.9	79	Low	Macitentan	No	No
Case 18 F, 25	Idiopathic PAH	7	19.4	Thyroid disease	II	NA	56	9.8	2.8	73	Low	Riociguat, macitentan, ralinepag	No	No

AF: atrial fibrillation, ASD: atrial septal defect, AV: atrioventricular, BMI: body mass index, BNP: brain natriuretic peptide, BPA: balloon pulmonary angioplasty, CAD: coronary artery disease, CCB: calcium channel blocker, CHD: congenital heart disease, CI: cardiac index, CKD: chronic kidney disease, COPD: chronic obstructive pulmonary disease, DM: diabetes mellitus, LV: left ventricle, LTOT: long-term oxygen therapy, MCTD: mixed connective tissue disease, mPAP: mean pulmonary artery pressure, NA: not applicable, NT-proBNP: N-terminal pro-brain natriuretic peptide, NYHA: New York Heart Association, PEA: pulmonary endarterectomy, RV: right ventricle, SLE: systemic lupus erythematosus, SSc: systemic sclerosis, SvO2: mixed venous oxygen saturation, VSD: ventricular septal defect, TAPSE: tricuspid annular plane systolic excursion.

symptoms would allow the identification of COVID-19 among this population, even during the pandemic and the resulting disruption of chronic care.[10] Ultimately, vaccination programs are fully activated and strong medical advice should be offered to all PH group 1 and 4 patients, and also to other vulnerable patient groups, to be vaccinated, continue to adhere to preventive infection measure and be protected from the disabling and, potentially, fatal complications of COVID-19 and its variants of concern.

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Conflict of interest

The authors do not declare any conflict of interest related to this manuscript.

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