Severe pulmonary hypertension associated with COPD: long-term results of a prospective French multicentre cohort

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To the Editor:

When present during the course of COPD, pulmonary hypertension (PH) is usually of moderate severity: the mean pulmonary artery pressure (mPAP) at rest ranges from 25 to 35 mmHg, with preserved cardiac output [1, 2]. However, a subset of COPD patients presents a particular vascular phenotype called severe PH, characterised by a much higher mPAP or a low cardiac index [1–8]. According to the latest world symposium on PH, severe PH-COPD is defined as mPAP ⩾35 mmHg or mPAP ⩾25 mmHg with low cardiac index (<2 $L \cdot min^{-1} \cdot m^{-2}$) [1, 2].

Some characteristics of severe PH-COPD had emerged from results of a very few retrospective studies including a quite low number of patients: high level of dyspnoea at exercise, profound hypoxaemia, normo- or hypocapnia, very low lung diffusing capacity for carbon monoxide (D_{LCO}) [3, 6], and poor prognosis [6]. In 2012, we designed a prospective multicentre cohort including incident COPD patients with severe PH followed over several years to provide a more complete description of this entity. In particular, we aimed at describing the characteristics of patients at inclusion and at follow-up, as well as survival. From December 2012 to December 2016, 99 incident patients (median age at inclusion 66.0 (interquartile range (IQR) 62.0–71.0) years; 82.8% males) from 13 French centres were prospectively included in the study and followed up. To be included in the severe PH-COPD registry by any of the centres of the French clinical research network, in addition to other criteria, the patients had to have severe PH with mPAP ⩾35 mmHg measured on right heart catheterisation and pulmonary artery occlusion pressure ⩽15 mmHg at rest, >6 weeks after an exacerbation. Thus, none of our patients had combined pre–post-capillary PH. All the severe PH-COPD patients of the cohort had mPAP ⩾35 mmHg because the study was designed before the 2013 world symposium on PH that proposed to include the association of mPAP ⩾25 mmHg and cardiac index <2 $L \cdot min^{-1} \cdot m^{-2}$ in the definition of severe group 3 PH. Before inclusion in the study, thoracic computed tomography scans were checked to rule out combined pulmonary fibrosis and emphysema, given the known association between this syndrome and severe PH. Median forced vital capacity and total lung capacity at inclusion were 80.5% (IQR 64–97%) of predicted and 109% (IQR 94–123%) of predicted, respectively. The protocol and first results were previously reported [9].

In brief, the inclusion period of the patients was 4 years, with a planned follow-up of 3 years after inclusion. The study confirmed the particular clinical, functional, and haemodynamic profile of the COPD patients presenting this vascular phenotype [3, 5, 6, 10] (marked dyspnoea, with 55.6% and 22.2% in New York Heart Association (NYHA) class III and IV, respectively; median forced expiratory volume in 1 s 50.0% (IQR 35.0–63.0%) of predicted; median arterial oxygen and carbon dioxide tension on room air 50.0 (IQR 44.8–62.0) mmHg and 36.0 (IQR 31.1–43.0) mmHg, respectively; median D_{LCO} 20.0% (IQR 16.5–30.6%) of predicted; median transfer coefficient of the lung for carbon monoxide 30.3% (IQR 21–39%) of predicted; median mPAP 42.0 (IQR 37.0–48.0) mmHg; median cardiac index 3 (IQR 2.4–3.6) $L \cdot min^{-1} \cdot m^{-2}$; median pulmonary vascular resistance 6.3 (IQR 4.2–7.9) WU; at study inclusion) [9]. At inclusion, all patients were naive of therapy targeted to pulmonary arterial hypertension (PAH). During the first year of follow-up, 64 patients had received at least one PAH-targeted therapy (most often phosphodiesterase-5 inhibitor or combination of endothelin receptor inhibitor and phosphodiesterase-5 inhibitor) and 35 did not receive any PAH medication [9]. The mean restricted survival was

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This prospective study dealing with 99 incident patients followed over several years, without any patients lost to follow-up, confirms, with good-quality data, that the prognosis associated with severe PH-COPD is very poor https://bit.ly/3DHjYIm

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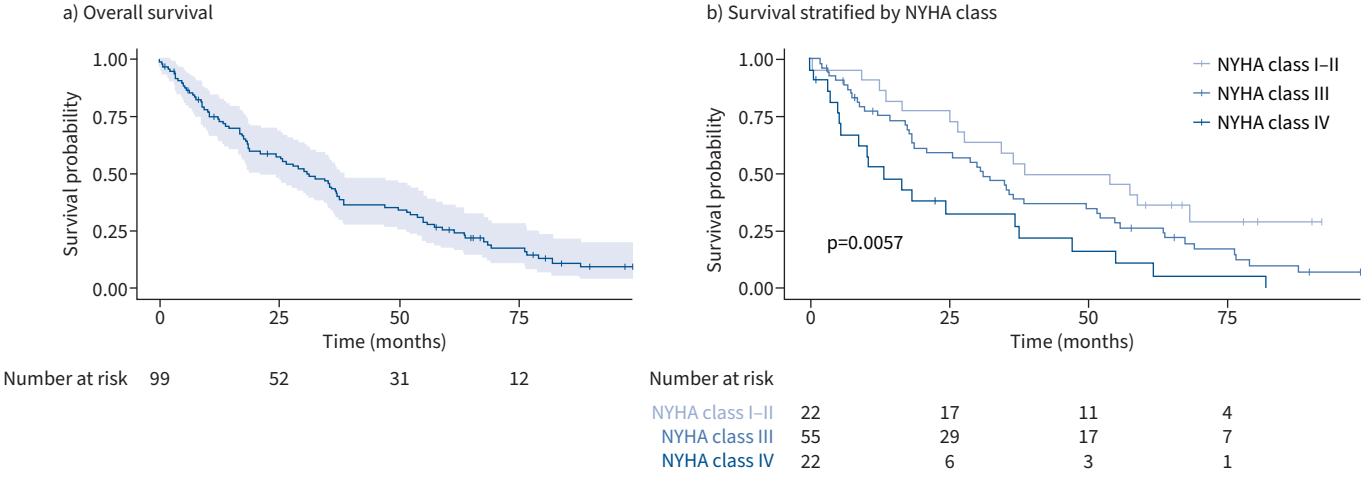

FIGURE 1 Kaplan–Meier survival curves. a) Overall survival. The shaded area represents the 95% confidence interval around the survival probability; the crosses on the curve represent censored patients. b) Survival stratified by New York Heart Association (NYHA) class.

15.0 (IQR 13.9–16.0) months, which confirmed that this phenotype is associated with poor prognosis [5, 6]. However, in this previous study, the median follow-up after inclusion was only 339 (IQR 218–375) days [9].

In the present study, we analysed the survival data for patients with severe PH-COPD up to March 2021 and were able to observe the long-term survival (at 1, 3 and 5 years after inclusion). The overall survival for the whole population and survival stratified by NYHA class at inclusion were analysed by the Kaplan–Meier method and NYHA class groups were compared by log-rank test. Univariate and multivariable Cox proportional hazards models were used to estimate hazard ratios (HRs) with 95% confidence intervals for mortality. Four continuous variables (cardiac index, total pulmonary resistance, number of adverse events without hospitalisation and number of hospitalisations for adverse events) and one categorical variable (NYHA class with 3 categories: I–II, III and IV) were included in the multivariable Cox model. These variables were selected by clinical relevance and missing data rates.

None of the 99 patients was lost to follow-up. Median duration of follow-up was 27 (IQR 10–57) months. Median survival was 31.2 (IQR 21.0–38.4) months. Six patients underwent lung transplantation. At 5 years after inclusion, only 20 patients remained alive without lung transplantation. Kaplan–Meier survival curves for the 99 patients are in figure 1 (overall survival in figure 1a and survival stratified by NYHA class at inclusion in figure 1b). Estimated survival probabilities were 75%, 43% and 25.5% at 1, 3 and 5 years, respectively. On univariate Cox regression analysis, mortality was significantly associated with the NYHA class (p=0.0075), age at baseline, tobacco consumption (ever smoking) (p=0.0334), total pulmonary resistance (p=0.0069), pulmonary vascular resistance (p=0.0164), and D_{LCO} (% predicted) (HR 0.96, 95% CI 0.94–0.99; p=0.031). We found no association between the use of PAH-targeted therapy and mortality (HR 0.67, 95% CI 0.41–1.08; p=0.1008).

On multivariable analysis, the only variable associated with mortality was the NYHA class (class IV *versus* I–II, adjusted HR 2.46, 95% CI 1.17–5.16; p=0.0178; class III *versus* I–II, adjusted HR 1.78, 95% CI 0.98–3.25; p=0.0594).

Recently, Vizza *et al.* [11] reported the survival results of a large series of 307 COPD patients with severe PH who were prospectively included in the COMPERA registry. Estimated transplant-free survival probabilities at 1, 3 and 5 years were 86%, 55%, and 38%, respectively, but the rate of patients lost to follow-up was high. The strength of our prospective study dealing with incident patients followed over several years, without any patients lost to follow-up, is its provision of good-quality data on the prognosis associated with severe PH-COPD. The study confirms that severe PH-COPD is associated with very poor prognosis. The very poor survival of patients with severe PH-COPD, despite the use of vasoactive treatment in most cases, should prompt physicians in charge of these patients to consider lung transplantation whenever possible, even though the patients do not fulfil the usual selection criteria.

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