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# Severe pulmonary hypertension associated with chronic obstructive pulmonary disease

A prospective French multicenter cohort

## Running Head

Severe pulmonary hypertension in COPD

Gaëlle Dauriat, MD<sup>1</sup>; Martine Reynaud-Gaubert, MD, PhD<sup>2</sup>; Vincent Cottin, MD, PhD<sup>3</sup>; Bouchra Lamia, MD, PhD<sup>4</sup>; David Montani, MD, PhD<sup>5,16</sup>; Mathieu Canuet, MD<sup>6</sup>; Clement Boissin, MD<sup>7</sup>; Cecile Tromeur, MD<sup>8</sup>; Ari Chaouat, MD, PhD<sup>9</sup>; Bruno Degano, MD, PhD<sup>10</sup>; Emmanuel Bergot, MD, PhD<sup>11</sup>; Olivier Sanchez, MD, PhD<sup>12</sup>; Gregoire Prevot, MD<sup>13</sup>; Olivier Sitbon, MD, PhD<sup>5,16</sup>; Gabriel Thabut, MD, PhD<sup>1</sup>; Drifa Belhadi<sup>14</sup>, Yolande Costa de Beauregard<sup>15</sup>, Amina Bencherif<sup>15</sup>, Marc Humbert, MD, PhD<sup>5,16</sup>; Gerald Simonneau, MD, PhD<sup>5,16</sup>; Cedric Laouenan, MD<sup>14</sup>; and Hervé Mal, MD, PhD<sup>1</sup>

<sup>1</sup>Service de pneumologie B, hôpital Bichat, Paris, France, Université Paris 7, Inserm UMR1152

<sup>2</sup>Service de pneumologie, hôpital Nord, Marseille, France

<sup>3</sup>Service de pneumologie hôpital Louis Pradel, Lyon, France

<sup>4</sup>Service de pneumologie, Normandie Université, UNIROUEN, EA 3830. CHU de Rouen et Groupe Hospitalier du Havre, France.

<sup>5</sup>Service de pneumologie, hôpital Bicêtre ; Le Kremlin Bicêtre, France

<sup>6</sup>Service de pneumologie, Nouvel Hôpital Civil, Strasbourg, France

<sup>7</sup>Service de pneumologie, hôpital Arnaud de Villeneuve, Montpellier, France

<sup>8</sup>Service de pneumologie, hôpital de la cavale blanche, Brest, France

<sup>9</sup>Service de pneumologie, hôpital Brabois, Nancy, France

<sup>10</sup>Service de pneumologie, hôpital Albert Michalon, Grenoble, France

<sup>11</sup>Service de pneumologie, hôpital côte de nacre, Caen France

<sup>12</sup>Service de pneumologie, hôpital européen Georges Pompidou, Paris, France

<sup>13</sup>Service de pneumologie, hôpital Larrey, Toulouse, France

<sup>14</sup>Unité de recherche clinique, hôpital Bichat, Paris, France

<sup>15</sup>Centre d'investigation clinique, hôpital Bichat, Paris, France

<sup>16</sup>Pulmonary Hypertension National Referral Center, Hôpital Bicêtre, Le Kremlin-Bicêtre, France

**Address for correspondence:**

Hervé Mal, Service de Pneumologie B et Transplantation Pulmonaire, Hôpital Bichat, 46 rue Henri Huchard, Paris 75018, France.

Phone: +33 140256912; Fax: 33 140256104. E-mail: herve.mal@bch.aphp.fr

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**Abbreviations:**

COPD: chronic obstructive pulmonary disease, PH: pulmonary hypertension; NYHA: New York Heart Association, BMI: body mass index, AE: acute exacerbation, FEV<sub>1</sub>: forced expiratory volume in 1 sec, FVC: forced vital capacity, TLC: total lung capacity, SVC: slow vital capacity, DLCO: lung diffusing capacity for carbon monoxide, KCO, diffusion coefficient for carbon monoxide, RV: residual volume, sPAP: systolic pulmonary artery pressure, mPAP: mean pulmonary artery pressure, dPAP: diastolic pulmonary artery pressure, RAP: right atrial pressure, PAOP: pulmonary artery occlusion pressure, pred: predicted, TPR: total pulmonary resistance, PVR: pulmonary vascular resistance, WU: Wood units, CAT: COPD Assessment Test™

## **Abstract**

### Background

A small proportion of patients with chronic obstructive pulmonary disease (COPD) patients present severe pulmonary hypertension (PH), defined by mean pulmonary artery pressure (mPAP)  $\geq$  35 mm Hg measured by right heart catheterization. Little is known about the characteristics of severe PH-COPD. The aim of the study based on a national registry was to describe this phenotype.

### Methods

We prospectively included and followed patients with incident PH-COPD. Clinical, functional, hemodynamic data at inclusion and follow-up were retrieved. Survival assessed by Kaplan-Meier analysis was the primary end-point.

### Results

From 2012 to 2016, 99 patients from 13 French centers were included in the study (82 males; median age 66.0 years [interquartile range 62.0-72.0]). At inclusion, most patients had marked dyspnea (55.6% and 22.2% New York Heart Association class III and IV, respectively). During 12 months before inclusion, 42.9% had an exacerbation requiring a hospitalization. Pulmonary function tests showed a moderate obstructive pattern with median [interquartile range] FEV<sub>1</sub> 50.0 [35.0-63.0] % predicted and low diffusing capacity for carbon monoxide, median 20.0 [16.5-30.6] % predicted. The median values for PaO<sub>2</sub> and PaCO<sub>2</sub> on room air were 50.0 [44.8-62.0] and 36.0 [31.1-43.0] mm Hg. Median values of mPAP, pulmonary artery occlusion pressure, cardiac index and pulmonary vascular resistance were 42.0 [37.0-48.0] mm Hg, 11.0 [9.0-14.0]

mm Hg, 3.0 [2.4-3.6] L/min/m<sup>2</sup>, and 6.3 [4.2-7.9] WU, respectively. Mean restricted survival was 15.0 [13.9-16.0] months.

### Conclusion

Severe PH-COPD is characterized by moderate airway obstruction but marked dyspnea and marked hypoxemia, low DLCO and high mPAP. This phenotype is associated with poor prognosis.

**Abstract word count:** 256

**Key words:** chronic obstructive pulmonary disease, pulmonary hypertension, lung transplantation

## **Introduction**

The development of pulmonary hypertension (PH) during the course of chronic obstructive pulmonary disease (COPD) is a well-known phenomenon with a prevalence depending on the severity of airway obstruction. When present, PH, defined as group 3 PH according to the classification of 6<sup>th</sup> World Symposium on Pulmonary Hypertension (1), is usually of moderate severity; the mean pulmonary artery pressure (mPAP) level at rest ranges from 25 to 35 mm Hg, with preserved cardiac output (2, 3). However, a subset of COPD patients present a much higher mPAP (2-11). In the most characteristic cases, the level mPAP is disproportionate to the degree of bronchopulmonary involvement. For these patients who seem to have a particular involvement of pulmonary circulation and who could be potential candidates for vasoactive therapy (2, 3), the term “out-of-proportion” PH has been replaced with “severe PH-COPD” defined by  $mPAP \geq 35$  mm Hg or  $mPAP \geq 25$  mm Hg with low cardiac index ( $< 2$  l/min/m<sup>2</sup>) (2, 3). However, little is known about the characteristics of COPD patients with severe PH. We designed a prospective multicenter study including COPD patients with severe PH followed over several years to provide a more complete description of this entity. Our results focus on the characteristics of patients at inclusion and at 6- and 12-month visits as well as survival.

## **Materials and methods**

In 2000, the French clinical research network led by the French Reference Center for Pulmonary Hypertension (Université Paris-Sud, Hôpital Kremlin-Bicêtre, Le Kremlin-Bicêtre, France) initiated a national prospective registry to collect data on pulmonary arterial hypertension (PAH) and other forms of PH from 17 university hospitals that followed at least five newly diagnosed PAH patients per year. The centers

contributing to this national prospective registry complete an inclusion form and follow-up forms (every 6 months) for each new patient included. Demographic, clinical, pulmonary function tests, biological, and hemodynamic data [right heart catheterization (RHC) and echocardiography] are collected in the registry at inclusion and follow-up. The registry, which has already provided important information on PAH (12), already includes patients with severe PH-COPD, but the information relative to the broncho-pulmonary disease is not well detailed, and the registry is a mix of incident and prevalent cases. To provide more precise information on this subset of PH patients, an additional prospective registry (severe PH-COPD registry), connected to the national PH registry and dealing only with incident patients, was set up in 2012. The primary end-point was survival. We anticipated a 30% 1-year mortality rate. We decided to enroll 100 patients with incident disease to obtain a 20% to 40% 95% confidence interval (CI). This sample size was considered a pragmatic objective given the low prevalence of severe PH-COPD and an inclusion period of 4 years. The planned follow-up was 3 years.

To be included in the severe PH-COPD registry by any of the centers of the French clinical research network, the patients had to fulfill the following criteria: 1) give informed consent to be included in the severe PH-COPD registry; 2) age > 18 years; 3) diagnosis of COPD with a pulmonary function test showing forced expiratory volume in 1 sec ( $FEV_1$ )/forced vital capacity (FVC) ratio < 70% and  $FEV_1 \leq 80\%$  of predicted; 4) severe PH with  $mPAP \geq 35$  mm Hg measured on RHC, pulmonary artery occlusion pressure (PAOP)  $\leq 15$  mm Hg at rest, well after an exacerbation (more than 6 weeks); 5) diagnosis of PH by RHC < 1 year before inclusion (incident case); 6) absence of evolving disease (other than PH and COPD) yielding a life expectancy < 6 months; and 7) possibility to ensure a regular medical follow-up. In

addition, patients had to be classified as having group 3 PH related to COPD with lack of an alternative overt cause of PH. However, the presence of additional factors that might affect pulmonary circulation (history of pulmonary embolism, previous thoracic surgery, obstructive sleep apnea, intravenous drug use, etc.) was authorized and recorded. We restricted the definition of severe PH-COPD to  $mPAP \geq 35$  mm Hg because the study was designed before the 2013 edition of the world symposium on PH, which proposed to include the association of  $mPAP \geq 25$  mm Hg and cardiac index  $< 2$  L/min /m<sup>2</sup> in the definition of severe group 3 PH (2). Before inclusion in the severe PH-COPD registry, thoracic CT scans were checked to exclude cases of combined pulmonary fibrosis and emphysema, given the known association between this syndrome and severe PH.

The patients included in the PH-COPD registry were simultaneously included in the national PAH registry, so the information collected in the severe PH-COPD registry was limited to items not already collected in the national registry. In particular, the information collected at inclusion and follow-up in the severe PH-COPD registry is listed in the online data supplement (Table E1, Table E2). After inclusion, patients were followed for 3 years, with a visit every 6 months. The PH-COPD registry was set up in agreement with the Commission Nationale de l'Informatique et des Libertés, dedicated to information technology and civil rights in France (December 2012). The registry was approved by the ethics committee of hospital Bichat, Paris, France (CEERB Paris Nord, November 2012, no. 12-071).

### Statistical analysis

Continuous variables are reported with median (interquartile range [IQR]) and categorical variables with number (percentage). Spearman correlation analysis was



used to explore the correlation of mPAP and PaO<sub>2</sub> with the number of exacerbations, FEV<sub>1</sub>, and lung diffusing capacity for carbon monoxide (DLCO) at inclusion.

The overall survival for the whole population and survival stratified by New York Heart Association (NYHA) class was analyzed by the Kaplan-Meier method and NYHA class groups were compared by log-rank test. Patients were censored after 18 months of follow-up or at their transplantation date. As the Kaplan-Meier curve did not drop below 50%, the mean survival time restricted to 18 months was used to describe survival.

Univariate and multivariable Cox proportional-hazards models were used to estimate hazard ratios (HRs) with 95% CIs for survival. Univariate Cox models were used to evaluate the association between each variable and survival. A multivariable Cox regression model was then used with variables selected by clinical relevance and missing data rates.

## **Results**

From December 2012 to December 2016, 100 patients from 13 French centers were prospectively included in the study. One patient was excluded from the analysis because he had prevalent disease. Thus, the remaining 99 patients with incident disease form the basis of the study. The flow chart of the study is given in Figure 1.

### Characteristics at inclusion

The full characteristics of the 99 patients at inclusion are reported in Table 1. Almost 60% were included in 3 centers and the others in the 10 remaining centers. The patients included in each center are described in Table E3 (supplementary material).

The diagnosis of severe PH was obtained at a median of 4 years after the diagnosis of COPD. The median age of patients at inclusion was 66.0 [62.0-72.0] years; 82 (82.8%) were male. The median body mass index (BMI) was 24.1 kg/m<sup>2</sup> [IQR 21.1-26.6] (range 16-38); BMI was > 30 kg/m<sup>2</sup> for 7% of cases. Patients were current smokers (10.2%), former smokers (85.7%), or never smokers (4.1%). Of the four never-smokers, two had been clearly exposed to occupational dust, one was a farmer with presumed professional exposure, and the last one had no identified occupational or domestic exposure but had a history of chronic asthma. The proportion of patients with NYHA class I, II, III and IV was 2%, 20.2%, 55.6%, and 22.2%, respectively. During 12 months before inclusion, 42 (42.9%) had an exacerbation requiring hospitalization (severe exacerbation). The median number of such exacerbations during the previous year was 1.0 [1.0-3.0]. The mean COPD assessment Test™ (CAT), performed in 78 of the 99 patients of the cohort was 20.0 [15.0-23.0], which indicates symptomatic impact. The prevalence of associated comorbidities was 37% (obesity n=7, diabetes n=12, coronary artery disease n=10, dysthyroidism n=4, chronic kidney failure n=4, hematologic disease n=3, atrial fibrillation n=1, other n=4) (Table 1). Medical history, including factors that may have an impact on the pulmonary circulation, was characterized by obstructive sleep apnea (n=21), history of thrombo-embolic disease (n=10), history of thoracic surgery (n=9) including lobectomy (n=6), history of intravenous drug use (n=1), benfluorex intake (n=1), depression n=8, and systemic hypertension (n=41) (Table 1).

Concerning the functional characteristics, the median FEV<sub>1</sub> value was 50.0 [IQR 35.0-63.0] % predicted and FEV<sub>1</sub>/FVC ratio 49.0 [38.0-58.0] %. Almost half of the patients (47.5%) were classified at either GOLD stage 3 (29.3%) or 4 (18.2%). DLCO and diffusion coefficient for carbon monoxide (KCO) values, available in 62 patients,

were 20.0 [16.5-30.6] % predicted and 30.3 [21.0-39.0] % predicted, respectively. Blood gas analysis was performed on room air in only 68 patients (68.7%), possibly because of the severity of the disease because most patients were on oxygen therapy (see below). The median values of PaO<sub>2</sub> and PaCO<sub>2</sub> on room air were 50.0 [44.8-62.0] mm Hg and 36.0 [31.1-43.0] mm Hg, respectively. The results of the 6-min walk test are available for 63 patients (not done in 36 patients including 20 cases considered with too-severe disease to perform the test). Despite the use of oxygen during the test in most cases (83.7%), the median walking distance was only 230 [150-354] m, with a median oxygen saturation 82.0 [77.0-86.0] % by the end of the 6 min. The median BODE index (Body-mass index, airflow Obstruction, Dyspnea, and Exercise) (available in 61 patients) was 5 (0-2: 14.7%; 3-4: 26.3%; 4-6: 22.9%; 7-10: 36.1%). RHC was performed by definition in all 99 patients. The median values for mPAP, pulmonary artery occlusion pressure (PAOP), cardiac output, cardiac index, and pulmonary vascular resistance (PVR) were 42.0 [37.0-48.0] mm Hg, 11.0 [9.0-14.0] mm Hg, 5.2 [4.4-6.4] L/min, 3.0 [2.4-3.6] L/min/m<sup>2</sup>, and 6.3 [4.2-7.9] WU, respectively.

We found no significant correlation between mPAP and FEV<sub>1</sub>, mPAP and DLCO, or mPAP and number of exacerbations at inclusion but a significant positive correlation between PaO<sub>2</sub> and DLCO ( $r = 0.399$ ,  $p=0.0089$ ).

On thoracic CT, available in 95 patients (96%), emphysema was present in 82, the distribution of emphysematous lesions judged as homogeneous or heterogeneous in 37.5% and 53.8%, respectively. The median diameters of the main pulmonary artery (data available in 65 patients) and ascending aorta (data available in 58 patients) were 34 [30-37] mm and 33 [31-36] mm, respectively. The median ratio of main

pulmonary artery diameter to ascending aorta diameter (in 58 patients) was 1 [0.89-1.08].

Most patients (n=81) were receiving long-term oxygen therapy at inclusion. Non-invasive ventilation was used in 18 patients, and 8 had continuous positive airway pressure. All patients were naïve of PAH-targeted therapy.

### Follow-up/survival

After inclusion in the registry, among 75 patients with available information, 58 (77%) were receiving PAH-targeted therapy at the 6-month visit (endothelin receptor inhibitor ambrisentan or bosentan, n=9; phosphodiesterase 5 inhibitor sildenafil or tadalafil, n=30; combination of endothelin receptor inhibitor and phosphodiesterase 5 inhibitor, n=15; subcutaneous treprostinil, n=1; inhaled iloprost, n=1; combination of inhaled iloprost and phosphodiesterase 5 inhibitor, n=2). At the 12-month visit, 64 patients had received at least 1 PAH-targeted therapy, and 35 did not receive any PAH medication. The distribution of patients according to NYHA class and death rate at 6 and 12 months after inclusion is in Figure 2. The evolution of FEV<sub>1</sub> and 6-min walking distance over time (at inclusion and at 6- and 12-month visits) is given in Figures E1 and E2 (supplementary material).

None of the 99 patients was lost to follow-up. The mortality rate was 13% (n=13), 24%(n=23), and 27% (n=26) at 6, 12, and 18 months, respectively (Figure 2). Lung transplantation was performed in 5 patients within 1 year after inclusion (Figure 1 and Figure 2).

Kaplan-Meier survival curve for the 99 patients is in Figure 3A. The restricted mean survival was 15.0 [13.9-16.0] months. Stratification by NYHA class (class I-II vs III vs IV), indicated that the higher the class, the poorer the survival (p=0.0034) (Figure

3B). On univariate Cox regression analysis (Table 2; Table E4, supplementary material), survival was significantly associated with the NYHA class ( $p=0.0087$ ), severity of exacerbations (occurrence of at least one exacerbation requiring hospitalization during the 12 months before inclusion) (HR: 2.29; 95% CI: 1.05-4.99;  $p=0.0375$ ), the number of exacerbations requiring hospitalization during the 12 months before inclusion (HR: 1.36; 95% CI: 1.02-1.82;  $p=0.0381$ ). The HR for survival with DLCO class ( $< 20\%$  vs  $\geq 20\%$  predicted), measured with 68 patients (see above), was 2.94 (95% CI: 0.95-9.11) but it failed to reach statistical significance ( $p=0.0623$ ). On multivariable analysis, survival was associated with the number of exacerbations requiring hospitalization during the 12 months before inclusion (HR: 1.42; 95% CI: 1.00-2.00;  $p=0.0498$ ) and NYHA class (class IV vs I-II) (HR: 6.82; 95% CI: 1.46-31.88;  $p=0.0147$ ) (Table 3). Among the 26 patients who had died after 18 months of follow-up, the rate of receiving at least one PAH medication and no PAH medication was 14% ( $n=9$ ) and 49% ( $n=17$ ).

## **Discussion**

In a prospective cohort of COPD patients presenting severe PH, 1) the patients were characterized by a particular clinical/functional profile associating a high level of symptoms including marked dyspnea and often a history of hospitalization for exacerbation, profound hypoxemia with hypocapnia, and low DLCO value but moderate level of airway obstruction; 2) this phenotype is associated with poor prognosis with mean survival of less than 1.5 years; and 3) survival was associated with NYHA class and number of exacerbations requiring hospitalization.

PH may develop during the course of COPD because airway obstruction is worsening. When present, PH is characterized by several main features: slow

progression, proven prognostic value, increased risk of hospitalization for acute exacerbation, and mPAP level at rest from 25 to 35 mm Hg in most cases with preserved cardiac output, increasing during an acute exacerbation and under exercise (3, 9, 13-16). In group 3 PH, the use of antiproliferative drugs approved for group 1 PH is not recommended because of an unproven benefit and because the general view is that the limitation of exercise capacity in COPD is not related to a failure of pulmonary circulation. Besides the usual hemodynamic phenotype, a subgroup of COPD patients presents with a more severe involvement of the pulmonary circulation (2-9, 11, 17). According to the 5<sup>th</sup> and the 6<sup>th</sup> world Symposium on Pulmonary Hypertension, these patients are classified as having severe PH-COPD defined by mPAP  $\geq$  35 mm Hg or mPAP  $\geq$  25 mm Hg with low cardiac index ( $< 2\text{l}/\text{min}/\text{m}^2$ ) (2, 3).

Some characteristics have emerged from data obtained from a very few retrospective studies including a quite low number of patients, (6, 9, 11, 18, 19): the prevalence of severe PH-COPD entity is low (involving  $\leq$  5% of COPD patients); the patients have marked exertional dyspnea, profound hypoxemia and low DLCO, which may contrast with preserved pulmonary function tests; and the prognosis is poor (6, 10). Our prospective study involving a significant number of incident patients with severe PH provides a more precise description of this entity. We confirm the particular clinical/functional profile combining marked dyspnea, profound hypoxemia, and low DLCO but moderate airway obstruction. The study provides some additional information for severe PH-COPD such as the associated comorbidities, the rate of severe exacerbations, and the response to exercise, but the most striking data are those related to prognosis. On retrospectively analyzing the data for 1000 COPD patients who underwent RHC routinely, Chaouat and coworkers identified a subgroup

of 11 with mPAP  $\geq$  40 mm Hg, not explained by comorbidities. As compared with a control group with mPAP < 40 mm Hg, this subgroup showed significantly worse survival (6). The median survival of the 11 patients with severe PH was 26 months. We found an even worse survival (mean survival of 15.0 months) in our cohort of incident patients. The very high mortality, one of the hallmarks of our severe PH-COPD subpopulation, is far higher than expected in COPD patients with this level of airway obstruction (20, 21).

The recommendations of the 5<sup>th</sup> and 6<sup>th</sup> World Symposium on Pulmonary Hypertension are to refer patients with severe PH-COPD to an expert center to consider inclusion in a randomized trial testing vasoactive drugs if available or to use PAH-approved drugs on a compassionate basis (2, 3). The very poor prognosis of severe PH-COPD despite the use of vasoactive treatment in most cases should prompt the physicians in charge of these patients to consider lung transplantation even though the patients do not fulfill the usual selection criteria. We found that most patients received a vasoactive drug during follow-up, despite the lack of clear evidence of the benefit of PAH-targeted therapy in COPD patients with severe PH. By contrast, very few underwent lung transplantation. The frequency of associated comorbidities and the older age of the patients perhaps prevented them from being considered for lung transplantation.

Severe PH-COPD is now a recognized entity, but a recurrent question is whether severe PH in this case is a consequence of the lung disease by itself or is coincidental, namely the association of a common disease (COPD) and a rare disease (PAH) (2, 3, 22). Several arguments favor the first hypothesis. First, the prognosis is much poorer than that with PAH, even in the high risk subpopulation (23); second, there is no strong evidence of a benefit of PAH-targeted therapy in

terms of improvement in exercise tolerance and symptoms in severe COPD-PH patients, in contrast with PAH patients (3); third, a recently published study based on the histology characteristics of lung explants from COPD patients who had undergone lung transplantation showed that the lungs of severe PH COPD patients appeared to have a specific histologic pattern, different from that observed in patients with COPD with moderate PH or without PH (4). The important point is that the 3 groups showed no significant differences in muscular-type pulmonary arteries, which are relevant in PAH (group 1), and no typical PAH lesions, such as plexiform lesions or onion-skin lesions (concentric laminar intimal fibrosis), were detected, which stresses at least the different morphologic phenotype of severe COPD-PH and PAH (4).

The main limitation of this study is that even if major data such as spirometry, hemodynamic and survival characteristics were available for all patients from our cohort, some data at inclusion concerning some important variables are missing. In particular, results of blood gas analysis on room air, DLCO, and 6-min walk test were missing in a significant number of patients, which hinders the optimal description of the entity and the interpretation of the tests of association between the above-mentioned variables and survival. However, in many cases, these data are missing because the severity of the respiratory condition precluded their measurement.

In conclusion, our study, based on a prospective cohort of patients presenting severe PH-COPD, confirms that this subgroup of COPD is characterized by a moderate level of airway obstruction but marked dyspnea and hypoxemia, low DLCO, and high mPAP. In addition, exercise capacity is very low and patients often had severe exacerbation within the year before inclusion. This pulmonary vascular phenotype is



associated with very poor prognosis, with mortality far higher than expected in COPD patients with this level of airway obstruction.

### **Contributions of the authors**

HM, GS, MH, and GD designed the study.

GT built the electronic file

MRG, VC, BL, DM, MC, CB, IF, AC, BD, EB, OS, GP, OS, GP, OS followed the patients overtime and filled the inclusion and follow-up questionnaires.

YCB and AB were responsible for the data collection

DB and CL performed the data analysis

HM and GD wrote the manuscript

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### **Conflict of interest statement**

Dr. Cottin reports personal fees and non-financial support from Actelion, grants, personal fees and non-financial support from Boehringer Ingelheim, personal fees from Bayer / MSD, personal fees from Novartis, personal fees and non-financial support from Roche / Promedior, personal fees from Sanofi, personal fees from Celgene, personal fees from Galapagos, personal fees from Galecto, personal fees from Shionogi, personal fees from Astra Zeneca, personal fees from Fibrogen, outside the submitted work; .

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## References

1. 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(1).
2. Seeger W, Adir Y, Barbera JA, Champion H, Coghlan JG, Cottin V, et al. Pulmonary hypertension in chronic lung diseases. *J Am Coll Cardiol*. 2013;62(25 Suppl):D109-16.
3. Nathan SD, Barbera JA, Gaine SP, Harari S, Martinez FJ, Olschewski H, et al. Pulmonary hypertension in chronic lung disease and hypoxia. *Eur Respir J*. 2019;53(1).
4. Bunel V, Guyard A, Dauriat G, Danel C, Montani D, Gauvain C, et al. Pulmonary Arterial Histologic Lesions in Patients With COPD With Severe Pulmonary Hypertension. *Chest*. 2019;156(1):33-44.
5. Mal H. Prevalence and diagnosis of severe pulmonary hypertension in patients with chronic obstructive pulmonary disease. *Current opinion in pulmonary medicine*. 2007;13(2):114-9.
6. Chaouat A, Bugnet AS, Kadaoui N, Schott R, Enache I, Ducolone A, et al. Severe pulmonary hypertension and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2005;172(2):189-94.
7. Scharf SM, Iqbal M, Keller C, Criner G, Lee S, Fessler HE. Hemodynamic characterization of patients with severe emphysema. *Am J Respir Crit Care Med*. 2002;166(3):314-22.

8. Carlsen J, Hasseriis Andersen K, Boesgaard S, Iversen M, Steinbruchel D, Bogelund Andersen C. Pulmonary arterial lesions in explanted lungs after transplantation correlate with severity of pulmonary hypertension in chronic obstructive pulmonary disease. *J Heart Lung Transplant*. 2013;32(3):347-54.
9. Andersen KH, Iversen M, Kjaergaard J, Mortensen J, Nielsen-Kudsk JE, Bendstrup E, et al. Prevalence, predictors, and survival in pulmonary hypertension related to end-stage chronic obstructive pulmonary disease. *J Heart Lung Transplant*. 2012;31(4):373-80.
10. Hurdman J, Condliffe R, Elliot CA, Swift A, Rajaram S, Davies C, et al. Pulmonary hypertension in COPD: results from the ASPIRE registry. *Eur Respir J*. 2013;41(6):1292-301.
11. Thabut G, Dauriat G, Stern JB, Logeart D, Levy A, Marrash-Chahla R, et al. Pulmonary hemodynamics in advanced COPD candidates for lung volume reduction surgery or lung transplantation. *Chest*. 2005;127(5):1531-6.
12. 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(9):1023-30.
13. Medrek SK, Sharafkhaneh A, Spiegelman AM, Kak A, Pandit LM. Admission for COPD Exacerbation Is Associated with the Clinical Diagnosis of Pulmonary Hypertension: Results from a Retrospective Longitudinal Study of a Veteran Population. *Copd*. 2017;14(5):484-9.
14. Kessler R, Faller M, Fourgaut G, Menecier B, Weitzenblum E. Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1999;159(1):158-64.
15. Oswald-Mammosser M, Apprill M, Bachez P, Ehrhart M, Weitzenblum E. Pulmonary hemodynamics in chronic obstructive pulmonary disease of the emphysematous type. *Respiration*. 1991;58(5-6):304-10.
16. Oswald-Mammosser M, Weitzenblum E, Quoix E, Moser G, Chaouat A, Charpentier C, et al. Prognostic factors in COPD patients receiving long-term oxygen therapy. Importance of pulmonary artery pressure. *Chest*. 1995;107(5):1193-8.
17. Boerrigter BG, Bogaard HJ, Trip P, Groepenhoff H, Rietema H, Holverda S, et al. Ventilatory and cardiocirculatory exercise profiles in COPD: the role of pulmonary hypertension. *Chest*. 2012;142(5):1166-74.
18. Brewis MJ, Church AC, Johnson MK, Peacock AJ. Severe pulmonary hypertension in lung disease: phenotypes and response to treatment. *Eur Respir J*. 2015;46(5):1378-89.
19. Hurdman J, Condliffe R, Elliot CA, Davies C, Hill C, Wild JM, et al. ASPIRE registry: assessing the Spectrum of Pulmonary hypertension Identified at a REferral centre. *Eur Respir J*. 2012;39(4):945-55.

20. Traver GA, Cline MG, Burrows B. Predictors of mortality in chronic obstructive pulmonary disease. A 15-year follow-up study. *Am Rev Respir Dis.* 1979;119(6):895-902.
21. Anthonisen NR, Wright EC, Hodgkin JE. Prognosis in chronic obstructive pulmonary disease. *Am Rev Respir Dis.* 1986;133(1):14-20.
22. Kovacs G, Agusti A, Barbera JA, Celli B, Criner G, Humbert M, et al. Pulmonary Vascular Involvement in Chronic Obstructive Pulmonary Disease. Is There a Pulmonary Vascular Phenotype? *Am J Respir Crit Care Med.* 2018;198(8):1000-11.
23. Hoepfer MM, Kramer T, Pan Z, Eichstaedt CA, Spiesshoefer J, Benjamin N, et al. Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. *Eur Respir J.* 2017;50(2).

## **Figure legends**

Figure 1 – Flow-chart of the study

Figure 2 - Distribution of New York Heart Association (NYHA) class, death rate, and lung transplantation rate at inclusion, and at 6- and 12-month follow-up

Figure 3 – Kaplan-Meier survival curves. (A) Overall survival, (B) Survival stratified by NYHA class

**Table 1 – Patient characteristics at baseline**

<b>Characteristics*</b>	<b>No. of patients</b>	<b>Baseline</b>
Age - years	99	66.0 [62.0-72.0]
Male sex - no. (%)	99	82 (82.8)
BMI - kg/m <sup>2</sup>	99	24.1 [21.1-26.6]
Ethnicity - no. (%)	73	
Caucasian		68 (93.2)
Black		2 (2.7)
Other		3 (4.1)
Smoking status - no. (%)	98	
Current smoker		10 (10.2)
Former smoker		84 (85.7)
Non-smoker		4 (4.1)
Cigarette consumption - pack-years	88	41.8 [39.0-70.0]
Time between diagnosis of COPD and inclusion in the study, years	87	4.0 [2.0-6.0]
Patients with at least one non-severe AE in the previous 12 months - no. (%)	96	25 (26.0)
No. of AEs	23	1.0 [1.0-3.0]
Patients with at least one severe AE in the previous 12 months - no. (%)	98	42 (42.9)
No. of hospitalizations for AEs	41	1.0 [1.0-2.0]
NYHA class - no. (%)	99	
I		2 (2.0)
II		20 (20.2)
III		55 (55.6)
IV		22 (22.2)
FEV <sub>1</sub> (% pred)	98	50.0 [35.0-63.0]
FEV <sub>1</sub> /FVC (%)	95	49.0 [38.0-58.0]
FVC (% pred)	96	80.5 [64.0-97.0]
TLC (% pred)	85	109.0 [94.0-123.0]
DLCO - no. (%)	68	
< 20		36 (52.9)
≥ 20		32 (47.1)
DLCO (% pred )	62	20.0 [16.5-30.6]
KCO (% pred)	61	30.3 [21.0-39.0]
SVC (% pred)	87	86.0 [71.0-99.0]
FRC (% pred)	80	140.5 [115.0-163.0]
RV (% pred)	84	140.0 [116.0-186.5]
6 min-walk distance (m)	63	230.0 [150.0-354.0]
Oxygen saturation by the end of the 6 min	60	82.0 [77.0-86.0]
Body surface (m <sup>2</sup> )	99	1.8 [1.7-2.0]
sPAP (mm Hg)	99	65.0 [57.0-77.0]
mPAP (mm Hg)	99	42.0 [37.0-48.0]
dPAP (mm Hg)	98	29.0 [25.0-36.0]
PAOP (mm Hg)	97	11.0 [9.0-14.0]

RAP (mm Hg)	92	8.0 [6.0-12.0]
Cardiac output (l/min)	99	5.2 [4.4-6.4]
Cardiac index (l/min/m <sup>2</sup> )	99	3.0 [2.4-3.6]
TPR (WU)	99	8.2 [6.2-10.4]
PVR (WU)	97	6.3 [4.2-7.9]
PaO <sub>2</sub> (mmHg)	67	50.0 [44.8-62.0]
PaCO <sub>2</sub> (mmHg)	58	36.0 [31.1-43.0]
CAT score	78	20.0 [15.0-23.0]
Oxygen therapy - no. (%)	99	81 (81.8)
Diuretics - no. (%)	99	25 (25.3)
Anticoagulant therapy- no. (%)	99	10 (10.1)
<b>Comorbidities</b>		
Any comorbidity-no.(%)	99	37 (37.4)
Atrial fibrillation – no.		1
Obesity - no.		7
Diabetes - no.		12
Coronary artery disease - no.		10
Chronic renal failure - no.		4
Hematologic disease - no.		3
Dysthyroidism - no.		4
Other comorbidity - no. †		4
<b>Medical history including factors that might affect pulmonary circulation</b>		
History of thrombo-embolic disease - no.		10
Obstructive sleep apnea - no.		21
History of thoracic surgery - no.		9
<i>Lobectomy - no.</i>		6
History of intravenous drug use - no.		1
Depression - no.		8
Systemic hypertension - no.		41

\*For continuous variables, values are reported as median [IQR]; † bronchopulmonary or bladder carcinomas

#### Abbreviations:

COPD: chronic obstructive pulmonary disease, NYHA: New York Heart Association, BMI: body mass index, AE: acute exacerbation, FEV<sub>1</sub>: forced expiratory volume in 1 sec, FVC: forced vital capacity, TLC: total lung capacity, SVC: slow vital capacity, DLCO:lung diffusing capacity for carbon monoxide, KCO, diffusion coefficient for carbon monoxide, RV: residual volume, sPAP: systolic pulmonary artery pressure, mPAP: mean pulmonary artery pressure, dPAP: diastolic pulmonary artery pressure, RAP: right atrial pressure, PAOP: pulmonary artery occlusion pressure, pred: predicted, TPR: total pulmonary resistance, PVR: pulmonary vascular resistance, WU: Wood units, CAT: COPD Assessment Test™

**Table 2 –Univariate Cox regression analysis of predictors of survival**

Variable	No.	HR [95%CI]	P-value
Professional exposure – Yes vs No	99	2.57 [1.12-5.91]	<b>0.0265</b>
Weight at baseline	99	1.00 [0.98-1.03]	0.7352
BMI	99	0.98 [0.89-1.08]	0.7038
NYHA class	99		<b>0.0087</b>
<i>III vs I-II</i>		3.08 [0.69-13.66]	
<i>IV vs I-II</i>		7.76 [1.72-35.07]	.
Interval between diagnosis of COPD and inclusion in the study, years	87	0.99 [0.94-1.06]	0.8374
CAT score	78	1.02 [0.95-1.08]	0.6010
Weight loss – Yes vs No	98	1.28 [0.44-3.71]	0.6529
Age at baseline	98	1.03 [0.98-1.08]	0.2622
Non-invasive ventilation – Yes vs No	99	1.46 [0.59-3.65]	0.4144
Continuous positive airway pressure – Yes vs No	99	0.92 [0.22-3.87]	0.9041
Sleep apnea syndrome	99		0.9114
Yes vs No		1.14 [0.45-2.85]	
Not searched vs No		1.44 [0.19-10.79]	.
Comorbidities – Yes vs No	99	1.26 [0.58-2.75]	0.5578
Oxygen therapy – Yes vs No	99	0.98 [0.37-2.59]	0.9623
Diuretics – Yes vs No	99	0.82 [0.33-2.04]	0.6647
Anticoagulant therapy – Yes vs No	99	1.08 [0.32-3.59]	0.9037
Tobacco consumption (pack-years)	92		0.2906
> 80 vs [0-20]		5.70 [0.59-54.91]	
[21-40] vs [0-20]		2.19 [0.27-17.78]	.
[41-60] vs [0-20]		4.24 [0.53-33.94]	.
[60-80] vs [0-20]		5.13 [0.62-42.64]	.
Hospitalizations for AE* – Yes vs No	98	2.29 [1.05-4.99]	<b>0.0375</b>
Number of hospitalizations for AE	97	1.36 [1.02-1.82]	<b>0.0381</b>
AEs without hospitalization – Yes vs No	96	0.74 [0.28-1.97]	0.5466
Number of AEs without hospitalization	94	0.82 [0.48-1.39]	0.4573
Body surface (m <sup>2</sup> )	99	1.92 [0.29-12.73]	0.4991
sPAPs (mm Hg)	99	1.00 [0.99-1.02]	0.6847
mPAP (mm Hg)	99	1.02 [0.97-1.06]	0.4803
dPAP (mm Hg)	98	1.01 [0.96-1.07]	0.6054
RAP (mm Hg)	92	1.01 [0.93-1.09]	0.8231
PAOP (mm Hg)	97	0.98 [0.88-1.09]	0.7481
CI (l/min/m <sup>2</sup> )	99	0.64 [0.40-1.02]	0.0618
TPR (WU)	99	1.08 [1.00-1.16]	<b>0.0476</b>
PVR (WU)	97	1.05 [0.94-1.17]	0.3601
FEV <sub>1</sub> (% pred)	98	1.00 [0.98-1.02]	0.9917



FVC (% pred)	96	0.99 [0.97-1.01]	0.1673
SVC (% pred)	87	0.99 [0.97-1.01]	0.5776
TLC (% pred)	85	0.98 [0.96-1.01]	0.1450
FRC (% pred)	80	0.99 [0.98-1.01]	0.2415
RV (% pred)	84	1.00 [0.99-1.01]	0.6021
FEV <sub>1</sub> /FVC (%)	95	1.01 [0.98-1.05]	0.4209
DLCO (% pred)	62	0.96 [0.90-1.01]	0.1265
DLCO (% pred) <20 vs ≥20	68	2.94 [0.95-9.11]	0.0623
PaO <sub>2</sub> (Room air) (mm Hg)	67	0.97 [0.93-1.01]	0.1317

\*severe AE

Data are hazards ratios (HRs) and 95% confidence intervals (CIs)

Abbreviations:

COPD: chronic obstructive pulmonary disease, NYHA: New York Heart Association, BMI: body mass index, AE: acute exacerbation, FEV<sub>1</sub>: forced expiratory volume in 1 second, FVC: forced vital capacity, TLC: total lung capacity, SVC: slow vital capacity, DLCO: lung diffusing capacity for carbon monoxide, RV: residual volume, sPAP: systolic pulmonary artery pressure, mPAP: mean pulmonary artery pressure, dPAP: diastolic pulmonary artery pressure, RAP: right atrial pressure, PAOP: pulmonary artery occlusion pressure, pred: predictedTPR: total pulmonary resistance, PVR: pulmonary vascular resistance, WU: Wood units, CAT: COPD Assessment Test™

**Table 3 – Multivariable Cox regression analysis of predictors of survival)**

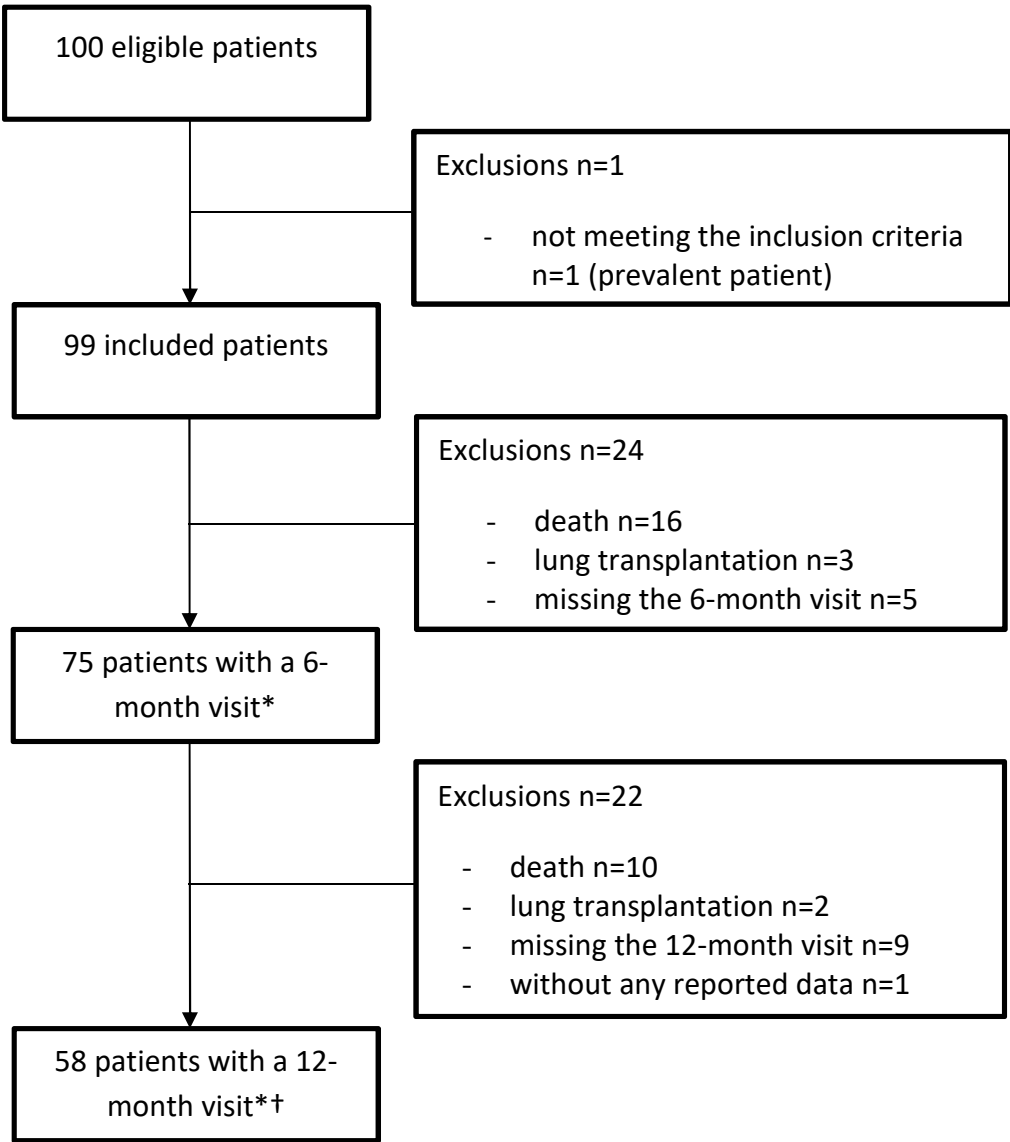
Variable	N	HR [95% CI]	P-value
CI (l/min/m <sup>2</sup> )	94	0.71 [ 0.38 ; 1.30 ]	0.2639
TPR (WU)		0.99 [ 0.88 ; 1.12 ]	0.8596
Number of AEs without hospitalization		0.79 [ 0.45 ; 1.39 ]	0.4194
Number of hospitalizations for AE		1.42 [ 1.00 ; 2.00 ]	<b>0.0498</b>
NYHA class			<b>0.0304</b>
<i>III vs I-II</i>		3.11 [ 0.68 ; 14.22 ]	0.1431
<i>IV vs I-II</i>		6.82 [ 1.46 ; 31.88 ]	<b>0.0147</b>

Data are hazards ratios (HRs) and 95% confidence intervals (CIs)

Abbreviations:

NYHA: New York Heart Association, AE: acute exacerbation, TPR: total pulmonary resistance, WU: Wood units

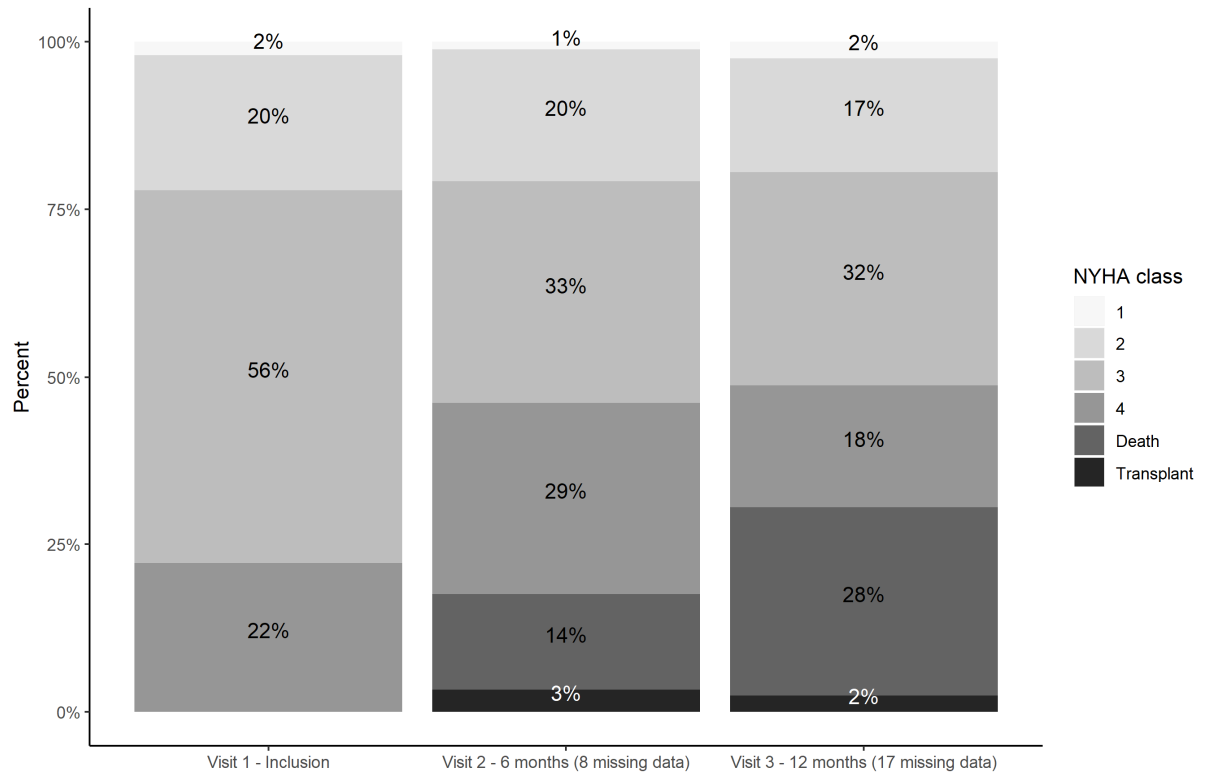
Figure 1 – Flow-chart of the study



\*Some patients who did not attend the 6-month visit attended the 12-month visit

†Some patients who did not attend the 12-month visit were seen at the subsequent visits

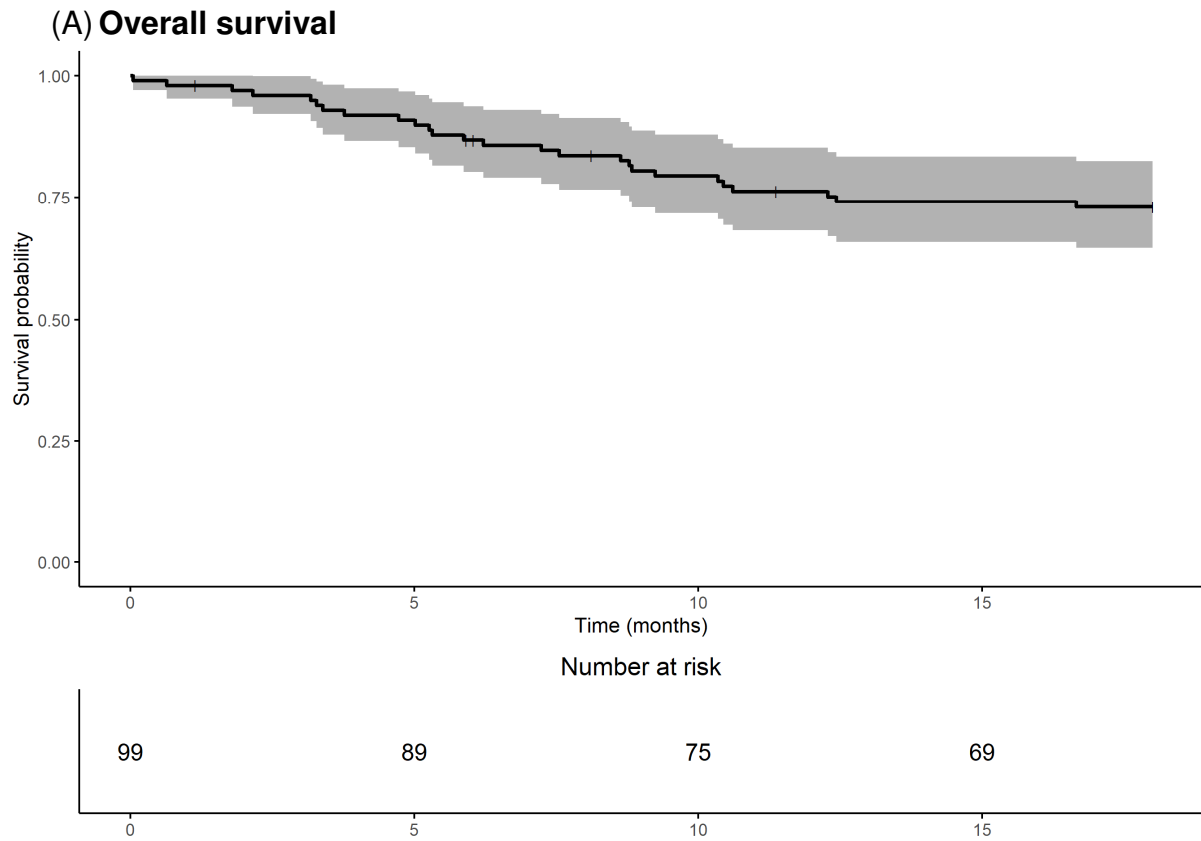
**Figure 2 Distribution of New York Heart association (NYHA) class, death rate, and lung transplantation rate at inclusion, and at 6- and 12-month follow-up**



**Abbreviations:**

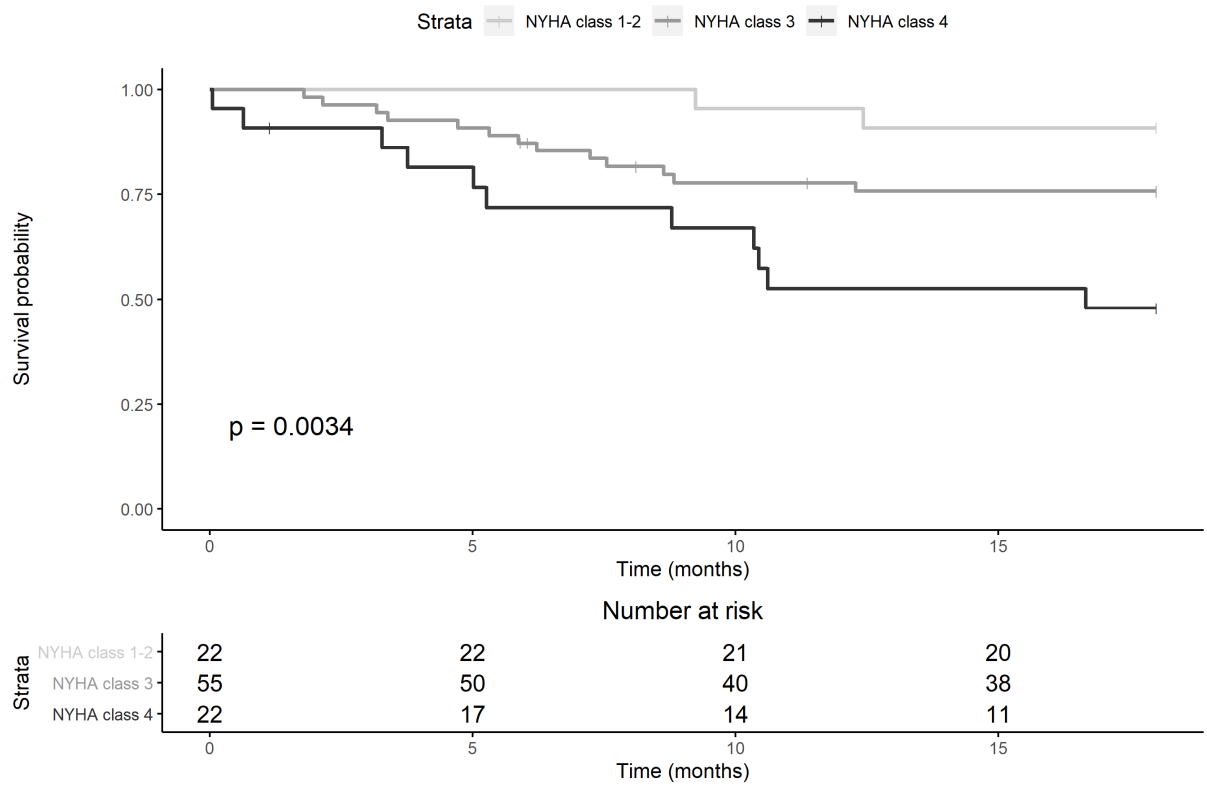
NYHA: New York Heart Association, LT: lung transplantation

**Figure 3 Kaplan-Meier survival curves. (A) Overall survival, B survival stratified by NYHA class**



**Note:** The grey part represents the 95% confidence interval around the survival probability; the crosses on the curve represent censored patients (patients were censored at the date of transplantation or after 18 months of follow-up)

**(B) Survival stratified by NYHA class**



Note: The crosses on the curves represent censored patients (patients were censored at the date of transplantation or after 18 months of follow-up)