Pulmonary hypertension associated with COPD: a phenotype analysis

Mathilde Steger [1], Matthieu Canuet [1], Guillaume Martin[1], Aissam Labani[2], Jean Charles Schwartz [2], Irina Enache[3,4], Armelle Schuller[1], Léo Meyer[2], Ari Chaouat [5,6], Romain Kessler[1,7], David Montani [8,9] and Marianne Riou [1,3,4,9]

[1]Chest Diseases Department, Nouvel hôpital civil, University Hospital of Strasbourg, Strasbourg, France. [2]Radiology Department, Nouvel hôpital civil, University Hospital of Strasbourg, Strasbourg, France. [3]Department of Physiology and Functional Exploration, Nouvel hôpital civil, University Hospital of Strasbourg, Strasbourg, France. [4]University of Strasbourg, Translational Medicine Federation of Strasbourg (FMTS), CRBS, Team 3072 "Mitochondria, Oxidative Stress and Muscle Protection", Strasbourg, France. [5]Chest Diseases Department – Medical Specialties Division, CHRU, Nancy, France. [6]University of Lorraine, Faculty of Medicine, INSERM UMR_S 116, Nancy, France. [7]INSERM-UNISTRA, UMR 1260 "Regenerative NanoMedicine", University of Strasbourg, Strasbourg, France. [8]University of Paris-Saclay, AP-HP, Chest diseases department, Hospital of Bicêtre, DMU 5 Thorinno, Inserm UMR_S999, Le Kremlin Bicêtre, France. [9]These authors contributed equally.

Corresponding author: Marianne Riou (marianne.riou@chru-strasbourg.fr)

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Results highlight the broad spectrum of pre-capillary PH in COPD, from PH associated with end-stage COPD, characterised by predominant alveolar wall damage with severe emphysema, to pulmonary vascular phenotype, mainly due to pulmonary vascular changes https://bit.ly/4f6ugmW

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Abstract

Background Pulmonary hypertension (PH) associated with COPD (PH-COPD) exhibits diverse phenotypes, challenging therapeutic management. This study aimed to describe the characteristics of COPD patients with distinct phenotypes, namely end-stage COPD with or without PH (group 1), other COPD patients with mild-to-moderate pre-capillary PH-COPD (group 2) and COPD patients with a pulmonary vascular phenotype (PVP) (group 3).

Methods We performed a retrospective analysis of COPD patients who underwent right heart catheterisation from 2015 to 2022.

Results 81 patients were included in group 1, 37 in group 2 and 35 in group 3. The groups differed in terms of clinical, functional, haemodynamic and imaging characteristics. Group 1 had significantly marked lung hyperinflation with increased total lung capacity and residual volume, a feature not observed in group 3. These results were confirmed by analysis of chest CT scans, which confirmed varying degrees of emphysema, as follows: severe in group 1, moderate in group 2 and mild in group 3, with median total emphysema indices of 55% (48–62), 32% (16–49) and 16% (3.4–31), respectively, p<0.0001.

Conclusions Our results highlight the broad spectrum of PH in COPD, from PH associated with end-stage COPD (phenotype/group 1), characterised by predominant alveolar wall damage with severe emphysema, to PVP (phenotype/group 3), mainly due to pulmonary vascular changes. Phenotype/group 2 represents an intermediate state combining features of both. In the current debate on how to distinguish PH-COPD phenotypes, it might be of interest to include quantitative thresholds for emphysema in future diagnostic and management algorithms.

Introduction

COPD is a heterogeneous disease with varying degrees of damage to the airways, lung parenchyma and vasculature [1]. As a major cause of chronic morbidity and the third leading cause of death worldwide, understanding the pathobiology and mechanisms of COPD is essential for the development of a personalised therapeutic approach, as patients may differ in terms of phenotype [2].

Pulmonary hypertension (PH) is a common complication and a prognosis factor in COPD [2–10]. Pre-capillary PH associated with COPD (PH-COPD) belongs to group 3 of the PH classification and is

usually mild or moderate, but may be severe in 1–5% of COPD patients [3, 11–13]. Some of these patients represent a distinct subgroup with a worse prognosis, very low lung diffusion capacity for carbon monoxide (D_{LCO}), relatively mild obstructive disease, severe hypoxaemia and predominant vascular impairment, described as the "pulmonary vascular phenotype" (PVP) [14]. These patients differ from the classic normo-/hypercapnic COPD patients with or without PH, but do not resemble the classic idiopathic pulmonary arterial hypertension (PAH) patients [15]. This phenotypic variability highlights the complex and not fully understood pathogenic mechanisms of PH-COPD, which may include emphysema, pulmonary vascular/capillary loss and small artery vascular remodelling due to the combined effects of inflammation, endothelial dysfunction, chronic hypoxia and mechanical/oxidative stress [16–19]. Therefore, the correct phenotyping of PH-COPD is essential for its appropriate management, especially as COPD patients with severe PH show different responses to PH-specific therapy [4, 20–23].

The primary objective of our study was to describe the clinical, functional and chest imaging characteristics of a cohort of COPD patients undergoing initial right heart catheterisation (RHC) and classified into different phenotypes.

Methods

Study design and ethics

Our single-centre observational study was conducted based on retrospective data of RHC performed on all COPD patients between January 2015 and December 2022 at an expert centre (University Hospital of Strasbourg) of the French PH network.

All investigated patients met the current definition of COPD, *i.e.* chronic respiratory symptoms associated with a post-bronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio <0.7 and all had a smoking history [1]. COPD management was in accordance with established Global Initiative for Chronic Obstructive Lung Disease recommendations prior to PH diagnosis and all the patients received optimised COPD therapy before RHC [1, 11]. Patients with a partial pressure of oxygen (P_{aO_2}) <60 mmHg received oxygen supplementation prior to PH assessment and noninvasive ventilation (NIV) if associated with hypercapnia.

Indications for initial RHC were as follows: 1) as part of the evaluation prior to lung transplantation in end-stage COPD patients; 2) when severe pre-capillary PH was suspected on echocardiography; and/or 3) because of severe hypoxaemia and/or dyspnoea that appeared "disproportionate" to the severity of the airflow obstruction [20]. Only patients with pre-capillary PH defined by a mean pulmonary arterial pressure (mPAP) >20 mmHg, a pulmonary arterial wedge pressure (PAWP) ⩽15 mmHg and a pulmonary vascular resistance (PVR) >2 Wood units (WU) were included. Patients with alpha-1 antitrypsin deficiency, incomplete haemodynamic or chest computed tomography (CT) scan data, isolated post-capillary or combined post- and pre-capillary PH (*i.e.* PAWP >15 mmHg), chronic thromboembolic PH, interstitial lung disease, or other causes of pre-capillary PH were excluded.

Enrolled patients were stratified into three groups. Group 1 included patients with end-stage COPD (FEV_1<30%), candidates for lung transplantation due to COPD severity, with or without PH. Other COPD patients with FEV_1 >30% were divided into two groups according to the PVR values based on the 2022 European Society of Cardiology (ESC) and European Respiratory Society (ERS) guidelines [11], as follows: group 2 included patients with mild-to-moderate pre-capillary PH (*i.e.* PVR between 2 and 5 WU) and group 3 included patients with severe PH, *i.e.* PVR >5 WU.

This study was approved by the Institutional Review Board of the French Learned Society of Respiratory Medicine (CEPRO 2022–042bis). Data on severe PH-COPD were retrieved from the French PH registry, set up in accordance with French bioethics legislation (Commission Nationale de l'Informatique et des Libertés No. 842063).

Data collection

Collected parameters included the following: 1) demographics, New York Heart Association functional class (NYHA FC), smoking history, cardiovascular comorbidities, BODE (body mass index, airflow obstruction, dyspnoea and exercise) index, 6-min walk distance test (6MWD) and data on oxygen therapy and/or NIV; 2) brain natriuretic peptide (BNP) and resting arterial blood gases in room air; 3) body plethysmography, spirometry and D_{LCO}, expressed as a percentage of Global Lung Function Initiative normal values; and 4) chest CT scans. All patients underwent RHC according to international practice guidelines [11, 24]. High-resolution chest CT scans were obtained for all patients and were independently validated by two expert radiologists. Methods are detailed in appendix 1.

Statistical analysis

Statistical analyses were performed using Prism 9 software (GraphPad). A p-value <0.05 was considered statistically significant. Continuous variables were presented as median and interquartile range (IQR) and were compared between groups using Wilcoxon–Mann–Whitney or Kruskal–Wallis tests. Categorical variables were compared using the Chi-square test or Fisher's exact test and were presented as absolute and relative frequencies. Spearman correlation analysis was used to explore correlation between functional, chest CT scans and RHC data.

Kaplan–Meier survival analysis was performed to compare survival for groups 2 and 3 from the date of first RHC to death (all-cause mortality) or the date of the last news. Survival after transplantation was analysed for group 1. Survival rates were compared using the log-rank test.

Results

Population

Of the 255 COPD patients who underwent a first RHC, 153 met the inclusion criterion (figure 1). 81 patients were undergoing pre-lung transplant evaluation for end-stage COPD (group 1), 37 patients had mild-to-moderate pre-capillary PH-COPD (group 2) and 35 patients had confirmed severe PH-COPD (group 3).

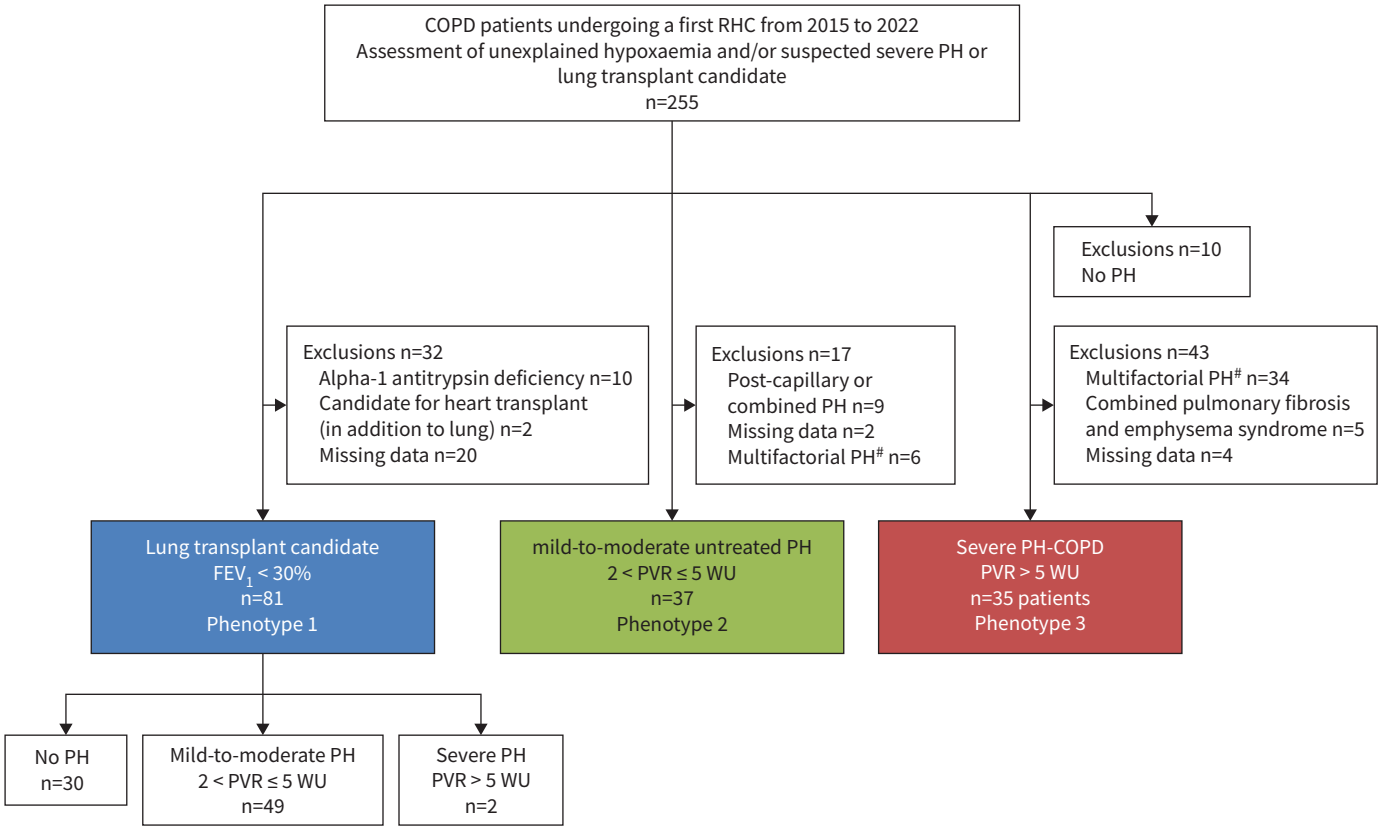

FIGURE 1 Flowchart of the study. All patients had a ventilation/perfusion lung scan to exclude chronic thromboembolic pulmonary hypertension (PH). Fluid challenge was performed during right heart catheterisation (RHC) when pulmonary arterial wedge pressure was between 12 and 15 mmHg to exclude post-capillary PH. #: Associated cardiac hyperflow: n=1; combined with associated post-capillary PH: n=11; chronic renal failure on dialysis+taking anorectic drugs: n=1; taking anorexigens: n=2; associated with post-capillary PH and chronic pulmonary artery obstruction: n=4; associated cirrhosis or liver transplantation: n=3; restrictive respiratory failure associated with scoliosis: n=2; combined with post-capillary PH and restrictive syndrome on obesity: n=1; associated with chronic pulmonary artery obstruction: n=4; pulmonary veno-occlusive disease: n=2; associated sarcoidosis: n=3; associated blood disease: n=1; patent foramen ovale requiring closure+poor tolerance of treatment and refusal of care: n=1; associated with interstitial lung disease (one indeterminate; the others related to scleroderma, to hypersensitivity pneumonitis and to rheumatoid arthritis): n=4. FEV_1: forced expiratory volume in 1 s; PVR: pulmonary vascular resistance; WU: Wood units.

Demographic and clinical characteristics

The demographic and clinical characteristics of the patients are summarised in table 1. Patients in group 3 were significantly older than those in groups 2 and 1, with a median age of 71 (IQR 69–74), 66 (63–74) and 60 (55–64) years, respectively (p<0.0001). Group 3 patients were also more likely to be male and had more cardiovascular comorbidities (p<0.0001). All patients had a history of smoking and the number of pack-years smoked appeared to be higher in group 3, but the difference was not significant.

Most COPD characteristics were significantly different between the three groups. The median FEV_1 % pred value was 67% (48–82) in group 3 *versus* 50% (32–64) in group 2 and 19% (16–22) in group 1 (p<0.0001). Patients with end-stage COPD had severe thoracic distension with a value of 130% (121–147) of predicted total lung capacity (TLC) compared to other groups (p<0.0001). However, the median TLC% was also significantly different between groups 3 and 2. Only the D_{LCO} was not significantly different between the three groups (p=0.2), but tended to be significantly lower in group 3. In this phenotype, patients were more hypoxaemic and hypocapnic with a median P_{aO_2} and carbon dioxide (P_{aCO_2}) of 50 mmHg (44–56) and 34 mmHg (28–38), respectively (p<0.0001). Group 1 patients were normo-/hypercapnic with a median P_{aCO_2} of 46 mmHg (41–50) and were more likely to be treated with NIV (p<0.0001).

Dyspnoea was more pronounced in groups 1 and 3 (92.6% and 100% in NYHA FC III or IV, respectively), compared to group 2 (59.5%). Group 3 had a higher median BNP level of 211 $ng \cdot l^{-1}$

TABLE 1 Demographic and clinical characteristics of the three groups of patients

Characteristics[#]	Group 1 (n=81)	Group 2 (n=37)	Group 3 (n=35)	p-value
Male sex (n (%))	39 (48)	23 (62)	31 (88.6)	0.0001
Age (years)	60 (55–64)	66 (63–74)	71 (69–74)	<0.0001
Body mass index ($kg \cdot m^{-2}$)	21.9 (19–26.9)	25.4 (23–29.4)	27.6 (24.2–31.2)	<0.0001
Smoking history (n (%))	81 (100)	37 (100)	35 (100)	–[¶]
Former smoker (n (%))	81 (100)	25 (67.5)	33 (94)	<0.0001
Pack-years	42.5 (30–60)	40 (30–60)	50 (40–70)	0.39
FEV_1 (% pred)	19 (16–22)	50 (32–64)	67 (48–82)	<0.0001
FVC (% pred)	51 (44–65)	77 (64–101)	87 (67–104)	<0.0001
FEV_1/FVC (%)	30 (25–36)	47 (38–59)	60 (53–66)	<0.0001
TLC (% pred)	130 (121–147)	108 (94–118)	93 (90–106)	<0.0001
RV (% pred)	261 (221–314)	148 (115–180)	98 (75–136)	<0.0001
D_{LCO} (% pred)	33 (25–40)	35 (27–49)	29.5 (22–40)	0.2[+]
P_{aO_2} (mmHg) on room air	62 (56–66)	60 (49–65)	50 (44–56)	<0.0001
P_{aCO_2} (mmHg) on room air	46 (41–50)	42 (36–45)	34 (28–38)	<0.0001
Oxygen therapy ($L \cdot min^{-1}$)	2 (1–3)	2 (0.5–3)	4 (2–4)	0.01
NIV (n (%))	37 (45.7)	5 (13.5)	2 (6)	<0.0001
BODE index	8 (7–9)	5 (3–6)	4 (3–6)	<0.0001
BNP ($ng \cdot L^{-1}$)	19 (10–36)	42 (28–71)	211 (112–525)	<0.0001
NYHA functional class (n (%))				
I	0	2 (5.5)	0	<0.0001
II	6 (7.4)	13 (35)	0	
III	33 (40.7)	20 (54)	23 (66)	
IV	42 (51.9)	2 (5.5)	12 (34)	
6MWD (m)	219 (130–296)	310 (225–345)	241 (166–332)	0.008
Clinical signs of right heart failure (n (%))	17 (21)	13 (35)	25 (71.4)	<0.0001
Number of AEs in the previous 12 months	2 (1–3)	0 (0–1)	0 (0–1)	<0.0001
Comorbidities				
Hypertension (n (%))	29 (35.8)	17 (46)	29 (83)	<0.0001
Diabetes (n (%))	8 (9.9)	6 (16.2)	18 (51)	<0.0001
Coronary artery disease (n (%))	19 (23.4)	8 (21.6)	24 (68)	<0.0001
Sleep apnoea syndrome (n (%))	9 (11)	11 (30)	9 (26)	0.02

[#]: For continuous variables, values are reported as median (interquartile range). [¶]: All patients had a history of smoking and had stopped before right heart catheterisation (pulmonary hypertension diagnosis) in most cases. [+]: p-value=0.06 for comparison between phenotypes 2 and 3 (Wilcoxon–Mann–Whitney test). 6MWD: 6-min walk distance; AE: acute exacerbation; BNP: brain natriuretic peptide; BODE: body mass index, airflow obstruction, dyspnoea, and exercise; D_{LCO}: lung diffusing capacity for carbon monoxide; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; NIV: noninvasive ventilation; NYHA: New York Heart Association; P_{aCO_2}: arterial carbon dioxide partial pressure; P_{aO_2}: arterial oxygen partial pressure; RV: residual volume; TLC: total lung capacity.

TABLE 2 Haemodynamic data of the three groups of patients[#]

Variables[¶]	Group 1 (n=81)	Group 2 (n=37)	Group 3 (n=35)
RAP (mmHg)	5 (4–8)	5 (3–7)	7 (3–11)
mPAP (mmHg)	23 (20–26)	27 (24–31)	46 (37–51)
PAWP (mmHg)	9 (6–11)	7 (5–10)	7 (5–10)
Cardiac output ($L \cdot min^{-1}$)[+]	5.4 (4.3–6.2)	5.3 (4.4–6.7)	3.8 (3.3–4.8)
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	3.1 (2.6–3.6)	2.9 (2.4–3.3)	2.1 (1.8–2.5)
PVR (WU)[§]	2.8 (2–3.3)	3.7 (3–4.3)	8.9 (6.3–10.6)
S_{vO_2} (%)	65.6 (61–68.7)	62.2 (58.9–66.1)	57.7 (3–11)

[#]: Right heart catheterisations were performed in room air in all patients. [¶]: For continuous variables, values are reported as median (interquartile range). [+]: Cardiac output was measured by the thermodilution technique. [§]: Pulmonary vascular resistance (PVR) was calculated as (mean pulmonary artery pressure (mPAP)−pulmonary arterial wedge pressure (PAWP))/cardiac output. RAP: right atrial pressure; S_{vO_2}: mixed venous oxygen saturation; WU: Wood units.

(122–525) (p<0.0001). Median 6MWD was significantly better in group 2 at 310 m (225–345) *versus* 241 m (166–332) in group 3. Group 1 patients had the lower median value of 219 m (130–296) (p<0.008).

When we compared group 1 patients according to the presence of PH, patients were similar in terms of lung volumes, 6MWD, BNP levels or chest CT data (e-table 1).

Haemodynamic characteristics

In group 1, 30 (37%) patients had no PH, 49 (60.5%) had mild-to-moderate PH-COPD and 2 (2.5%) had severe untreated PH-COPD. Group 1 patients had lower median values for mPAP, higher cardiac index and lower PVR than the other groups: 23 mmHg (20–26), 3.1 $L \cdot min^{-1} \cdot m^{-2}$ (2.6–3.6) and 2.8 WU (2–3.3), respectively, *versus* 27 mmHg (24–31), 2.9 $L \cdot min^{-1} \cdot m^{-2}$(2.4–3.3) and 3.7 WU (3–4–3) for group 2, and 46 mmHg (37–51, 2.1 $L \cdot min^{-1} \cdot m^{-2}$(1.8–2.5) and 8.9 WU (6.3–10.6) for group 3; p<0.0001 (table 2).

Chest CT data

CT analyses showed a significant difference between the three groups for the median total emphysema index, which was 16% (3.4–31) in group 3, 32% (16–49) in group 2 and 55% (48–62) in group 1; p<0.0001. The qualitative severity of emphysema was also higher in group 1 (table 3 and e-figure 1). In addition, the PA:A ratio was statistically higher in group 3 at 1.03 (0.9–1.1), p<0.0001.

Group 2 versus *patients with mild-to-moderate PH in group 1*

Patients in group 2 had a significantly higher median of mPAP and PVR of 27 mmHg and 3.7 WU, respectively, than the 49 patients in group 1 with mild-to-moderate PH, where median mPAP and PVR were 25 mmHg and 3 WU, respectively (p=0.0006). The opposite was observed for emphysema, with a median total lung emphysema of 32.5% in group 2 and 55.1% in group 1 with mild-to-moderate PH; p<0.0001 (figure 2).

TABLE 3 Chest computed tomography (CT) data

Variables[#]	Group 1 (n=81)	Group 2 (n=37)	Group 3 (n=33)[+]	p-value
Total emphysema index (%)	55 (48–62)	32 (16–49)	16 (3.4–31)	<0.0001
PA:A ratio	0.82 (0.74–0.91)	0.94 (0.84–1.0)	1.03 (0.9–1.1)	<0.0001
Severity of emphysema				
Mild CLE (n (%))	3 (4)	7 (19)	9 (26)	0.0007
Moderate CLE (n (%))	6 (7)	7 (19)	7 (20)	0.07
Confluent CLE (n (%))	27 (33)	13 (35)	12 (34)	0.97
Advanced destructive emphysema (n (%))	45 (56)	10 (27)	5 (14)	<0.0001
Paraseptal emphysema (n (%))[¶]	37 (46)	16 (43)	16 (46)	0.97

[#]: For continuous variables, values are reported as median (interquartile range). [¶]: Paraseptal emphysema was never found alone and always in association with centrolobular emphysema. [+]: Two chest CT scans from phenotype 3 were not interpretable. CLE: centrilobular emphysema; PA:A ratio: ratio of main pulmonary artery diameter to ascending aorta diameter.

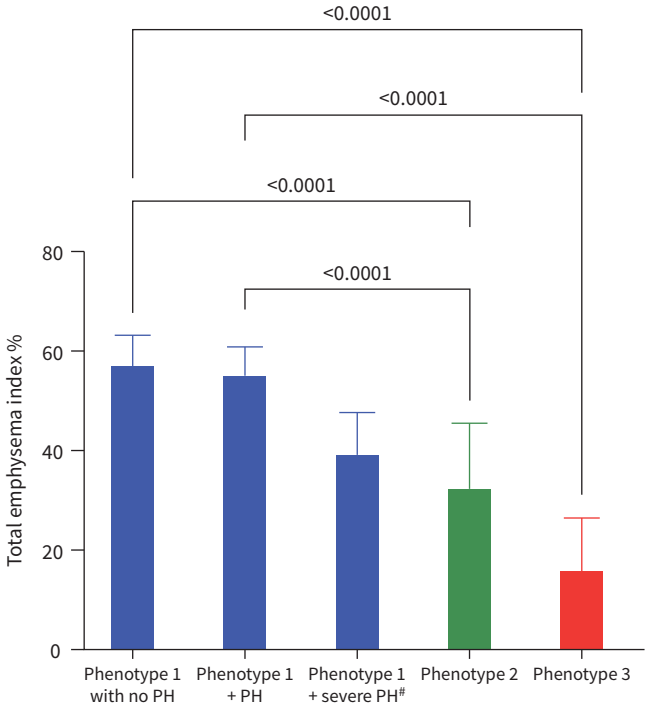

FIGURE 2 Comparison of total emphysema index (%) between the three phenotypes. Cluster 1 was divided into three groups according to the severity of pulmonary hypertension (PH). #: Note that only n=2 for the subgroup of phenotype 1+severe PH. Results are expressed as median+95% confidence interval.

Correlations

In our population, mPAP was positively correlated with PA:A ratio (r=0.68, p<0.0001; figure 3a) and negatively correlated with emphysema (r=−0.57, p<0.0001; figure 3b). The total emphysema index was correlated with functional lung tests, *i.e.* residual volume (RV) (r=0.69, p<0.0001), TLC (r=0.65, p<0.0001) and FEV_1 (r =−0.64, p<0.0001) (figures 3c–e). To a lesser degree, P_{aO_2} was correlated with the total emphysema index (r=0.36; p<0.0001) and inversely with PVR (r=−0.41; p<0.0001) (figures 3f and g). There was also a weak positive correlation between D_{LCO} and P_{aO_2} (r=0.24; p=0.009), but not between D_{LCO} and emphysema or between D_{LCO} and PVR.

Survival analyses

16 patients (45.7%) died (all causes) during the study period in group 3 and 22 (59.5%) in group 2 (e-table 2). The Kaplan–Meier estimated survival rates were not significantly different with survival at 1, 3 and 5 years of 94%, 65% and 42% for group 3 and 77%, 56% and 34% for group 2 (p=0.21; figure 4a). Survival after transplantation was not significantly different between group 1 patients with and without PH (figure 4b).

Discussion

Our results highlight the heterogeneity of pre-capillary PH in COPD. Indeed, we described three distinct clinical, functional, radiological and haemodynamic phenotypes, namely 1) end-stage COPD with FEV_1 <30%, with or without PH; 2) moderately severe COPD (FEV_1 50%) with mild-to-moderate pre-capillary PH; and 3) mild COPD (FEV_1 67%) with severe pre-capillary PH, whose characteristics were similar to those of PVP [14, 25]. Indeed, as reported in previous studies, phenotype/group 3 patients were more likely to be older men, have more cardiovascular comorbidities and a greater cumulative smoking history (+10 pack-years compared with the other groups), suggesting a specific role for tobacco in systemic and pulmonary endothelial dysfunction [7, 13, 15, 21, 23, 26, 27].

Regarding our three groups of patients, groups 1 and 3 were very opposite in terms of clinical (except for similarly severe dyspnoea), functional, imaging and haemodynamic characteristics, whereas group/phenotype 2 was more intermediate. PVP was associated with more hypoxaemia, hypocapnia and less severe airflow obstruction compared to the other two groups [4, 14, 27]. More interestingly, TLC and RV were highly increased in the pre-lung transplant candidates, reflecting lung hyperinflation, which was not

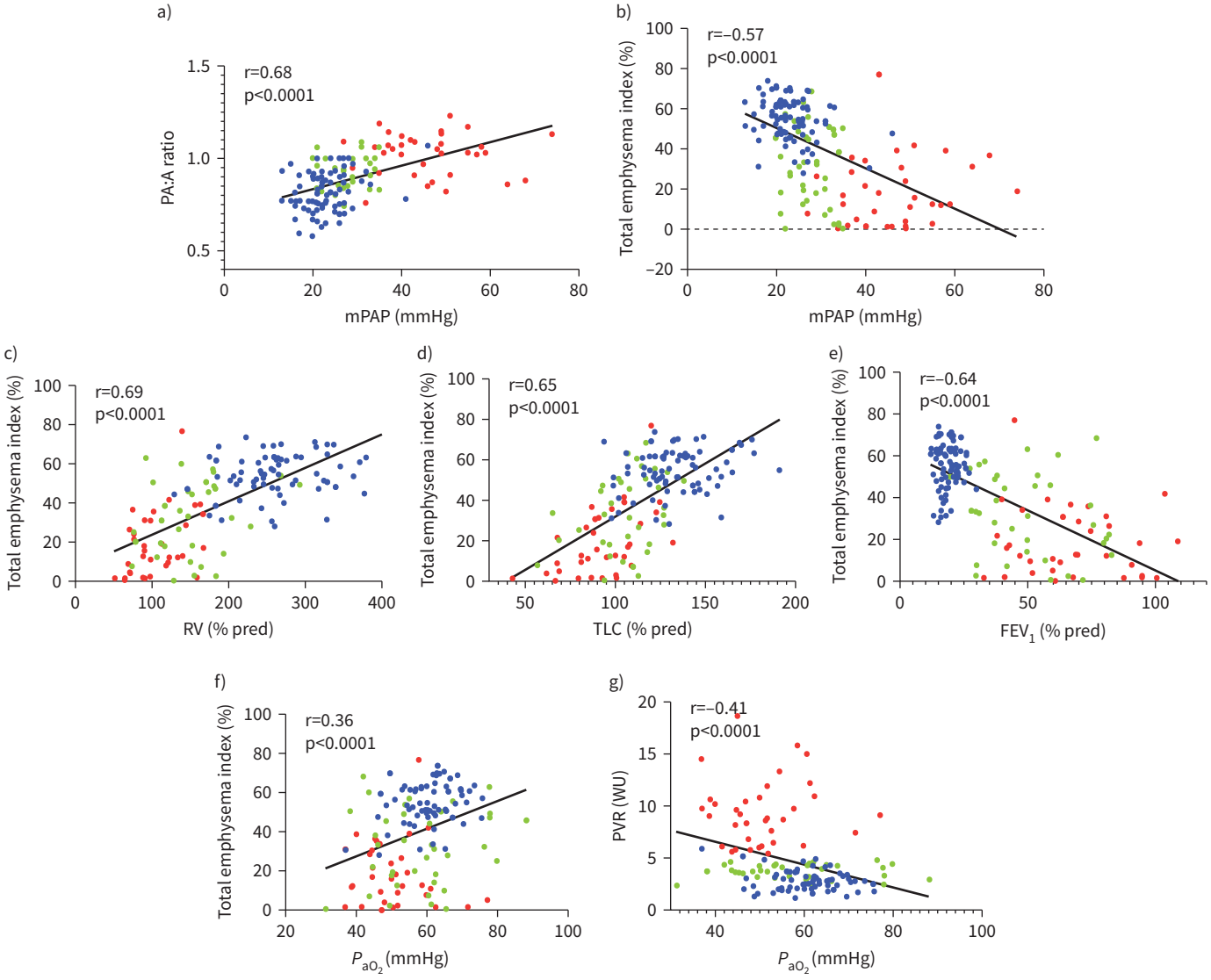

FIGURE 3 Correlation test between a) mean pulmonary artery pressure (mPAP) and ratio of main pulmonary artery diameter to ascending aorta diameter (PA:A), b) mPAP and emphysema, c) residual volume (RV) and emphysema, d) total lung capacity (TLC) and emphysema, e) forced expiratory volume in 1 s (FEV_1) and emphysema, and f) arterial oxygen partial pressure (P_{aO_2}) and emphysema, and g) pulmonary vascular resistance (PVR) and P_{aO_2}. Patients in groups 1, 2 and 3 are represented in blue, green and red, respectively.

the case in phenotype/group 3. As TLC and RV were highly positively correlated with the total emphysema index measured by CT scan analysis, emphysema severity seems to be the main cause explaining the variation in lung volumes in our patients. However, severe PH in group 3 may be associated with reduced lung compliance, which may contribute to lower TLC in this group [28].

Interestingly, CT analysis described different degrees of parenchymal destruction with severe emphysema in group 1 (total emphysema index of 55%), moderate emphysema in group 2 (32%) and relatively mild emphysema in group 3 (16%). This suggests that severe PH-COPD results from a distinct pathological mechanism than alveolar septa loss, supported by our negative correlation between mPAP and the total emphysema index, as previously reported by Zeder *et al.* [26].

Remodelling of small pulmonary vessels has been described as a major cause of severe PH-COPD. Bunel *et al.* [18] analysed explanted lungs from end-stage COPD with characteristics were similar to our group 1 and reported a lower capillary density and some degree of remodelling of the pulmonary arterioles that increased with PH severity. However, their 10 severe PH-COPD patients differed from our group 3 and could

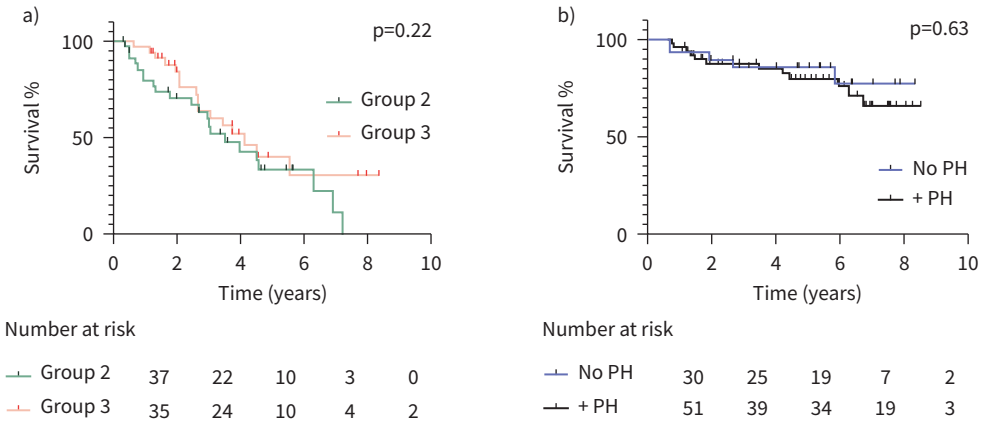

FIGURE 4 Kaplan–Meier overall survival curve between a) groups/phenotypes 2 and 3 and b) post-transplant survival curve in group/phenotype 1. PH: pulmonary hypertension.

be reclassified as moderate PH-COPD (PVR of 4.2 WU) according to the 2022 ESC/ERS guidelines [11]. Recently, Zeder *et al.* [26] showed that, in end-stage COPD, the degree of pulmonary arterial remodelling increases progressively with the severity of PH, but less so than in idiopathic PAH. Unfortunately, lung transplantation is often contraindicated in COPD patients with PVP due to age and comorbidities [29]. Therefore, descriptive histological analyses of their explanted lungs have not been published but would be useful for a better understanding of pulmonary vascular disease.

In addition, we distinguished two phenotypes with mild-to-moderate PH, namely phenotype/group 2 with moderately severe COPD (FEV_1 50%) not considered for lung transplantation and phenotype/group 1 with 60.5% patients having FEV_1 <30%. However, group 2 had more severe haemodynamics and less emphysema than group 1. This suggests different PH mechanisms between them, although it remains moderate, with more parenchymal remodelling in phenotype 1 and more vascular remodelling in phenotype 2. In fact, group/phenotype 2 appears to be an intermediate state between phenotypes/groups 1 and 3, with mixed parenchymal and vascular involvement. Regular monitoring of these patients with respiratory function tests and echocardiography is essential to ensure that they do not progress to one of the more extreme phenotypes (1 or 3).

Understanding pulmonary vascular lesions in PH-COPD is currently the main difficulty. Classically, lung hyperinflation due to emphysema, increased pulmonary vascular stiffness, hypoxia-induced vasoconstriction and the direct effect of chronic tobacco smoking have been described as the main causes of pulmonary vascular lesions in COPD [14, 16, 18, 19, 30]. At the molecular level, the role of hypoxia-inducible factors, in combination with individual susceptibility and environmental factors, has been described to influence the development toward a vascular or nonvascular phenotype in COPD [31].

However, these mechanisms are difficult to capture in clinical practice. Some authors have suggested that D_{LCO} may discriminate patients in terms of pulmonary vascular involvement [14, 32]. This seems to be applicable for patients with mild COPD, as shown in groups 2 and 3 (although low for these two groups). However, in our study, patients with end-stage COPD also had a very low D_{LCO} (33%). D_{LCO}, which reflects the state of the pulmonary alveolocapillary barrier, can be altered by severe capillary destruction/pulmonary vascular rarefaction such as microvascular remodelling. Therefore, D_{LCO} may not be a good parameter to discriminate between vascular and nonvascular phenotypes in severe emphysema.

In any case, given our findings, when severe PH is confirmed in a COPD patient, it is advisable to compare haemodynamic, clinical, lung function and chest CT imaging data [32]. This may provide clues to the mechanism of vascular remodelling, especially when discussing the specific treatment of PAH [11, 32].

One of the strengths of our study was the concomitant analysis of chest CT scans in all patients. As previously described, the PA:A ratio appeared to be proportional to the degree of PH [33–35] and a ratio >1 is consistent with the suggested threshold for noninvasive prediction of severe PH-COPD. Our data confirmed that analysis of the degree of emphysema is important for better classification of patients.

Indeed, end-stage COPD patients, whether or not they had PH, had significantly more advanced destructive emphysema than the other two phenotypes and phenotype/group 3 was more associated with less advanced destructive emphysema and a lower total emphysema index, as described in the ASPIRE registry [4]. In the debate about the most effective ways to distinguish PH-COPD phenotypes, it might be interesting to introduce quantitative thresholds for the degree of emphysema in future diagnostic and management algorithms (figure 5). Quantification of small pulmonary vessels might also be useful [36]. Assessment of pulmonary microvascular blood flow using gadolinium-enhanced magnetic resonance imaging may also become an imaging biomarker for therapeutic interventions targeting the pulmonary microvasculature [37].

Survival

Our results confirm the poor prognosis of PH-COPD, with cumulative survival rates in groups 1 and 2 lower than predicted by the BODE index [38]. KOVACS *et al*. [7] reported that end-stage COPD patients with severe PH had the worst survival. However, as patients in group 1 received lung transplantation, we were unable to compare survival rates between the three groups. Many factors may contribute to the poor survival in severe PH-COPD through endothelial and epithelial dysfunction [14], such as smoking history, older age or cardiovascular comorbidities. In group 3, D_{LCO} tended to be worse and hypoxaemia was significantly more severe. These two parameters are known to correlate with mortality [14, 25, 31] and may reflect the microvascular impairment described in severe PH-COPD [18]. Interestingly, there was no significant difference in survival between groups 2 and 3. However, all patients in group 3 were treated with mono- or dual-specific PH therapy [25], suggesting its potentially beneficial role in terms of survival, as suggested in a previous retrospective cohort [7].

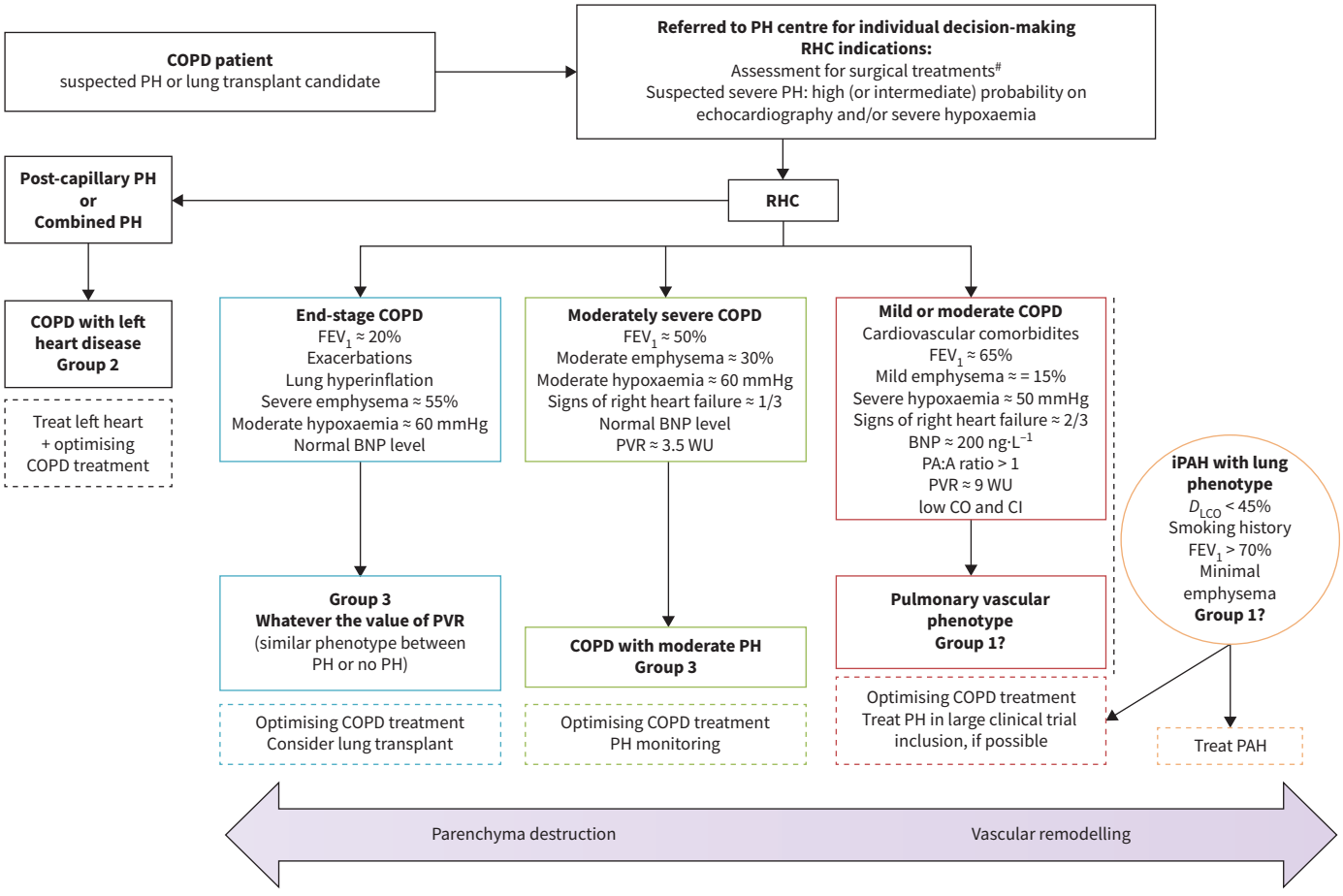

FIGURE 5 Phenotyping of pulmonary hypertension associated with COPD (PH-COPD) based on the three groups/phenotypes of the study. #: Lung transplantation or, in some cases, volume reduction surgery. BNP: brain natriuretic peptide; D_{LCO}: lung diffusing capacity for carbon monoxide; FEV_1: forced expiratory volume in 1 s; iPAH: idiopathic pulmonary arterial hypertension; PA:A: ratio of pulmonary artery diameter to ascending aorta diameter; PAH: pulmonary arterial hypertension; PH: pulmonary hypertension; PVR: pulmonary vascular resistance, RHC: right heart catheterisation; WU: Wood units.

Limitations

This study has several limitations, including its monocentric and observational nature. Recruitment of COPD patients at our expert PH and lung transplantation centre may have induced an inclusion bias, as group 1 patients were selected before the start of the pre-lung transplantation assessment. This may partly explain the younger age and fewer comorbidities in this group. In addition, patients with post-capillary PH, representing an important subgroup of PH patients [39], were excluded to better phenotype pre-capillary PH-COPD. Regarding the survival analysis, it would be interesting to know the causes of death in group 2, which were mostly unknown because they were not followed-up after RHC in our centre. Finally, as certain PAH mutations have been associated with radiological abnormalities and impaired functional tests (*KDR*, *SOX 17* or *TBX4*), it would have been interesting to have genetic data on our patients, especially those with severe PH.

Conclusions

In conclusion, our results support the complexity of PH-COPD, with phenotypes ranging from PH associated with end-stage disease (phenotype 1), characterised by predominant parenchymal remodelling with severe emphysema, to PVP (phenotype 3), mainly due to pulmonary vascular remodelling. Phenotype 2 appears to be an intermediate state combining the two compartments. At present, it remains difficult to distinguish patients with PVP from those with idiopathic PAH with a respiratory phenotype, who may be one and the same group, especially in the presence of airflow obstruction. In the current debate on how to distinguish PH-COPD phenotypes, it might be worthwhile to include quantitative emphysema thresholds in future diagnostic and management algorithms. Further studies are needed to validate these findings and assess their implications for management strategies [40].

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