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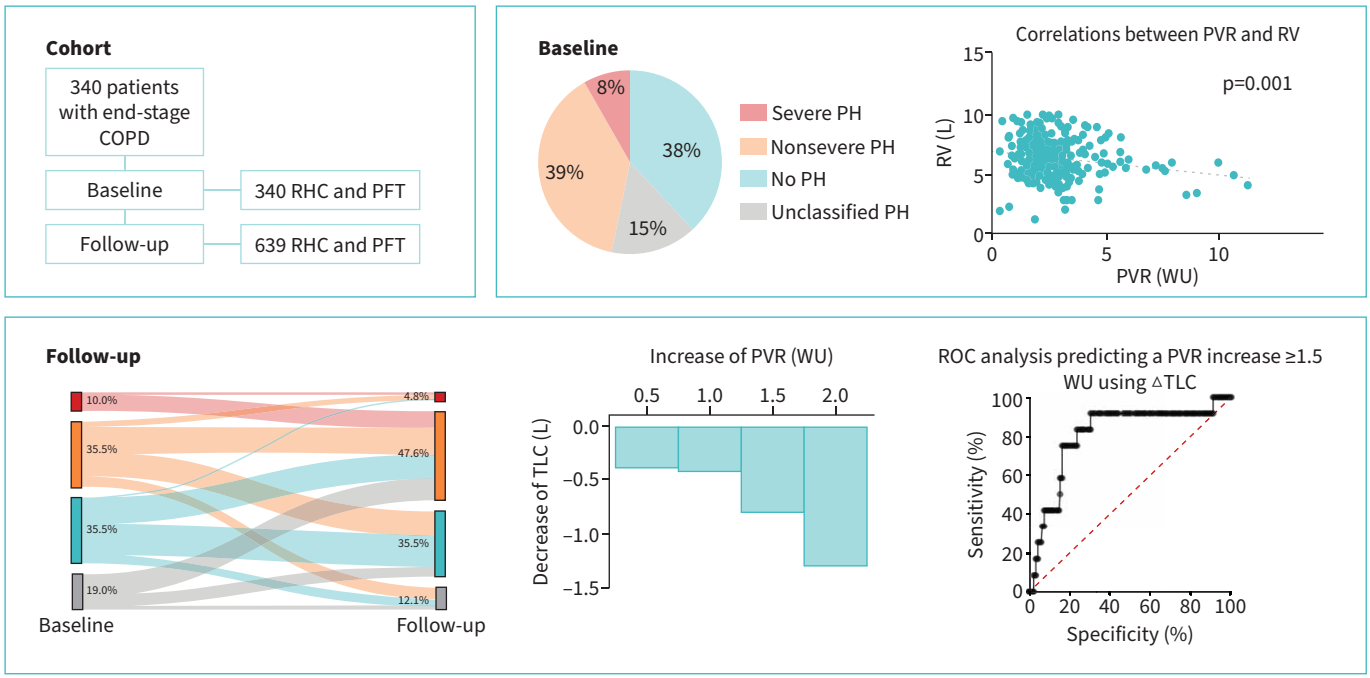

Conclusion: The 2022 ESC/ERS guidelines facilitate a refined classification of patients with COPD-PH. Unbiased longitudinal invasive follow-up and assessment of lung volumes by plethysmography provided evidence of an association of PVR and lung volume.

GRAPHICAL ABSTRACT Summary of the main study findings. AUC: area under the curve; ESC: European Society of Cardiology; ERS: European Respiratory Society; PFT: pulmonary function test; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; RHC: right heart catheterisation; ROC: receiver operating characteristic; RV: residual volume; TLC: total lung capacity; WU: Wood unit.

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Classification and course of pulmonary hypertension associated with end-stage COPD

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In patients with end-stage COPD, unbiased longitudinal invasive haemodynamic assessment and plethysmography revealed an association between lung volume and pulmonary vascular resistance
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Abstract

Background Pulmonary hypertension (PH) associated with COPD contributes to morbidity and mortality. Further characterisation to improve management is warranted. The aim of the study was to apply the recently proposed PH classification and to assess the association of lung volume involvement and PH over the course of disease in patients with advanced COPD.

Methods Patients with COPD undergoing transplant evaluation, including right heart catheterisation were included irrespective of the likelihood of having PH. Spirometry, plethysmography and computed tomography were used to assess the degree of parenchymal and vascular involvement. Follow-up investigation was performed for 18±12 months. The 2022 European Society of Cardiology/European Respiratory Society guidelines were used for classification of PH.

Results In total, 340 patients were included and 639 right heart catheters were assessed. The majority of patients were classified as no PH (n=131, 38%) or nonsevere PH (n=133, 39%), whereas severe COPD-PH was present in 26 patients (8%). Patients with severe COPD-PH had similar degrees of airflow obstruction but lower lung volumes. Further, pulmonary vascular resistance (PVR) correlated negatively with residual volume. Interstitial lung abnormalities were present in 11 patients (3%) and scattered across all PH groups. Follow-up (n=141, 41.5%) demonstrated a low rate of deterioration to severe COPD-PH (4%). However, an increase of PVR was common and was associated with a decrease of total lung capacity.

Conclusion Unbiased longitudinal invasive follow-up and assessment of lung volumes by plethysmography provided evidence of an association of lung volume and PVR.

Introduction

Pulmonary hypertension (PH) associated with lung disease is common and contributes to increased mortality [1, 2]. COPD is the most frequent chronic lung disease but rarely associated with severe PH. The exact pathogenesis of PH associated with COPD (COPD-PH) remains unknown. An association with the degree of parenchymal involvement seems obvious, but reports of a distinct pulmonary vascular phenotype, which is characterised by less severe airflow limitation but more advanced gas exchange impairment [2–4], suggest a more complex association.

Furthermore, recently it has been demonstrated that patients classified as idiopathic pulmonary arterial hypertension (IPAH) with a smoking-related lung phenotype have a similar course as patients with PH

associated with lung disease [5, 6]. Whereas causes of death might differ, common mechanisms likely contribute to overlaps between the groups. Smoking as a commonality has been suggested to induce a loss of the alveolocapillary unit, resulting in vanishing of pulmonary capillaries [7, 8].

However, the contribution of parenchymal involvement in COPD-PH remains unknown. Whereas the impact of parenchymal abnormalities on IPAH with a lung phenotype seems to be minor, the degree of parenchymal destruction as disease defining component seems to be conclusive in group 3 PH. Furthermore, it remains unknown whether parenchymal abnormalities precede pulmonary vascular involvement or *vice versa*. Understanding the interactions between lung volumes and pulmonary vascular involvement could have implications for the management of PH and may support more personalised treatment strategies by balancing pulmonary vasodilation and ventilation.

End-stage COPD is characterised by severe airway disease and emphysematous destruction of the lung. Studying the association of parenchymal and vascular changes over time might add to pathophysiological understanding of underlying pathomechanism in COPD-PH. Furthermore, application of the recently proposed classification of PH might add to further characterise this entity.

Materials and methods

Study design

This was a retrospective, single-centre study at the Department of Medicine V, University of Munich approved by the local medical ethics committee (#18-064).

Study population

We reviewed all patients with the diagnosis of severe COPD who underwent at least one right heart catheterisation (RHC) from August 2010 until June 2022. In all cases, the diagnosis of COPD was in line with the guidelines of Global Initiative for Chronic Obstructive Lung Disease [9]. Comorbidities and surgical or endoscopic lung volume reduction were assessed in the context of transplant evaluation. All patients were adult and none of them received a previous specific pulmonary arterial hypertension (PAH) therapy at baseline or had a pulmonary arterial wedge pressure (PAWP) >15mmHg. Patients with combined pulmonary fibrosis and emphysema (CPFE) were excluded. CPFE was defined according to the research definition of CPFE proposed by the American Thoracic Society/European Respiratory Society (ERS)/Japanese Respiratory Society/Latin American Thoracic Association research statement [10].

Procedures

Baseline and follow-up RHC were performed to assess transplant urgency and perioperative risk assessment. RHCs were performed without bias, irrespective of noninvasive signs of PH. The procedure was performed by using a Swan–Ganz catheter. Cardiac output (CO) was detected by thermodilution.

We defined PH according to the 2022 European Society of Cardiology (ESC)/ERS guidelines [11] for the diagnosis and treatment of PH as follows:

1) No PH (mean pulmonary arterial pressure (mPAP) $\leqslant$20 mmHg)
2) Unclassified PH (mPAP >20 mmHg and pulmonary vascular resistance (PVR) $\leqslant$2 Wood units (WU))
3) Nonsevere PH (mPAP >20 mmHg and PVR >2 WU and $\leqslant$5 WU)
4) Severe PH (mPAP >20 mmHg and PVR >5 WU)

Data of pulmonary function tests were collected contemporaneously to each RHC and included spirometry and body plethysmography such as 6-min walk distance (6MWD) and capillary blood gas analysis. N-terminal pro brain natriuretic peptide (NT-proBNP) was measured by laboratory tests. All medical examinations were performed as required by applicable guidelines. Follow-up data were collected 18±12 months afterwards.

Imaging

In the pre-transplantation setting, computer tomography (CT) of the lung was performed routinely and was analysed in terms of interstitial lung abnormalities (ILAs) by a thoracic radiologist according to the current recommendations [12]. The most common CT scans available were high-resolution CT, CT pulmonary angiography and contrast-enhanced CT.

Statistical analysis

Parameters are given as mean±SD or as a median with the first and third quartile. To identify differences in continuous variables, a t-test was used for two unpaired, parametric variables and ANOVA was used for

more than two unpaired, parametric variables. The Mann–Whitney-U test was used for two unpaired, nonparametric variables, while the Kruskal–Wallis test was used for more than two unpaired, nonparametric variables. To perform *post hoc* tests, we used Tukey (parametric) and Dunn's (nonparametric) multiple comparison test. The Chi square test and Fisher's exact test compared categorical variables, with Fisher's exact test applied for small sample size. Correlation between data was examined using Pearson's correlation coefficient and two-tailed p-values. We performed multiple logistic regression analysis and reported results as odds ratios with p-values. A receiver-operating characteristic (ROC) plot was used to evaluate the performance of a binary classification system by plotting the trade-offs between sensitivity and specificity with area under the curve (AUC) indicating the model's overall ability to distinguish between classes. p-values less than 0.05 were considered to indicate statistical significance. All statistical analyses were performed with Graph Pad Prism version 8.3.0.

Results

Baseline characteristics

In total, 340 patients with severe COPD were included in the study. Thereof, 168 (49%) were male and median age was 58 (54–62). In 141 patients (42%), at least one follow-up RHC was performed and 639 RHCs were assessed in total. Baseline characteristics are shown in table 1. Patients with post-capillary PH (n=22) were excluded from the study.

Classification and characteristics

Patients were classified according to the recent proposed ESC/ERS guidelines. As shown in table 2, the majority of patients were classified as having no PH (n=131, 38%) and nonsevere PH (n=133, 39%), respectively. Severe PH was present in 26 patients (8%). Finally, 50 patients (15%) with elevated mPAP did not fulfil the criteria of pre- or post-capillary PH and were defined as unclassified PH.

Haemodynamic parameters differed according to the applied classification, as shown in table 2. Lower PVR in patients with unclassified PH was associated with both a higher PAWP and CO, respectively. Whereas comorbidities did not differ in patients with unclassified PH, body mass index was statistically significant higher compared to no PH or nonsevere PH (p=0.002 and 0.0013, respectively). Atrial fibrillation was more common in severe PH while arterial hypertension occurred less. Furthermore, NT-proBNP and peripheral oxygen saturation at the end of 6MWD were significantly different in severe PH. In patients with severe PH, residual volume (RV) and total lung capacity (TLC) were lower, while forced expired volume in 1 s and forced vital capacity did not differ compared to other groups.

There was a significant correlation of NT-proBNP (r=0.286, p<0.001) and RV (r=−0.181, p=0.001) with PVR at baseline, whereas other parameters did not correlate (figure 1).

Course of PH

Median follow-up RHC was 402 days after initial assessment. In total, 141 patients (42%) had RHC performed within 18±12 months. Of patients without PH, the majority (n=24, 48%) remained unchanged and 19 patients (38%) developed nonsevere PH. In patients with unclassified PH, the majority developed nonsevere PH (n=16, 59%) whereas eight patients (30%) where re-classified as non-PH. In patients with nonsevere PH, a mixed change in classification was observed, as shown in figure 2. Only four patients (8%) developed severe PH. In patients with severe PH, a PAH-specific therapy was initiated in six patients (43%), thereof five patients (83%) were re-classified as nonsevere PH at follow-up. Of patients with severe PH without initiation of PAH-specific therapy, the majority remained unchanged.

Association of haemodynamics with parenchymal disease

Next, patients were grouped according to the degree of increase in PVR to the follow-up RHC, as shown in table 3. An increase of PVR of at least 0.5, 1.0, 1.5 and 2.0 WU to follow-up was observed in 91 (35%), 48 (19%), 22 (9%) and 10 (4%) patients, respectively. Dependent on the defined threshold, an increase of PVR was associated with a decrease in 6MWD and an increase of NT-proBNP to a different degree without reaching statistical significance consistently. However, irrespective of the degree of PVR change, an increase of PVR was consistently associated with a decrease of TLC, as shown in table 3. An increase of PVR of at least 0.5, 1.0, 1.5 and 2.0 WU was associated with decrease of TLC of −0.36±1.58, −0.40±1.35, −0.79±1.41 and −1.29±1.40 L, respectively.

Furthermore, in linear regression analysis an increase of PVR⩾1.5 WU was independently associated with a decrease of TLC (OR 0.4795, 95% CI 0.2100–0.9764; p=0.0584) while controlling for other follow-up parameters. In ROC analysis, the AUC for predicting an increase of PVR ⩾1.5 WU *versus* an increase of PVR<1.5 WU was 0.81 (95% CI 0.6697–0.9403), see figure 3.

TABLE 1 Baseline characteristics of the total study cohort

Characteristic	n[#]
Patients, n	340
Male, n (%)	168 (49)
Age (years)	58 (54–62)
BMI (kg·m^{-2})	22 (19–25)
AAT1-deficiency, n (%)	50 (15)
Nicotine use	
Current smoker, n (%)	15 (4)
Former smoker, n (%)	316 (93)
Nonsmoker, n (%)	9 (3)
Previous nicotine use (pack-years)	35 (35–40)
PFT, n=298–333	
FVC (L)	1.8 (1.4–2.3)
FVC (%)	49 (39–59)
TLC (L)	8.1 (6.9–9.3)
TLC (%)	137 (122–153)
RV (L)	6.0 (5.0–7.3)
RV (%)	291 (247–345)
FEV_1 (L)	0.61 (0.49–0.77)
FEV_1 (%)	22 (18–26)
Tiffenau index (%)	36 (31–41)
RHC, n=284–340	
mPAP (mmHg)	22 (19–26)
mRAP (mmHg)	6 (4–8)
PCWP (mmHg)	9 (7–12)
PVR (WU)	2.4 (1.8–3.2)
CO (L·min^{-1})	5.4 (4.7–6.1)
CI (L·min^{-1}·m^{-2})	3.1 (2.6–3.4)
S_{vO_2} (%)	71 (67–75)
6MWD (m), n=237	245 (175–310)
S_{pO_2} after 6MWD (%)	90 (86–94)
NT-proBNP (pg·mL^{-1}), n=297	73 (41–137)
P_{O_2} (mmHg)[¶], n=309	63 (55–71)
P_{O_2} (mmHg)[+], n=142	56 (48–62)
P_{CO_2} (mmHg), n=309	43 (39–49)
Comorbidities, n (%)	
Arterial hypertension	152 (45)
Atrial fibrillation	17 (5)
Coronary heart disease	66 (19)
Diabetes mellitus	26 (8)
Thromboembolic events	14 (4)
Lung volume reduction, n (%)	105 (31)

[#]: Parameters are given as median with first and third quartile. [¶]: All. [+]: No oxygen supply. 6MWD: 6-min walk distance; AAT1: alpha-1 antitrypsin; BMI: body mass index; CI: cardiac index; CO: cardiac output; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; mPAP: mean pulmonary artery pressure; mRAP: mean right atrial pressure; NT-proBNP: N-terminal pro-brain natriuretic peptide; P_{CO_2}: partial pressure of carbon dioxide; PCWP: pulmonary capillary wedge pressure; PFT: pulmonary function test; P_{O_2}: partial pressure of oxygen; PVR: pulmonary vascular resistance; RHC: right heart catheterisation; RV: residual volume; S_{pO_2}: peripheral oxygen saturation; S_{vO_2}: mixed venous oxygen saturation; TLC: total lung capacity; WU: Wood unit.

Imaging

CT scans of 338 patients (99%) were available in different modes of acquisitions. The main parenchymal abnormality advanced destructive emphysema with hyperexpansion of secondary pulmonary lobules with distortion of pulmonary architecture and airway disease. ILAs were present in 11 patients (3%), distributed as follows: one patient in the no PH group, two patients in the unclassified PH group, seven patients in the nonsevere PH group and one patient in the severe PH group.

Discussion

Applying the 2022 ESC/ERS guidelines for the diagnosis of PH demonstrated that the majority of patients with end-stage COPD were classified as having no PH or nonsevere PH. Unclassified PH and severe PH

TABLE 2 Baseline characteristics of patients according to the respective pulmonary hypertension (PH) group

Characteristic	No PH	Unclassified PH	Nonsevere PH	Severe PH	p-value
Patients, n (%)	131 (38)	50 (15)	133 (39)	26 (8)	
Male, n (%)	68 (52)	29 (58)	59 (44)	12 (46)	0.3519
Age (years)	58 (53–62)	56 (54–60)	57 (54–62)	60 (56–62)	0.2025
BMI (kg·m^{-2})	21 (19–24)	24 (22–27)	21 (19–25)	23 (19–24)	**0.0005**
Comorbidities, n (%)					
Arterial hypertension	66 (50)	20 (40)	60 (45)	6 (23)	**0.0006**
Atrial fibrillation	9 (7)	1 (2)	4 (3)	3 (12)	**0.0188**
Coronary heart disease	36 (27)	7 (14)	18 (14)	5 (19)	0.0577
Diabetes mellitus	10 (8)	5 (10)	9 (7)	2 (8)	0.8901
Thromboembolic events	7 (5)	0 (0)	6 (5)	1 (4)	0.8901
Lung volume reduction, n (%)	43 (33)	12 (24)	41 (31)	9 (35)	0.3577
AAT1-deficiency, n (%)	21 (16)	11 (22)	16 (12)	2 (8)	0.2526
Nicotine use					
Current smoker, n (%)	6 (4)	1 (2)	7 (5)	1 (3)	0.8903
Former smoker, n (%)	123 (94)	46 (92)	123 (93)	24 (93)	0.9043
Nonsmoker, n (%)	2 (2)	3 (6)	3 (2)	1 (4)	0.4149
Previous nicotine use (pack-years)	40 (30–40)	35 (25–40)	35 (25–45)	30 (20–42)	0.7941
PFT					
VC (L)	1.8 (1.5–2.3)	1.8 (1.4–2.3)	1.7 (1.2–2.2)	1.9 (1.1–2.4)	0.4593
VC (%)	51 (42–59)	47 (39–63)	48 (36–59)	47 (39–62)	0.5636
TLC (L)	7.9 (6.7–9.2)	8.9 (7.5–10.1)	8.1 (6.9–9.2)	7.1 (6.9–8.2)	**0.0144**
TLC (%)	135 (123–153)	148 (123–159)	136 (122–153)	125 (110–136)	**0.0231**
RV (L)	6.0 (4.8–7.2)	6.8 (5.2–8.0)	6.1 (5.1–7.2)	5.4 (4.9–5.9)	**0.0155**
RV (%)	292 (246–343)	321 (256–376)	288 (253–353)	264 (222–295)	**0.0151**
FEV_1 (L)	0.62 (0.51–0.80)	0.63 (0.49–0.76)	0.59 (0.47–0.72)	0.67 (0.47–0.98)	0.2277
FEV_1 (%)	22 (18–27)	22 (18–24)	21 (17–26)	23 (20–30)	0.0580
Tiffenau index	36 (30–41)	35 (30–40)	35 (31–41)	40 (35–44)	0.0579
RHC					
mPAP (mmHg)	18 (17–19)	23 (22–25)	25 (23–28)	33 (31–48)	**<0.0001**
mRAP (mmHg)	5 (3–7)	7 (5–10)	7 (4–9)	5 (4–8)	**<0.0001**
PCWP (mmHg)	8 (6–10)	12 (11–14)	10 (8–12)	10 (8–13)	**<0.0001**
PVR (WU)	1.9 (1.6–2.5)	1.7 (1.3–1.9)	2.9 (2.5–3.5)	6.8 (5.6–8.5)	**<0.0001**
CO (L·min^{-1})	5.2 (4.5–5.9)	6.4 (5.7–7.2)	5.4 (4.8–5.9)	4.7 (3.5–5.2)	**<0.0001**
CI (L·min·m^{-2})	3.0 (2.6–3.4)	3.4 (3.0 4.1)	3.1(2.7–3.4)	2.5 (2.1–3.0)	**<0.0001**
S_{vO_2} (%)	71(67–75)	71 (68–77)	72 (69–75)	63 (61–69)	**0.0002**
6MWD (m)	245 (175–310)	260 (150–320)	240 (165–300)	265 (210–315)	0.8244
S_{pO_2} after 6MWD (%)	92 (89–95)	92 (90–94)	89 (85–94)	87 (82–88)	**0.0007**
NT-proBNP (pg·mL^{-1})	65 (35–104)	77 (40–116)	76 (42–163)	145 (66–799)	**0.0017**
Oxygen supply, n (%)	71 (54)	33 (66)	81 (61)	13 (50)	0.3570
P_{O_2} (mmHg)[#]	63 (56–68)	63 (57–73)	65 (54–75)	59 (53–65)	0.1804
P_{O_2} (mmHg)[¶]	57 (48–63)	56 (48–62)	54 (48–60)	54 (39–59)	0.4103
P_{CO_2} (mmHg)	41 (38–46)	45 (42–50)	45 (41–51)	44 (34–53)	**0.0006**
CT scans					
ILA, n (%)	1 (0)	2 (4)	7 (5)	1 (4)	0.2188

[#]: All. [¶]: No oxygen supply. Parameters are given as median with first and third quartile. p-value based on the Kruskal–Wallis test and Chi square calculations. 6MWD: 6-min walk distance; AAT1: alpha-1 antitrypsin; BMI: body mass index; CI: cardiac index; CO: cardiac output; CT: computed tomography; FEV_1: forced expiratory volume in 1 s; ILA: interstitial lung abnormality; mPAP: mean pulmonary artery pressure; mRAP: mean right atrial pressure; NT-proBNP: N-terminal pro-brain natriuretic peptide; P_{CO_2}: partial pressure of carbon dioxide; PCWP: pulmonary capillary wedge pressure; PFT: pulmonary function test; P_{O_2}: partial pressure of oxygen; PVR: pulmonary vascular resistance; RHC: right heart catheterisation; RV: residual volume; S_{pO_2}: peripheral oxygen saturation; S_{vO_2}: mixed venous oxygen saturation; TLC: total lung capacity; VC: vital capacity. Bold font indicates statistical significance.

were less common. Follow-up assessment demonstrated a mixed course with mainly mild changes and re-classifications. Approximately half of patients with no PH or unclassified PH were classified as nonsevere PH, while approximately one-third of patients with nonsevere PH were classified as non-PH at follow up. *De novo* development of severe PH was a rare event. Severe PH was associated with lower lung volumes while having a similar degree of airflow limitation. Furthermore, an increase of PVR over time was associated with a decrease in TLC. A summary of our findings is shown in the graphical abstract.

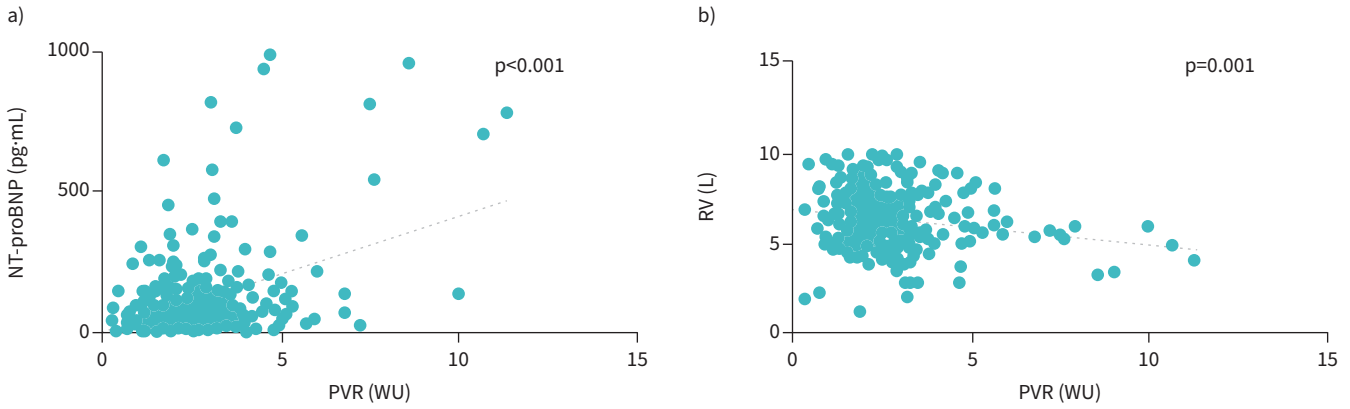

FIGURE 1 Correlation at baseline between pulmonary vascular resistance (PVR) and a) N-terminal pro-brain natriuretic peptide (NT-proBNP) and b) right ventricle (RV).

In our cohort, the prevalence of nonsevere PH and severe PH were 39% and 8%, respectively. Keeping different cut-offs in mind, this is in line with previous reports confirming that COPD-PH is common but only in a minority severe [13]. Patients with elevated mPAP (>20 mmHg) but low PVR (⩽2 WU) and low PAWP (⩽15 mmHg) were defined as unclassified PH and affected 15% of the entire cohort. These patients are frequently characterised by elevated pulmonary blood flow [11].

In an unbiased approach, we followed invasively patients irrespective of the likelihood of having PH to provide an up-to-date risk assessment on the transplant waiting list. Our study provides data that changes of PH classification, potentially resulting in a treatment attempt is rare. Severe PH developed only in a minority of patients (4%). Approximately 60% of patients with unclassified PH developed nonsevere PH upon follow-up, supporting that follow-up of these patients is recommended [11].

Since the transition of nonsevere PH to severe PH was a rare event, patients were additionally classified according to the degree of PVR increase. Whereas an increase of PVR <1.5 WU was frequently observed, an increase of ⩾1.5 WU was less common.

It has been suggested that developing severe COPD-PH is largely independent of spirometry and more commonly associated with preserved spirometry but usually accompanied by hypoxaemia and a significant reduction in diffusing capacity of the lung for carbon monoxide (D_{LCO}) [3, 11]. Therefore, the pulmonary vascular phenotype of COPD has been proposed [2, 14]. Similarly, Hoeper *et al.* [5] described a phenotype of patients diagnosed with IPAH and a lung phenotype, with significant similarities to the

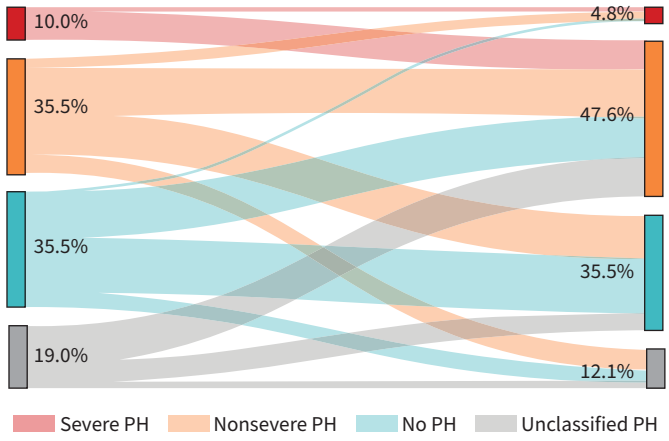

FIGURE 2 Sankey plot of the classification of pulmonary hypertension (PH) at baseline (left) and follow-up (right).

TABLE 3 Changes in clinical and functional parameters according to the degree of increase in pulmonary vascular resistance (ΔPVR)

Parameter	ΔPVR ⩾0.5 WU, n=91	ΔPVR <0.5 WU, n=168	p-value
Δ 6MWD (m)	−45 (−95–−3)	−15 (−50–25)	**0.0015**
Δ NT-proBNP (pg·mL^{-1})	6 (−15–37)	0 (−28–20)	0.0789
Δ VC (L)	−0.09 (−0.26–0.12)	−0.12 (−0.38–0.19)	0.7532
Δ TLC (L)	−0.45 (−1.20–0.67)	0.18 (−0.47–0.79)	**0.0038**
Δ RV (L)	0.13 (−0.76–1.26)	0.23 (−0.50–1.02)	0.7393
Δ FEV_1 (L)	−0.02 (−0.08–0.04)	−0.02 (−0.09–0.04)	0.4814
	ΔPVR ⩾1.0 WU, n=48	**ΔPVR <1.0 WU, n=211**	**p-value**
Δ 6MWD (m)	−43 (−99–15)	−25 (−55–15)	0.1365
Δ NT-proBNP (pg·mL^{-1})	6 (−12–47)	0 (−25–24)	0.2365
Δ VC (L)	−0.04 (−0.25–0.17)	−0.12 (−0.38–0.17)	0.3536
Δ TLC (L)	−0.74 (−1.40–0.90)	0.10 (−0.58–0.75)	**0.0149**
Δ RV (L)	−0.16 (−0.92–1.20)	0.20 (−0.45–1.03)	0.3449
Δ FEV_1 (L)	−0.03 (−0.08–0.05)	−0.02 (−0.09–0.04)	0.5542
	ΔPVR ⩾1.5 WU, n=22	**ΔPVR<1.5 WU, n=237**	**p-value**
Δ 6MWD (m)	−58 (−99–23)	−25 (−60–15)	0.2624
Δ NT-proBNP (pg·mL^{-1})	1350 (−16–32)	1 (−24–26)	0.8817
Δ VC (L)	0.09 (−0.13–0.36)	−0.12 (−0.38–0.12)	**0.0153**
Δ TLC (L)	−1.06 (−1.89–0.23)	0.10 (−0.65–0.79)	**0.0063**
Δ RV (L)	−0.68 (−1.31–1.37)	0.21 (−0.52–1.02)	0.2623
Δ FEV_1 (L)	0.01 (−0.07–0.08)	−0.02 (−0.09–0.03)	0.0993
	ΔPVR ⩾2.0 WU, n=10	**ΔPVR <2.0 WU, n=249**	**p-value**
Δ 6MWD (m)	−70 (−113–−15)	−25 (−60–19)	0.0972
Δ NT-proBNP (pg·mL^{-1})	−7 (−93–89)	1 (−23–26)	0.6337
Δ VC (L)	−0.02 (−0.1–0.46)	−0.12 (−0.36–0.16)	0.0791
Δ TLC (L)	−1.59 (−2.36–−0.73)	0.09 (−0.71–0.80)	**0.0035**
Δ RV (L)	−0.82 (−1.79–1.64)	0.20 (−0.62–1.03)	0.2794
Δ FEV_1 (L)	0.01 (−0.07–0.18)	−0.02 (−0.09–0.04)	0.2070

Parametric parameters are given as a median with first and third quartile. p-value based on the Mann–Whitney U-test. 6MWD: 6-min walk distance; FEV_1: forced expiratory volume in 1 s; NT-proBNP: N-terminal pro-brain natriuretic peptide; RV: residual volume; TLC: total lung capacity; VC: vital capacity. Bold font indicates statistical significance.

patients of group 3 PH, *i.e.* more advanced lung disease. In contrast to interstitial lung disease (ILD), where an increase in mPAP has been associated with parenchymal involvement [15, 16], this association in patients with COPD remains unclear. In our analysis, only patients with end-stage COPD were included; therefore, a selection bias is present. However, in contrast to the reports that severe COPD-PH is associated with less airflow obstruction, in our analysis the degree of airflow obstruction was similarly reduced between the groups, suggesting a phenotype of severe COPD with severe PH (8%).

Despite similar airflow limitation, there was less RV and TLC, respectively, in patients with severe COPD-PH and RV was negatively correlated with PVR. This may indicate that patients with severe COPD-PH have less emphysema and air trapping and that there is an inverse association of emphysema and COPD-PH in general. Along these lines, Zeder *et al.* [17] demonstrated using explant tissue that patients with end-stage COPD and severe PH have less emphysema compared to those with COPD with no or mild PH.

An increase of PVR over time was associated with a decrease of TLC, an observation that may have different causes. First, an additional affection of the interstitium may cause an increase of PVR. Along these lines, a restrictive physiology from ILD accompanying emphysema is known in patients with CPFE. Patients with CPFE are prone to develop PH [18], indicating a contribution of ILD to PH development. Patients with CPFE have been excluded in our analysis and affected individuals are characterised by normal or mildly abnormal lung volumes and the absence of airflow obstruction. In contrast, our patients with COPD-PH were characterised by severe airflow limitation and lung hyperinflation in severe PH. Consequently, the slight reduction in TLC may not clearly reflect parenchymal changes leading to PH; rather, it could also result from

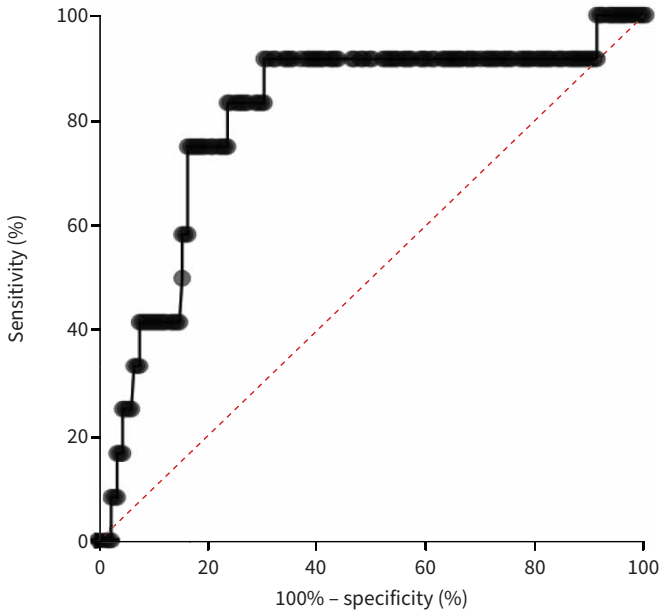

FIGURE 3 Receiver operating characteristic analysis predicting a pulmonary vascular resistance increase ⩾1.5 Wood units using change in total lung capacity.

other factors, such as increased cardiac dimensions compressing the lungs or elevated blood volume due to congestive heart failure, as evidenced by significantly higher NT-proBNP levels. Nevertheless, coexisting pathologies may exist contributing to PH in patients with COPD. Evaluation of D_{LCO} values could offer further insight into a potential interstitial component; however, obtaining these values was precluded by the severity of the underlying COPD. Furthermore, the term ILA has been proposed to describe incidental abnormalities affecting the lung parenchyma of at least 5% of a lung zone without qualifying for an ILD [12]. ILAs have been reported in patients with COPD and were associated with an unfavourable course [19, 20]. ILAs were associated with reduced TLC in patients with COPD, possibly as a result of both a restrictive lung deficit and an additional reduction in the physiological burden of emphysema [20]. In addition, parenchymal abnormalities have been described in patients with COPD-PH [2, 6]; however, no difference was found between patients with mild to moderated compared to severe COPD-PH [2]. SEEGER *et al.* [21] defined severe PH in lung disease as an mPAP ⩾35 mmHg or ⩾25 mmHg in combination with a cardiac index of <2 $L \cdot min^{-1} \cdot m^{-2}$, and suggested that the extent of parenchymal abnormalities observed in CT scans could serve as a distinguishing criterion between group 1 and group 3 PH, with implications for therapeutic decision. Assessment of ILAs in end-stage COPD is difficult due to the severe emphysematous destruction. In our analysis, ILAs were infrequent and showed no preference for specific groups or PVR ranges. However, it is important to note that ILAs were present in only 3%, with isolated occurrences across various groups. This low prevalence significantly restricts the ability to draw meaningful conclusions. Furthermore, the different CT scan modalities used may limit the diagnosis of ILAs.

Second, since patients with PAH do not show a significant restrictive ventilator pattern, the association of PVR and TLC may be specific for patients with COPD. PVR is the combination of the vascular resistances of alveolar vessels (arterioles, capillaries and venules) and extra-alveolar vessels (pulmonary arteries and veins) [22]. Hyperinflation has partially opposing effects on alveolar and extra-alveolar vessels and leads to the loss of alveolar vessels by pruning, which results in a proportional shift towards larger vessels [23]. These are the hallmarks of severe COPD associated with PH. Whether a specific characteristic or a combination thereof causes the association of lung volumes and PVR remains unknown.

However, various other factors may influence lung volumes in patients with COPD-PH, with differences in body weight potentially accounting for minor variations in lung volume measurements. Additionally, respiratory muscle weakness, stemming from low CO in COPD patients with severe PH, affects both inspiratory and expiratory reserve volumes.

The vascular phenotype of COPD is characterised by severe PH occurring in the presence of mild to moderate airway obstruction (*e.g.*, Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages

1–2) [24]. However, in our study, we also identified cases of severe PH in patients with advanced COPD and pronounced airway obstruction (GOLD stages 3–4). This observation suggests that severe PH can develop across all degrees of airflow limitation, supporting the hypothesis that it may represent a primarily vascular-driven process. A positive correlation between vascular endothelial growth factor A (VEGF-A) levels and the tricuspid annular plane systolic excursion/systolic pulmonary artery pressure ratio, a marker of right ventricular function, highlights a role of VEGF-A in vascular remodelling and introduces VEGF-A as a potential biomarker for vascular involvement in COPD-PH [25]. Furthermore, patients with severe COPD-PH exhibit significant microvascular remodelling and reduced capillary density, distinct from the histological features observed in moderate COPD-PH [7]. Our study also indicates that additional factors may influence PH progression. Specifically, an increase in PVR over time was correlated with a decline in TLC. Whether these processes are driven by parenchymal changes, mechanical phenomena or extrapulmonary comorbidities remains an ongoing area of investigation.

These considerations lead to an important question: does low TLC contribute to severe PH due to parenchymal stiffness resulting from alveolocapillary changes or is it a consequence of potential confounders such as respiratory muscle weakness, low CO, congestive heart failure and impaired left ventricular diastolic function? To further investigate these complexities, additional assessments of both inspiratory and expiratory muscle strength may prove valuable. Longitudinal CT evaluations measuring parenchymal density could assess emphysema severity, impacting lung volumes and confirming reductions in lung volumes. Analysing cardiac silhouette size may also provide insights, as right ventricular distension and remodelling may further contribute to decreased lung volumes. In the context of PAH, a vascular-driven disease, advanced imaging techniques have been integral to ongoing research efforts focused on understanding PH and evaluating right ventricular function and the pulmonary vasculature [26, 27]. Insights gained from these studies in PAH may, in turn, inform future research into group 3 PH, helping to elucidate the interrelationships between pulmonary pathology, right heart function and lung volumes in these patients.

The study aimed to refine the classification of COPD-PH and explore the link between parenchymal and vascular changes. Identifying features predictive of PH development could enhance risk stratification by enabling earlier detection of high-risk individuals. Additionally, the findings could influence treatment strategies to balance pulmonary vasodilation and ventilation, often conflicting in COPD patients with PH. This could guide the use of therapies targeting PVR or improve lung mechanics. Ultimately, this approach could foster more personalised treatments, such as tailored combination therapies addressing both vascular and pulmonary aspects of the disease.

The results should be interpreted within their obvious limitations, which significantly impact the generalisability of the findings. This was a retrospective single-centre study of a highly selected patient population. Only patients with end-stage airflow limitation were included, as this is generally the prerequisite for being placed on the transplant waiting list. Older patients exceeding the transplant age limit are not represented in the study. Furthermore, patients with a phenotype of mild COPD with severe PH were likely regarded as PAH with lung comorbidities in the transplant setting and therefore not included in this study. This cohort could, however, represent the vascular phenotype we have previously discussed [14, 24]. Therefore, our results may not be applicable to broader COPD populations, especially those with less severe disease or different phenotypes. Additionally, follow-up RHC data is only available for a subset of the cohort, which may introduce further bias. Patients who were removed from the waiting list, whether due to transplantation, death or other reasons, do not have follow-up RHC data, which may result in an underestimation of the development and progression of PH in the context of COPD. Consequently, these factors must be considered when interpreting the study's findings and their applicability to general COPD populations outside the transplant setting.

Prospective validation in multicentre cohorts with standardised inclusion criteria could improve the robustness and generalisability of findings. Expanding age limits and incorporating patients with mild COPD but severe PH, as well as ensuring comprehensive longitudinal follow-up data across all patient subgroups, would provide a more comprehensive understanding of the disease's progression and its management.

In conclusion, we provide evidence that the 2022 ESC/ERS guidelines based on recently gained knowledge enables a more granular classification of patients with COPD-PH. Applying this new classification allowed us to identify characteristics which may further phenotype distinct patient populations. Unbiased longitudinal invasive follow-up and assessment of lung volumes by plethysmography provided evidence of an association of PVR and TLC, independent of underlying manifest ILA. Moreover, this classification system could optimise treatment and monitoring by enabling early detection of PH in COPD patients and

guiding personalised therapies targeting both vascular and pulmonary dysfunction. However, the lack of a mechanistic explanation warrants prospective studies or trials to address the limitations of our study.

Provenance: Submitted article, peer reviewed.

Ethics statement: This was a retrospective, single-centre study at the Department of Medicine V, University of Munich, approved by the local medical ethics committee (#18-064).

Conflicts of interest: The authors declare no conflicts of interest.

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