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Phenotyping of patients with mild pulmonary hypertension

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ABSTRACT

Background Revised haemodynamic criteria for pulmonary hypertension (PH)—mean pulmonary artery pressure (mPAP) >20 mm Hg and pulmonary vascular resistance (PVR) >2 Wood Units (WU)—have defined new subsets of patients with mild PH. We aimed to characterise their clinical profile and prognosis.

Methods We included consecutive incident, treatment-naïve patients undergoing right heart catheterisation at a PH referral centre. Patients with mPAP 21–24 mm Hg and pulmonary artery wedge pressure (PAWP) ≤15 mm Hg were stratified by PVR values to identify those with unclassified PH (PVR≤2 WU) and mild precapillary PH (PVR>2 WU). Patients with mild precapillary PH were compared with matched controls with normal haemodynamics and with patients meeting previous pulmonary arterial hypertension (PAH) haemodynamic criteria (mPAP≥25 mm Hg, PAWP≤15 mm Hg, PVR>3 WU).

Results Among 259 patients with mPAP 21–24 mm Hg and PAWP≤15 mm Hg, 76% had left heart or lung disease. In unclassified PH, mPAP elevation was mainly due to high stroke volume index (SVI) or backward transmission from borderline PAWP. In mild precapillary PH, SVI was the only independent haemodynamic predictor of survival. Survival was similar between mild precapillary PH and PAH patients. A limited number of patients with PAH risk factors progressed to overt PAH and, in the absence of comorbidities, appeared to benefit from PAH therapies.

Conclusions Unclassified PH is mainly related to pulmonary overflow or backward transmission from borderline PAWP. Mild precapillary PH is typically associated with comorbidities and not necessarily an early PAH stage. SVI is a key prognostic marker. Careful clinical phenotyping is essential to identify the small subset who may benefit from targeted therapies.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Mild elevations in mean pulmonary artery pressure and pulmonary vascular resistance are associated with worse outcomes, but their significance, particularly regarding early pulmonary arterial hypertension (PAH) development, remains unclear. Previous studies have not fully characterised the clinical phenotype or prognostic implications of patients identified under the revised haemodynamic definitions.

WHAT THIS STUDY ADDS

⇒ This study shows that most patients with mild precapillary pulmonary hypertension (PH) have underlying comorbidities rather than early-stage PAH, with stroke volume index emerging as the key independent predictor of prognosis. Survival among these patients is comparable to that of those with established PAH, but true progression to PAH is rare and mostly limited to individuals with recognised risk factors.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings support a more cautious interpretation of mild haemodynamic abnormalities, highlighting the need for thorough clinical phenotyping rather than immediate therapeutic decisions. These insights may refine patient risk stratification and inform targeted screening strategies for early PAH detection.

INTRODUCTION

Since the first Pulmonary Hypertension World Conference held in Geneva in 1973, a mean pulmonary artery pressure (mPAP) threshold of ≥25 mm Hg was arbitrarily established and widely adopted to define pulmonary hypertension (PH). It was noted at that time that mPAP values in healthy individuals do not exceed 20 mm Hg; however, a more conservative threshold of 25 mm Hg was selected to ensure diagnostic specificity.[1]

This haemodynamic definition remained unchanged for nearly five decades. In 2015, the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) guidelines introduced a refinement by incorporating a pulmonary vascular resistance (PVR) criterion >3 Wood Units (WU) to define precapillary PH.[2 3] Notably, all clinical trials demonstrating the efficacy of targeted pulmonary arterial hypertension (PAH) therapies enrolled patients meeting these haemodynamic criteria (mPAP≥25 mm Hg and PVR>3 WU).[4 5]

Recent evidence has confirmed that in healthy subjects at rest, mPAP is consistently <20 mm Hg and PVR ≤2 WU. Moreover,

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even modest elevations of mPAP (>20 mm Hg) and PVR (>2 WU) have been associated with adverse outcomes. However, the prognostic implications of these mild haemodynamic abnormalities have primarily been explored over the past decade, mainly through studies involving large cohorts of veterans[6 7] or specific populations such as those with connective tissue diseases (CTDs),[8–10] idiopathic pulmonary fibrosis[11] or chronic thromboembolic disease.[12 13]

In light of these findings, the sixth World Symposium on PH and the 2022 ESC/ERS guidelines proposed a revised haemodynamic definition of PH, lowering the mPAP threshold to >20 mm Hg and the PVR threshold to >2 WU to identify precapillary PH.[4 5 14] Despite these updates, little is known regarding the clinical and haemodynamic characteristics of patients classified under the new criteria.

The EVIDENCE-PAH UK study by Karia *et al*[15] represents the largest effort to characterise this population at PH referral centres. This study compared patients with an mPAP of 21–24 mm Hg, irrespective of pulmonary artery wedge pressure (PAWP), to those with normal haemodynamics (mPAP <21 mm Hg) and those with PH as per the historical definition (mPAP ≥25 mm Hg), encompassing all PH groups (group 1: 30%, group 2: 36%, group 3: 16%, group 4: 16%, group 5: 2%). The results indicated a direct association between mPAP values, age and the presence of left heart and/or lung disease. Most patients with mPAP between 21 and 24 mm Hg exhibited underlying comorbidities associated with increased mortality. Although the new haemodynamic definition demonstrated prognostic relevance (and this was confirmed also in patients with lung and left heart disease), it remains unclear whether patients classified as having precapillary PH under the new criteria may represent an early stage of PAH. Therefore, detailed phenotypic characterisation of this subgroup is crucial.

The objectives of the present study were: (1) to characterise the clinical, functional and haemodynamic profile of patients with 'mild PH' (mPAP 21–24 mm Hg) and PAWP≤15 mm Hg referred to a tertiary PH referral centre and (2) to compare patients with 'mild precapillary PH' (mPAP 21–24 mm Hg, PAWP ≤15 mm Hg and PVR >2 WU) to patients with entirely normal pulmonary haemodynamics (mPAP <21 mm Hg, PAWP ≤15 mm Hg and PVR ≤2 WU) and to patients with a confirmed diagnosis of PAH (group 1 PH) according to the 2015 ESC/ERS haemodynamic criteria (mPAP ≥25 mm Hg, PAWP ≤15 mm Hg and PVR >3 WU).

METHODS

Population

This study was conducted in accordance with the principles of the Declaration of Helsinki[16] and within the framework of routine clinical care. Data were collected from all consecutive incident, treatment-naïve patients aged ≥18 years referred to the Pulmonary Vascular Disease Centre of Bologna University between 2002 and 2023.

The primary study population included patients who, at right heart catheterisation (RHC), showed a mPAP of 21–24 mm Hg and a PAWP ≤15 mm Hg. These patients were further stratified according to PVR (≤2 WU, 2–3 WU, >3 WU). Those fulfilling the 2022 ESC/ERS PH guideline definition of precapillary PH with borderline mPAP (mPAP 21–24 mm Hg, PVR>2 WU and PAWP≤15 mm Hg; 'mild precapillary PH') were compared with two matched control groups: patients with normal pulmonary haemodynamics (mPAP <21 mm Hg, PAWP ≤15 mm Hg and PVR≤2 WU; 'normal haemodynamics') and patients diagnosed with PAH according to the 2015 ESC/ERS haemodynamic criteria (mPAP ≥25 mm Hg, PAWP ≤15 mm Hg and PVR>3 WU; 'PAH according to ESC/ERS 2015 guidelines').

Patients not receiving targeted PAH therapy were followed up every 6–12 months, either at our centre or at the referring centre, according to patient preference. In the latter case, patients or referring physicians were contacted to obtain follow-up information. Repeat RHC was performed if clinical deterioration suggested worsening PH and reassessment was expected to inform diagnosis, prognosis or therapy.

Patients in the PAH group received treatment according to the ESC/ERS PH guidelines in place during their respective follow-up periods.[2–5 17 18] If treatment goals were not achieved, sequential combination therapy was initiated, following a goal-oriented strategy. Although therapeutic recommendations evolved during the study period, the prescription of sequential combination therapy remained relatively consistent, aligning with the treatment goals established at our centre.[19 20] Following the significant changes to PAH treatment strategies in 2015, when the ESC/ERS guidelines on PAH were published recommending initial dual oral combination therapy,[2 3] time-stratified analyses were performed.

Patients treated with targeted PAH therapies underwent systematic reassessment after 3–6 months, including clinical, laboratory, exercise and haemodynamic evaluations.

Patients referred to our centre after the sixth World Symposium on PH,[14] with mild precapillary PH, no cardiopulmonary comorbidities and a high risk of developing overt PAH (ie, risk factors for group 1 PH) were considered for targeted PAH therapy following multidisciplinary team discussion.[4 5]

Assessment

Baseline assessments included both non-invasive and invasive parameters. Non-invasive parameters comprised: age, gender, PAH risk factors [bone morphogenetic protein receptor type 2 (BMPR2) mutation, drugs and toxins with a definite association with PAH, CTD, congenital heart disease (CHD), HIV infection, portal hypertension], WHO functional class (WHO-FC), 6 min walk distance (6MWD), brain natriuretic peptide (BNP)/N–terminal pro-BNP (NT-proBNP) values (categorised in

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four risk groups according to Hoeper *et al*),[21] creatinine, estimated glomerular filtration rate (calculated using the CKD-EPI equation),[22] use of diuretics and oxygen therapy, smoking status, systemic oxygen saturation, history of pulmonary embolism (PE) and persistence of chronic thromboembolic pulmonary defects after at least 3 months of adequate anticoagulation (chronic thromboembolic pulmonary disease, CTEPD). Genetic testing was performed when clinically indicated, particularly in patients with idiopathic PAH and in relatives of patients with known PAH-predisposing mutations.

Risk stratification was performed using the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL Lite 2) risk score,[23] a tool that has been validated for use in cases where missing values are present,[23] and that can be applied at baseline to populations with non-group 1 PH as well.[24]

To evaluate the presence of left heart disease, the following were assessed: body mass index (BMI), obesity (BMI ≥30 kg/m^2), systemic hypertension, atrial fibrillation, echocardiographic parameters [left atrial (LA) size, left ventricular ejection fraction (LVEF), mitral Doppler measurements (E/e′ ≥ 14 and E/A ratio) and valvular heart disease (defined as at least moderate stenosis or regurgitation or presence of left heart valvular prosthesis)]. Diabetes mellitus and coronary artery disease were also tracked. LA volume was classified as normal (≤34 mL/m^2), mildly dilated (35–41 mL/m^2), moderately dilated (42–48 mL/m^2) or severely dilated (>48 mL/m^2).[25] LVEF was categorised as preserved (≥50%), mildly reduced (41%–49%) or reduced (≤40%).[26] The H2FPEF score[27] and HFpEF-ABA score[28] were also calculated.

To assess lung disease, pulmonary function test (including diffusing capacity for carbon monoxide), high-resolution CT scan and the diagnosis of obstructive sleep apnoea syndrome were evaluated.

Definitions of left heart and lung disease are provided in online supplemental table S1.

RHC was performed under stable clinical conditions after volume optimisation. Parameters measured included heart rate (HR), right atrial pressure (RAP), systolic/diastolic/mPAP (sPAP/dPAP/mPAP), PAWP (a borderline value of PAWP was considered between 13 and 15 mm Hg;[4 5] the recently proposed probable PAWP range of uncertainty of 12–15 mm Hg was also considered),[29] and cardiac output (CO). Derived haemodynamic variables included PVR [(mPAP–PAWP)/CO], cardiac index (CI) (CO/body surface area), stroke volume (SV) (CO/HR), stroke volume index (SVI) (CI/HR) and pulmonary arterial compliance (PAC) [SV/(sPAP–dPAP)]. The upper limit of normality of pulmonary SVI (47 mL/m^2)[4 5] was considered to define pulmonary overflow.

Statistical analysis

Categorical variables are presented as counts and percentages [n (%)], while continuous variables are reported as medians with IQR. No imputations were made for missing data.

A 1:1 propensity score matching procedure was performed to select patients with normal haemodynamics and patients with PAH according to the ESC/ERS 2015 guidelines, matching for CTD, age and gender. A logistic regression model was used to estimate the propensity score and a calliper matching algorithm was used to select the matchings.

Comparisons between groups were conducted using Pearson's χ^2 test or Fisher's exact test for categorical variables, applying Bonferroni correction for multiple comparisons. Continuous variables were compared using the Mann-Whitney test or Dunn test with Bonferroni correction. Changes from baseline to follow-up were analysed using the paired Wilcoxon signed-rank test. A two-tailed $p<0.05$ was considered statistically significant.

The prognostic value of selected variables was assessed by Cox proportional hazards models. Variables with a $p<0.2$ at univariate analysis were entered into the multivariable model. We included in the multivariate analyses of patients with mPAP between 21–24 mm Hg and PAWP≤15 mm Hg demographic variables (age and gender), aetiological risk factors for the different forms of PH (CTD, CHD, HIV, portal hypertension, left heart disease, lung disease, CTEPD), the REVEAL Lite 2 score as a non-invasive risk stratification tool and haemodynamic parameters. Different multivariate analysis models were developed for the haemodynamic variables that had Pearson correlation coefficients (absolute value) of at least 0.6. The model with the highest Harrell C-index and the lowest Akaike information criterion was considered. All-cause mortality was the primary outcome. Causes of death were independently reviewed by two investigators (FDa and RB) based on medical records. Patients lost to follow-up were censored as alive at last contact.

Survival was analysed using Kaplan-Meier curves, and differences between groups were compared using the log-rank test. Baseline RHC served as the starting point for survival analysis.

All statistical analyses were performed using STATA/SE V.15.1 (StataCorp).

RESULTS

Characteristics of patients with mPAP 21–24 mm Hg and PAWP ≤15 mm Hg

The clinical and haemodynamic characteristics of the 259 patients with a baseline mPAP between 21–24 mm Hg and PAWP ≤15 mm Hg are shown in table 1. 125 patients (48%) underwent baseline RHC before 2015. Comorbidities and cardiopulmonary parameters used for the identification of left heart or lung disease are reported in online supplemental table S2. Overall, 178 patients (69%) exhibited evidence of left heart and/or lung disease, while 25 (10%) had both.

Among patients classified as unclassified PH (mPAP >20 mm Hg, PVR ≤2 WU, PAWP ≤15 mm Hg), 45 (44%) had a PAWP between 13 and 15 mm Hg, 63 (62%) had an SVI >47 mL/m^2 and 80 (78%) had either a PAWP

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Table 1 Clinical and haemodynamic characteristics of patients with mPAP between 21–24 mm Hg and PAWP ≤15 mm Hg

		According to baseline PVR			
		PVR ≤2 WU	PVR 2–3 WU	PVR >3 WU	
	Overall cohort	Unclassified PH	Mild precapillary PH		P value
n	259	102	100	57	
Age, years	67 (56–75)	63 (52–73)*†	69 (58–76)*	71 (64–77)†	0.001
Male gender, n (%)	90 (35)	34 (33)	39 (39)	17 (30)	0.473
REVEAL Lite 2 score	4 (3–6)	4 (3–5)†	4 (3–6)‡	5 (4–7)†‡	<0.001
Known BMPR2 mutation, n (%)	1 (0.3)	0	1 (1)	0	0.450
PAH associated drugs/toxins, n (%)	1 (0.3)	1 (1)	0	0	0.450
Connective tissue disease, n (%)	51 (20)	13 (13)†	20 (20)	18 (32)†	0.016
Systemic sclerosis	32 (63)	5 (39)	13 (65)	14 (77)	
Rheumatoid arthritis	5 (10)	3 (23)	0	2 (11)	
SLE	5 (10)	2 (15)	3 (15)	0	
Sjögren	5 (10)	1 (8)	3 (15)	1 (6)	
Other	4 (8)	2 (15)	1 (5)	1 (6)	
Congenital heart disease, n (%)	35 (14)	24 (24)*†	8 (8)*	3 (5)†	0.001
Corrected	9 (26)	4 (17)	3 (38)	2 (67)	
HIV infection, n (%)	3 (1)	0	2 (2)	1 (2)	0.370
Portal hypertension, n (%)	15 (6)	11 (11)	3 (3)	1 (2)	0.020
Left heart disease, n (%)	128 (49)	53 (52)	52 (52)	23 (40)	0.300
Lung disease, n (%)	75 (29)	15 (15)†	24 (24)‡	36 (63)†‡	<0.001
CTEPD, n (%)	36 (14)	8 (8)*	23 (23)*‡	5 (9)‡	0.004
O_2 treatment, n (%)	30 (12)	5 (5)†	9 (9)‡	16 (28)†‡	<0.001
Diuretic treatment:					0.979
None	101 (39)	43 (42)	36 (36)	22 (39)	
Furosemide/HCT≤50 mg/die	103 (40)	38 (37)	41 (41)	24 (42)	
Furosemide 75–125 mg/die	38 (15)	14 (14)	16 (16)	8 (14)	
Furosemide >125 mg/die	17 (6)	7 (7)	7 (7)	3 (5)	
Haemodynamics:					
Heart rate, bpm	70 (63–80)	73 (65–80)	70 (62–80)	74 (64–80)	0.835
RAP, mm Hg	5 (4–7)	7 (5–8)*†	5 (4–6)*‡	4 (3–5)†‡	<0.001
mPAP, mm Hg	22 (21–23)	22 (21–23)*†	23 (22–23)*‡	23 (22–24)†‡	<0.001
PAWP, mm Hg	10 (8–12)	12 (11–14)*†	10 (9–12)*‡	7 (6-9)†‡	<0.001
CI, L/min/m^2	2.9 (2.5–3.5)	3.5 (3.0–4.5)*†	2.8 (2.5–3.2)*‡	2.4 (2.1–2.8)†‡	<0.001
SVI, mL/m^2	41 (35–52)	52 (42–65)*†	40 (35–45)*‡	34 (28–39)†‡	<0.001
PVR, WU	2.3 (1.7–2.9)	1.6 (1.3–1.8)*†	2.5 (2.2–2.8)*‡	3.7 (3.3–4.4)†‡	<0.001
PAC, mL/mm Hg	3.05 (2.34–3.84)	3.83 (3.24–4.89)*†	2.87 (2.25–3.31)*‡	2.38 (1.76–2.78)†‡	<0.001

* P<0.05 between respective pairs.
† P<0.05 between respective pairs.
‡ P<0.05 between respective pairs.
BMPR2, Bone morphogenetic protein receptor type 2; CI, cardiac index; CTEPD, chronic thromboembolic pulmonary disease; HCT, hydrochlorothiazide; HIV, human immunodeficiency virus; mPAP, mean pulmonary arterial pressure; PAC, pulmonary arterial compliance; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; REVEAL, Registry to Evaluate Early and Long-term PAH Disease Management; SLE, systemic lupus erythematosus; SVI, stroke volume index; WU, Wood Units.

between 13 and 15 mm Hg and/or an SVI>47 mL/m^2. Applying the recently proposed threshold for borderline PAWP of 12 mm Hg,[30] 93 patients (91%) exhibited either a PAWP between 12–15 mm Hg and/or an SVI >47 mL/m^2.

Patient follow-up details are reported in online supplemental table S3, and survival data are presented in figure 1. The median follow-up duration was 3.6 (1.1–6.2) years. A total of 214 patients (83%) underwent at least one clinical follow-up, after a median

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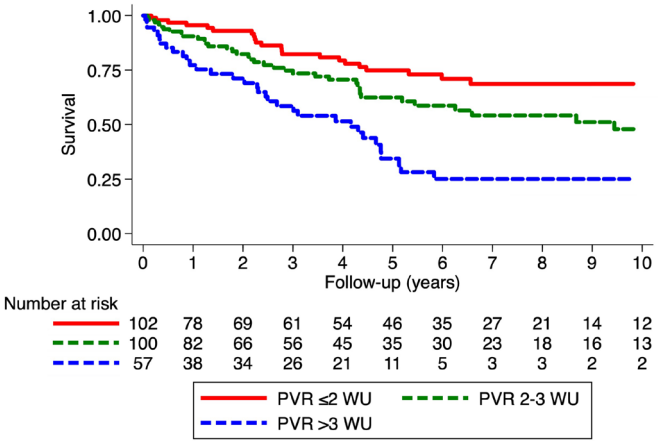

Figure 1 Kaplan-Meier curves of patients with mPAP between 21 and 24 mm Hg and PAWP ≤15 mm Hg according to value of PVR. Pairwise comparisons p value: PVR ≤2 WU vs PVR 2–3 WU: p=0.010; PVR ≤2 WU vs PVR >3 WU: p<0.001; PVR 2–3 WU vs PVR >3 WU: p=0.003. mPAP, mean pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; WU, Wood Units.

of 4.2 (1.1–7.9) years, accounting for a total of 1141 patient-years.

Among the 50 patients (19%) who underwent repeat RHC, after a median of 2 (0.7–5.3) years, the following outcomes were observed:

- patients developed a PAWP >15 mm Hg.
- 21 patients maintained a mPAP <25 mm Hg, PAWP ≤15 mm Hg and PVR <3 WU.
- 11 patients progressed to mPAP ≥25 mm Hg, PAWP ≤15 mm Hg and PVR >3 WU (including 2 eventually diagnosed with CTD-PAH, 6 with PH due to lung disease, 2 with CTEPH and 1 with group 5 PH).

Nine patients underwent RHC reassessment after initiation of targeted PAH therapies (see below). No patient received a diagnosis of idiopathic PAH according to the 2015 ESC/ERS PH guidelines during follow-up. RHC was performed more frequently in younger patients, and in patients with a longer follow-up, with CTD or CTEPD and with a more severe haemodynamic profile with higher mPAP and PVR (online supplemental table S4a). Patients with at least one clinical follow-up evaluation have a lower prevalence of CTD and oxygen treatment, have a higher prevalence of CTEPD, have a lower HR and a higher PAWP and SVI (online supplemental table S4b).

Detailed outcomes in patients progressing to CTD-PAH, CTEPH or group 5 PH

Two patients developed CTD-PAH during follow-up:

- One patient with 25% interstitial lung disease demonstrated significant haemodynamic deterioration after 7 years, despite stable lung involvement. Phosphodiesterase-5 inhibitor (PDE5-I) therapy was initiated with clinical and haemodynamic benefit. The treatment was well tolerated and the patient died 6 years later from respiratory infection.
- The other patient, with severe peripheral vascular disease and aortic stenosis (successfully treated by transcatheter valve implantation), showed haemodynamic worsening 1 year after transcatheter aortic valve implantation. PDE5-I therapy was started without clinical benefit, and the patient died 5 months later due to intestinal ischaemia.

Two patients developed CTEPH:

- One was diagnosed 1 year later and started on PDE5-I therapy, achieving haemodynamic normalisation, despite concomitant left heart disease (ischaemic heart disease and atrial fibrillation).
- The second patient developed CTEPH after 21 years of follow-up, without major comorbidities and is currently listed for pulmonary endarterectomy.

One patient developed group 5 PH:

- The diagnosis was made 5 years later in a patient with sickle cell disease; endothelin receptor antagonist (ERA) therapy was initiated with clinical and haemodynamic benefit and was well tolerated.

The latter three patients remained alive at the end of follow-up.

Predictors of prognosis in patients with mPAP 21–24 mm Hg and PAWP ≤15 mm Hg

Predictors of all-cause mortality in patients with mild precapillary PH are reported in table 2. In multivariate analysis, SVI emerged as the only independent haemodynamic predictor of prognosis.

Univariate and multivariate Cox regression analyses of the overall population of patients with mPAP between 21–24 mm Hg and PAWP≤15 mm Hg is shown in online supplemental table S5. Of note, in this population PVR retained an independent prognostic role but, while at univariate analysis, PVR>3 WU was associated with worse prognosis compared with PVR 2–3 WU [HR (95% CI) 1.94 (1.22 to 3.09); p=0.005], this difference was not statistically significant at multivariate analysis [HR (95% CI) 1.50 (0.90 to 2.51); p=0.118]. Receiving a baseline RHC after 2015 was not predictive of prognosis neither in patients with mild precapillary PH [HR (95% CI) 0.74 (0.45 to 1.24); p=0.259], nor in the overall population of patients with mPAP between 21–24 mm Hg and PAWP ≤15 mm Hg [HR (95% CI) 0.86 (0.55 to 1.34); p=0.494].

Comparison of patients with mild precapillary PH versus patients with normal haemodynamics and PAH (ESC/ERS 2015 criteria)

The 157 patients with mild precapillary PH were matched 1:1 to patients with normal haemodynamics and patients with PAH defined by ESC/ERS 2015 guidelines. Matched control patients were selected from a cohort of 307 individuals with normal haemodynamics and 1033 treatment-naïve PAH patients (online supplemental figure S1). Groups were matched for the unmodifiable independent prognostic

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Table 2 Predictors of all-cause death in patients with mild precapillary PH

	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age, years	1.03 (1.01 to 1.05)	0.001	1.03 (1.00 to 1.05)	0.019
Male gender	1.43 (0.90 to 2.28)	0.133	2.09 (1.21 to 3.61)	0.008
REVEAL Lite 2	1.26 (1.12 to 1.42)	<0.001	1.25 (1.08 to 1.44)	0.002
Connective tissue disease	1.89 (1.17 to 3.06)	0.009	1.74 (1.02 to 2.98)	0.042
Congenital heart disease	0.86 (0.35 to 2.14)	0.750		
HIV infection	0.70 (0.09 to 5.20)	0.729		
Portal hypertension	1.70 (0.42 to 6.98)	0.460		
Left heart disease	1.50 (0.93 to 2.41)	0.094		
Lung disease	2.27 (1.42 to 3.62)	0.001	2.18 (1.30 to 3.66)	0.003
CTEPD	0.37 (0.17 to 0.81)	0.013		
Haemodynamics				
Heart rate, bpm	1.01 (0.99 to 1.03)	0.127		
RAP, mm Hg	1.09 (1.02 to 1.17)	0.012		
mPAP, mm Hg	1.12 (0.91 to 1.38)	0.282		
PAWP, mm Hg	0.99 (0.91 to 1.10)	0.956		
CI, l/min/m^2	0.50 (0.32 to 0.77)	0.002		
SVI, ml/m^2	0.94 (0.91 to 0.97)	<0.001	0.96 (0.93 to 0.99)	0.025
PVR, WU	1.55 (1.23 to 1.96)	<0.001		
PVR>3 WU	1.99 (1.25 to 3.19)	0.004		
PAC, ml/mm Hg	0.84 (0.64 to 1.10)	0.213		

CI, cardiac index; CTEPD, chronic thromboembolic pulmonary disease; HIV, human immunodeficiency virus; HR, hazard ratio; mPAP, mean pulmonary arterial pressure; PAC, pulmonary arterial compliance; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; REVEAL, Registry to Evaluate Early and Long-term PAH Disease Management; SVI, stroke volume index.

factors in patients with mild precapillary PH, that is, age, gender and CTD.

Among patients with PAH, 86 (55%) had idiopathic/heritable/drug-induced PAH, 38 (24%) had CTD-PAH, 13 (8%) had CHD-PAH and 20 (13%) had portopulmonary or HIV-PAH. At the end of follow-up, 85 (54%) patients were treated with monotherapy, 56 (36%) with double combination therapy and 16 (10%) with triple combination therapy.

The characteristics of the three matched groups are summarised in table 3. Baseline RHC was performed before 2015 in 239 (51%) patients and after 2015 in 232 (49%) patients. Patients with mild precapillary PH showed a significantly higher prevalence of left heart and lung disease compared with PAH patients. Comorbidities, cardiopulmonary parameters used for the identification of left heart or lung disease, and follow-up data are reported in online supplemental table S6. Survival data are presented in figure 2.

No statistically significant survival difference was observed between patients with PAH versus patients with mild precapillary PH, both unadjusted [HR (95% CI) 1.01 (0.75 to 1.37), p=0.946; this was confirmed also restricting the analysis to patients who received a baseline RHC before 2015: HR (95% CI) 1.03 (0.72 to 1.47), p=0.863; or after 2015: HR (95% CI) 0.80 (0.42 to 1.52), p=0.488], adjusted for age, gender and CTD [HR (95% CI) 1.04 (0.77 to 1.41), p=0.808; this was confirmed also restricting the analysis to patients who received a baseline RHC before 2015: HR (95% CI) 1.09 (0.77 to 1.56), p=0.622; or after 2015: HR (95% CI) 0.67 (0.35 to 1.30), p=0.234] and adjusted for unmodifiable independent predictors of prognosis in the merged group [HR (95% CI) 1.12 (0.82 to 1.54), p=0.481, online supplemental table S7; this was confirmed, also restricting the analysis to patients who received a baseline RHC before 2015: HR (95% CI) 1.31 (0.90 to 1.91), p=0.157; or after 2015: HR (95% CI) 0.62 (0.32 to 1.23), p=0.170]. Since we observed a similar proportion of male and CTD patients in both the group of 1033 PAH patients and the group of 157 patients with mild precapillary PH (online supplemental figure S1), the latter of which were significantly older, we compared the survival rates of the entire group of 1033 PAH patients with those of patients with mild precapillary PH. We confirmed that the age-adjusted prognosis was comparable [HR (95% CI) 1.16 (0.90 to 1.49), p=0.260].

Treatment effect in patients with mild precapillary PH and PAH risk factors

Since 2018, 383 treatment-naïve patients with at least one PAH risk factor underwent RHC at our centre. Risk

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Table 3 Clinical and haemodynamic characteristics of patients with mild precapillary PH versus patients with normal haemodynamics and patients with PAH according to ESC/ERS 2015 PH guidelines

	Normal haemodynamics	Mild precapillary PH	PAH (ESC/ERS 2015 PH guidelines)	P value
Age, years	69 (59–75)	70 (61–76)	70 (59–77)	0.359
Male gender, n (%)	59 (38)	56 (36)	54 (34)	0.839
REVEAL Lite 2 score	4 (3–5)*†	5 (3–6)*‡	7 (5–9)‡†	<0.001
Known BMPR2 mutation, n (%)	2 (1)	1 (1)	6 (4)	0.093
Connective tissue disease, n (%)	31 (20)	38 (24)	40 (25)	0.449
Systemic sclerosis	23 (74)	27 (71)	32 (80)	
Rheumatoid arthritis	1 (3)	2 (5)	1 (2)	
SLE	4 (13)	3 (8)	3 (8)	
Sjögren	1 (3)	4 (11)	0	
Other	2 (7)	2 (5)	4 (10)	
Congenital heart disease, n (%)	21 (13)	11 (7)	13 (8)	0.127
Corrected	5 (24)	5 (45)	4 (31)	
HIV infection, n (%)	2 (1)	3 (2)	6 (4)	0.370
Portal hypertension, n (%)	12 (8)	4 (3)‡	18 (11)‡	0.009
Left heart disease, n (%)	65 (41)†	75 (48)‡	42 (27)‡†	<0.001
Lung disease, n (%)	23 (15)*	60 (38)*‡	35 (22)‡	<0.001
CTEPD, n (%)	10 (6)*†	28 (18)*‡	0‡†	<0.001
O_2 treatment, n (%)	2 (1)*†	25 (16)*‡	43 (27)‡†	<0.001
Diuretic treatment:	†		†	0.050
None	72 (46)	58 (37)	45 (29)	
Furosemide/HCT≤50 mg/die	65 (41)	65 (42)	77 (49)	
Furosemide 75–125 mg/die	15 (10)	24 (15)	24 (15)	
Furosemide >125 mg/die	5 (3)	10 (6)	11 (7)	
Haemodynamics:				
Heart rate, bpm	72 (65–81)†	70 (63–80)‡	78 (70–88)‡†	<0.001
RAP, mm Hg	5 (3–6)†	4 (3–6)‡	6 (4–10)†‡	<0.001
mPAP, mm Hg	17 (15–19)*†	23 (22–24)*‡	46 (39–57)‡†	<0.001
PAWP, mm Hg	9 (7–11)	9 (7–11)‡	8 (7–10)‡	0.010
CI, L/min/m^2	3.0 (2.5–3.8)*†	2.7 (2.3–3.1)*‡	2.3 (2.0–3.0)‡†	<0.001
SVI, mL/m^2	42 (35–50)*†	38 (33–44)*‡	31 (24–38)‡†	<0.001
PVR, WU	1.5 (1.1–1.8)*†	2.8 (2.4–3.4)*‡	9.0 (6.6–13.0)‡†	<0.001
PAC, ml/mm Hg	3.85 (3.13–4.89)*†	2.67 (2.05–3.20)*‡	1.11 (0.77–1.48)‡†	<0.001

* P<0.05 between respective pairs.
† P<0.05 between respective pairs.
‡ P<0.05 between respective pairs.
BMPR2, Bone morphogenetic protein receptor type 2; CI, cardiac index; CTEPD, chronic thromboembolic pulmonary disease; ESC/ERS, European society of cardiology/European respiratory society; HCT, hydrochlorothiazide; HIV, human immunodeficiency virus; mPAP, mean pulmonary arterial pressure; PAC, pulmonary arterial compliance; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; REVEAL, Registry to Evaluate Early and Long-term PAH Disease Management; SLE, systemic lupus erythematosus; SVI, stroke volume index.

factors included CTD (n=149), CHD (n=132), portal hypertension (n=73), genetic predisposition (n=12), HIV (n=6) and drug/toxin exposure (n=3); 8 patients had multiple risk factors.

Among them, 24 patients (1 with BMPR2 mutation, 18 with CTD, 1 with CTD and portal hypertension, and 4 with CHD) had mPAP 21–24 mm Hg, PAWP ≤15 mm Hg and PVR >2 WU. No patients with mild precapillary PH and HIV or PAH-related drugs/toxins were identified. No patients with mild precapillary PH without PAH risk factors were treated with targeted therapies.

Of these 24 patients, 15 (63%) had evidence of left heart or lung disease. The remaining nine patients received

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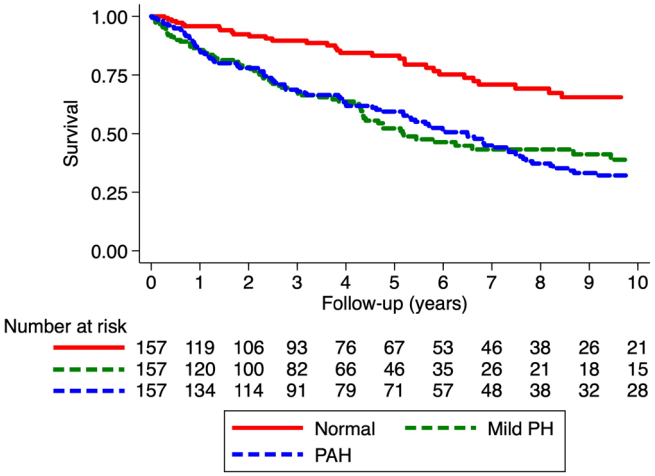

Figure 2 Kaplan-Meier curves of matched patients with mild precapillary PH versus patients with normal haemodynamics and patients with PAH according to ESC/ERS 2015 PH guidelines. Pairwise comparisons p value: normal haemodynamics versus mild precapillary PH: p<0.001; normal haemodynamics versus PAH according to ESC/ERS 2015 PH guidelines: p<0.001; mild precapillary PH versus PAH according to ESC/ERS 2015 PH guidelines: p=0.777. ESC/ERS, European Society of Cardiology/European Respiratory Society; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension.

targeted PAH therapy (6 with PDE5-Is and three with ERAs). The median age of these patients was 64 (61–75) years; eight (89%) were females, one had BMPR2 mutation and eight had CTD (including one concomitant portal hypertension).

No treatment-related adverse events were reported. All patients were alive at the end of follow-up, except one who died 5 years later of respiratory infection (the RHC performed 1 year before death showed stable haemodynamics with PVR <3 WU).

Baseline and follow-up data after 4 (4–5) months of treatment (WHO-FC, 6MWD, BNP/NT-proBNP levels and haemodynamics) are presented in table 4. Importantly, no significant deterioration in systemic oxygen saturation was observed [98% (95–99) before vs 96% (94–96) after; p=0.219] and no patient documented a PAWP of more than 13 mm Hg after initiation of PAH therapies.

DISCUSSION

In the present study, we phenotyped patients with a mPAP between 21–24 mm Hg and a PAWP≤15 mm Hg, referred to a tertiary PH centre, and we compared patients with mild precapillary PH, defined according to the ESC/ERS 2022 PH guidelines (mPAP between 21–24 mm Hg, PAWP≤15 mm Hg and PVR >2 WU) with patients fulfilling the ESC/ERS 2015 criteria for PAH and with patients with normal haemodynamics.

The main findings were as follows: (1) patients with mPAP 21–24 mm Hg and PAWP≤15 mm Hg exhibited a high prevalence of left heart and/or lung disease; lung disease was particularly prevalent in those with PVR >3 WU, while in patients with PVR ≤2 WU ('unclassified PH'), the mPAP elevation seemed mainly related to a high SVI or to a backward transmission of a borderline elevated PAWP; (2) PVR was an independent predictor of prognosis in patients with mPAP 21–24 mm Hg and PAWP ≤15 mm Hg. However, in patients with mild precapillary PH, SVI was the only independent haemodynamic predictor of prognosis, together with age, gender, CTD and the presence of lung disease; (3) patients with mild precapillary PH had a prognosis comparable to patients with PAH according to the ESC/ERS 2015 definition, even after adjustment for age, gender, CTD, portal hypertension, left heart and lung disease and (4) patients with mild precapillary PH, risk factors for PAH and no left heart or lung disease was rare but, despite the small sample size of our cohort, they seem to benefit from targeted PAH therapies.

Characteristics of patients with mPAP 21–24 mm Hg and PAWP ≤15 mm Hg

In our cohort, 69% of patients with mPAP 21–24 mm Hg and PAWP ≤15 mm Hg had evidence of left heart and/or lung disease, consistent with previous reports.[15 31] Our study extends existing knowledge by aiming to deeply phenotype this population, focusing on whether such haemodynamic findings might represent an early stage of PAH. Importantly, we excluded patients with elevated PAWP, given that PAH is defined by a precapillary haemodynamic profile.

Further characterisation based on PVR values revealed that patients with unclassified PH (mPAP >20 mm Hg, PAWP ≤15 mm Hg and PVR ≤2 WU) predominantly exhibited a mild mPAP elevation attributable to high SVI or borderline PAWP increases. This is consistent with the formula mPAP=SV×PVR×HR+PAWP. The elevated SVI observed in these patients may be partly explained by a higher prevalence of uncorrected CHD, obesity and portal hypertension, while the masked postcapillary component is suggested by the higher prevalence of patients with borderline increase of PAWP, despite optimal diuretic therapy, and by the development, over time, of only postcapillary overt PH.

Conversely, among patients with PVR >3 WU, lung disease was the predominant comorbidity. These patients exhibited lower PAWP and SVI values, in line with known reductions in left ventricular filling and SVI in severe lung disease,[32] especially in concomitance with a low RAP.[33]

Haemodynamic predictors of prognosis in patients with mild precapillary PH

Previous studies assessing the prognostic relevance of mPAP and PVR have been limited by incomplete haemodynamic profiling.[6 7 15] Our study confirms that increasing PVR is associated with stepwise increases in mortality in patients with mPAP 21–24 mm Hg and PAWP≤15 mm Hg

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Table 4 Functional, exercise, natriuretic peptides and haemodynamic characteristics of patients with mPAP between 21–24 mm Hg and PVR >2 WU treated with targeted PAH therapy, at baseline and 3–6 months after treatment

	Baseline	3–6 months after treatment	P value
WHO-FC, n (%)			0.151
I	0	3 (37)	
II	5 (50)	4 (37)	
III	4 (50)	2 (26)	
6MWD, m	445 (380–485)	484 (420–510)	0.015
BNP/NT-proBNP, n (%)			0.801
<50/<300 ng/L	3 (33)	3 (33)	
50–200/300–650 ng/L	4 (45)	5 (56)	
200–800/650–1100 ng/L	2 (22)	1 (11)	
>800/>1100 ng/L	0	0	
Haemodynamics			
HR, bpm	69 (64–75)	70 (59–79)	0.499
RAP, mm Hg	6 (4–8)	7 (4–7)	0.719
mPAP, mm Hg	23 (23–24)	22 (18–23)	0.182
PAWP, mm Hg	9 (7–11)	11 (9–11)	0.217
CI, L/min/m^2	2.6 (2.4–2.8)	2.8 (2.6–3.2)	0.041
SVI, mL/m^2	39 (36–41)	41 (37–50)	0.028
PVR, WU	3.2 (2.8–3.3)	2.2 (1.9–2.7)	0.007
PAC, mL/mm Hg	2.71 (2.50–2.98)	3.34 (2.76–3.50)	0.037

BNP, brain natriuretic peptide; CI, cardiac index; HR, heart rate; mPAP, mean pulmonary arterial pressure; 6MWD, 6-minute walking distance; NT-proBNP, N-terminal proBNP; PAC, pulmonary arterial compliance; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SVI, stroke volume index; WHO-FC, WHO-functional class; WU, Wood Units.

and that PVR remained independently prognostic after adjustment.

However, among patients with mild precapillary PH, SVI emerged as the only independent haemodynamic predictor of outcome. This finding is consistent with prior evidence of the prognostic importance of SVI and its association with the severity of left heart and lung disease[32 34–36] and suggests that this is the haemodynamic parameter that should be considered for prognostication in this patient population.

Phenotyping and follow-up of patients with mild precapillary PH

Our findings do not support the hypothesis that mild precapillary PH represents an early stage of PAH, particularly in the absence of predisposing factors. This is evidenced by both follow-up data and phenotyping characteristics of our large, prospectively phenotyped referral cohort.

PAH is a progressive disease, especially if left untreated. We documented a low incidence of progression to PAH during follow-up: only two patients, both with systemic sclerosis, eventually developed PAH, indicating a 7% incidence in this CTD patient population, consistent with previous reports.[8] Other risk factors, such as portal hypertension, have been linked to PAH development in patients with mild precapillary PH,[37] but were underrepresented in our cohort, precluding firm conclusions.

Consistent with other studies, most patients who developed PH during follow-up developed forms other than PAH, mainly postcapillary or group 3 PH.[8 38 39] Notably, all patients included had normal PAWP at baseline, emphasising the relevance of postcapillary PH development in this subset of patients. Regarding chronic thromboembolic disease, our results diverged from a recent study suggesting no progression of CTEPD without PH to CTEPH (according to ESC/ERS 2015 criteria) over a 3-year period.[13] However, it is worth noting that in our cohort, one patient developed CTEPH after a much longer observation period (21 years) and that only one (2.8%) patient with CTEPD and mPAP 21–24 mm Hg underwent pulmonary endarterectomy, compared with 8.9% in the study of Reddy *et al*.[13] Considering patients with CTEPD with mPAP 21–24 mm Hg and PAWP≤15 mm Hg the risk of progression to CTEPH according to ESC/ERS 2015 criteria was 6% in our cohort.

Finally, it is worth mentioning that PH-related death was rare, with only one patient dying of right heart failure due to interstitial lung disease-associated PH.

From a prognostic standpoint, patients with mild precapillary PH had similar survival to those with PAH

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(ESC/ERS 2015 definition), even after adjustment for major prognostic factors. This finding, already documented in systemic sclerosis patients,[40] suggests that the poor prognosis associated with mild precapillary PH is not driven by pulmonary vasculopathy per se, but rather reflects the severity of the underlying comorbidities. Thus, mild haemodynamic alterations may serve more as markers of poor prognosis than direct causes.

Furthermore, patients with mild precapillary PH exhibited a higher burden of comorbidities compared with those with PAH, again indicating they represent distinct clinical phenotypes with different pathophysiological mechanisms.

Treatment effects of targeted PAH therapies in patients with mild precapillary PH

In our cohort, a highly selected subgroup of patients with mild precapillary PH, risk factors for PAH and no significant cardiac or pulmonary comorbidities appeared to benefit from targeted PAH therapies. Although the small cohort size may limit the interpretive value, we observed improvements in exercise capacity and haemodynamics (increased CI, SVI and PAC; decreased PVR; no change in mPAP), consistent with the findings of the EDITA study.[41] Nevertheless, randomised controlled trials are needed to validate these observations and evaluate the long-term benefits.

The limitations of our study include its observational, single-centre design and the heterogeneity of follow-up strategies, with only approximately one-fifth of patients undergoing repeat RHC. As a result, we cannot exclude the possibility of haemodynamic changes over time in the remaining cohort. However, patients who did not undergo repeat RHC had a less severe haemodynamic profile at baseline, and 83% of the overall cohort received at least one follow-up evaluation. No significant differences in mPAP and/or PVR were observed between patients with at least one follow-up evaluation, although a higher prevalence of CTEPD was noted in this group. Another limitation is the lack of cardiopulmonary exercise testing or provocative testing during haemodynamic evaluation.

In conclusion, patients with mild precapillary PH frequently have comorbid left heart and/or lung disease, which largely explains their mild haemodynamic abnormalities and prognosis. SVI was the only independent haemodynamic predictor of outcome. The similar survival between patients with mild precapillary PH and those with PAH according to ESC/ERS 2015 criteria supports the concept that mild haemodynamic alterations are markers of underlying disease severity rather than drivers of poor prognosis. True early-stage PAH in this population appears rare and requires careful clinical characterisation to identify the minority of patients who may benefit from targeted PAH therapy.

Contributors Study design: FDa and RB. Collection of data: FDa, DG, AB, FDo, RB and FC. Data analysis: FDa and RB. Statistical analysis: FDa and EN. Drafting of the manuscript: FDa, AM, NG and MP. Critical revision for important intellectual content: FDa, RB and NG. Revision, editing and approval of the final manuscript: all authors. FDa is responsible for the overall content as guarantor, accepts full responsibility for the finished work and/or the conduct of the study, has access to the data and controls the decision to publish.

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Patient consent for publication Not applicable.

Ethics approval This study involved human participants, and data from all consecutive patients with PH referred to the Pulmonary Vascular Disease Centre of Bologna University were included in a prospective electronic registry (ARChivio elettronico ipertensione polmonAre; ARCA), approved by the Ethics Committee of St. Orsola-Malpighi Hospital (109/2016/U/Oss). Participants gave informed consent to participate in the study before taking part.

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