Phenotyping of idiopathic pulmonary arterial hypertension: a registry analysis

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Summary

Background Among patients meeting diagnostic criteria for idiopathic pulmonary arterial hypertension (IPAH), there is an emerging lung phenotype characterised by a low diffusion capacity for carbon monoxide (DLCO) and a smoking history. The present study aimed at a detailed characterisation of these patients.

Methods We analysed data from two European pulmonary hypertension registries, COMPERA (launched in 2007) and ASPIRE (from 2001 onwards), to identify patients diagnosed with IPAH and a lung phenotype defined by a DLCO of less than 45% predicted and a smoking history. We compared patient characteristics, response to therapy, and survival of these patients to patients with classical IPAH (defined by the absence of cardiopulmonary comorbidities and a DLCO of 45% or more predicted) and patients with pulmonary hypertension due to lung disease (group 3 pulmonary hypertension).

Findings The analysis included 128 (COMPERA) and 185 (ASPIRE) patients with classical IPAH, 268 (COMPERA) and 139 (ASPIRE) patients with IPAH and a lung phenotype, and 910 (COMPERA) and 375 (ASPIRE) patients with pulmonary hypertension due to lung disease. Most patients with IPAH and a lung phenotype had normal or near normal spirometry, a severe reduction in DLCO, with the majority having no or a mild degree of parenchymal lung involvement on chest computed tomography. Patients with IPAH and a lung phenotype (median age, 72 years [IQR 65–78] in COMPERA and 71 years [65–76] in ASPIRE) and patients with group 3 pulmonary hypertension (median age 71 years [65–77] in COMPERA and 69 years [63–74] in ASPIRE) were older than those with classical IPAH (median age, 45 years [32–60] in COMPERA and 52 years [38–64] in ASPIRE; p<0·0001 for IPAH with a lung phenotype *vs* classical IPAH in both registries). While 99 (77%) patients in COMPERA and 133 (72%) patients in ASPIRE with classical IPAH were female, there was a lower proportion of female patients in the IPAH and a lung phenotype cohort (95 [35%] COMPERA; 75 [54%] ASPIRE), which was similar to group 3 pulmonary hypertension (336 [37%] COMPERA; 148 [39%] ASPIRE]). Response to pulmonary arterial hypertension therapies at first follow-up was available from COMPERA. Improvements in WHO functional class were observed in 54% of patients with classical IPAH, 26% of patients with IPAH with a lung phenotype, and 22% of patients with group 3 pulmonary hypertension (p<0·0001 for classical IPAH *vs* IPAH and a lung phenotype, and p=0·194 for IPAH and a lung phenotype *vs* group 3 pulmonary hypertension); median improvements in 6 min walking distance were 63 m, 25 m, and 23 m for these cohorts respectively (p=0·0015 for classical IPAH *vs* IPAH and a lung phenotype, and p=0·64 for IPAH and a lung phenotype *vs* group 3 pulmonary hypertension), and median reductions in N-terminal-pro-brain-natriuretic-peptide were 58%, 27%, and 16% respectively (p=0·0043 for classical IPAH *vs* IPAH and a lung phenotype, and p=0·14 for IPAH and a lung phenotype *vs* group 3 pulmonary hypertension). In both registries, survival of patients with IPAH and a lung phenotype (1 year, 89% in COMPERA and 79% in ASPIRE; 5 years, 31% in COMPERA and 21% in ASPIRE) and group 3 pulmonary hypertension (1 year, 78% in COMPERA and 64% in ASPIRE; 5 years, 26% in COMPERA and 18% in ASPIRE) was worse than survival of patients with classical IPAH (1 year, 95% in COMPERA and 98% in ASPIRE; 5 years, 84% in COMPERA and 80% in ASPIRE; p<0·0001 for IPAH with a lung phenotype *vs* classical IPAH in both registries).

Interpretation A cohort of patients meeting diagnostic criteria for IPAH with a distinct, presumably smoking-related form of pulmonary hypertension accompanied by a low DLCO, resemble patients with pulmonary hypertension due to lung disease rather than classical IPAH. These observations have pathogenetic, diagnostic, and therapeutic implications, which require further exploration.

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Research in context

Evidence before this study

Idiopathic pulmonary arterial hypertension (IPAH), originally observed mainly in young, otherwise healthy individuals, is increasingly diagnosed in older patients with comorbidities. Among these patients, a distinct lung phenotype is emerging, characterised by a history of smoking and a low diffusion capacity for carbon monoxide (DLCO; <45% of the predicted value) without overt signs of parenchymal lung disease. This disease phenotype is not well characterised. When we searched PubMed on Oct 19, 2021, and on Dec 17, 2021, using the search terms "pulmonary arterial hypertension" AND "smoking" AND "diffusion capacity" in English we found only three case series describing patients with this phenotype.

Added value of this study

This study demonstrates that patients diagnosed with IPAH who present with a lung phenotype share many features with patients with pulmonary hypertension associated with lung disease including sex and age distribution, functional impairment at diagnosis, response to pulmonary hypertension medications, and survival. At the same time, these patients have very little in common with patients who present with a classical IPAH phenotype—ie, patients without cardiopulmonary comorbidities and a DLCO of 45% or more of the predicted value.

Implications of the available evidence

We expect our findings to lead to a reclassification of some forms of pulmonary hypertension. A better characterisation of patients with IPAH and a lung phenotype will also allow an evaluation of the safety and efficacy of PAH medications in this cohort. Finally, our data support the hypothesis that there is a distinct pulmonary vasculopathy, seemingly related to extensive tobacco exposure, which adds another component to the spectrum of smoking-related lung injury.

Introduction

The current clinical classification of pulmonary hypertension consists of five major groups: group 1, pulmonary arterial hypertension (PAH); group 2, pulmonary hypertension associated with left heart disease; group 3, pulmonary hypertension associated with lung disease; group 4, chronic thromboembolic pulmonary hypertension; and group 5, pulmonary hypertension due to systemic or multifactorial conditions.[1,2] The criteria for the diagnosis and classification of pulmonary hypertension have been outlined in guidelines published in 2015,[1] but in some patients, the individual classification is not always straightforward. This problem is frequently encountered in patients with idiopathic PAH (IPAH), the most common form of PAH. Originally, IPAH, formerly called primary pulmonary hypertension, was described as a disease occurring mostly in younger, otherwise healthy individuals, predominantly women.[3] Such patients represent the classical phenotype of IPAH. However, registries from Europe and the USA have shown that IPAH is now more frequently diagnosed in older patients, many of whom have cardiac or pulmonary comorbidities.[4–6] In such patients, it is not always easy to distinguish IPAH from group 2 or group 3 pulmonary hypertension. Several disease phenotypes have been reported, including a subtype of patients diagnosed with IPAH who present with a lung phenotype, mainly characterised by a history of smoking and a low lung diffusion capacity for carbon monoxide (DLCO), but otherwise no or only subtle signs of parenchymal lung disease. In accordance with current guidelines, these patients are classified as IPAH rather than group 3 pulmonary hypertension.[7–9]

In a recent cluster analysis from the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA), a European pulmonary hypertension registry, only 106 (12·6%) of 841 patients diagnosed with IPAH presented with the classical phenotype while 301 (35·8%) had a left heart phenotype and 434 (51·6%) had a lung phenotype.[10] The high proportion of patients with a lung phenotype was a surprise. To further characterise these patients, we used the COMPERA database to identify those with IPAH and a lung phenotype and to compare them with patients with classical IPAH and those classified as pulmonary hypertension associated with lung disease—ie, group 3 pulmonary hypertension, focussing on demographics, disease characteristics at diagnosis, response to pulmonary hypertension therapy, and survival. Data obtained from the Assessing the Spectrum of Pulmonary Hypertension Identified at a Referral Centre (ASPIRE) registry were used for independent validation.[11]

Methods

Databases

Details of COMPERA (registered at Clinicaltrials.gov, NCT01347216) have been reported previously.[5,10] COMPERA is an ongoing pulmonary hypertension registry launched in 2007 that prospectively collects baseline, follow-up, and outcome data of newly diagnosed patients who receive targeted therapies for any form of pulmonary hypertension. Pulmonary hypertension centres from several European countries participate (Austria, Belgium, Germany, Greece, Hungary, Italy, Latvia, Lithuania, the Netherlands, Slovakia, Switzerland, and the UK), with about 80% of the enrolled patients coming from Germany. COMPERA has been approved by the ethics committees of all participating centres, and all patients provided written, informed consent before inclusion.

Details of the ASPIRE registry have been previously reported.[8,11] The ASPIRE Registry includes data on patients undergoing investigation for suspected pulmonary hypertension at the Sheffield Pulmonary Vascular Disease

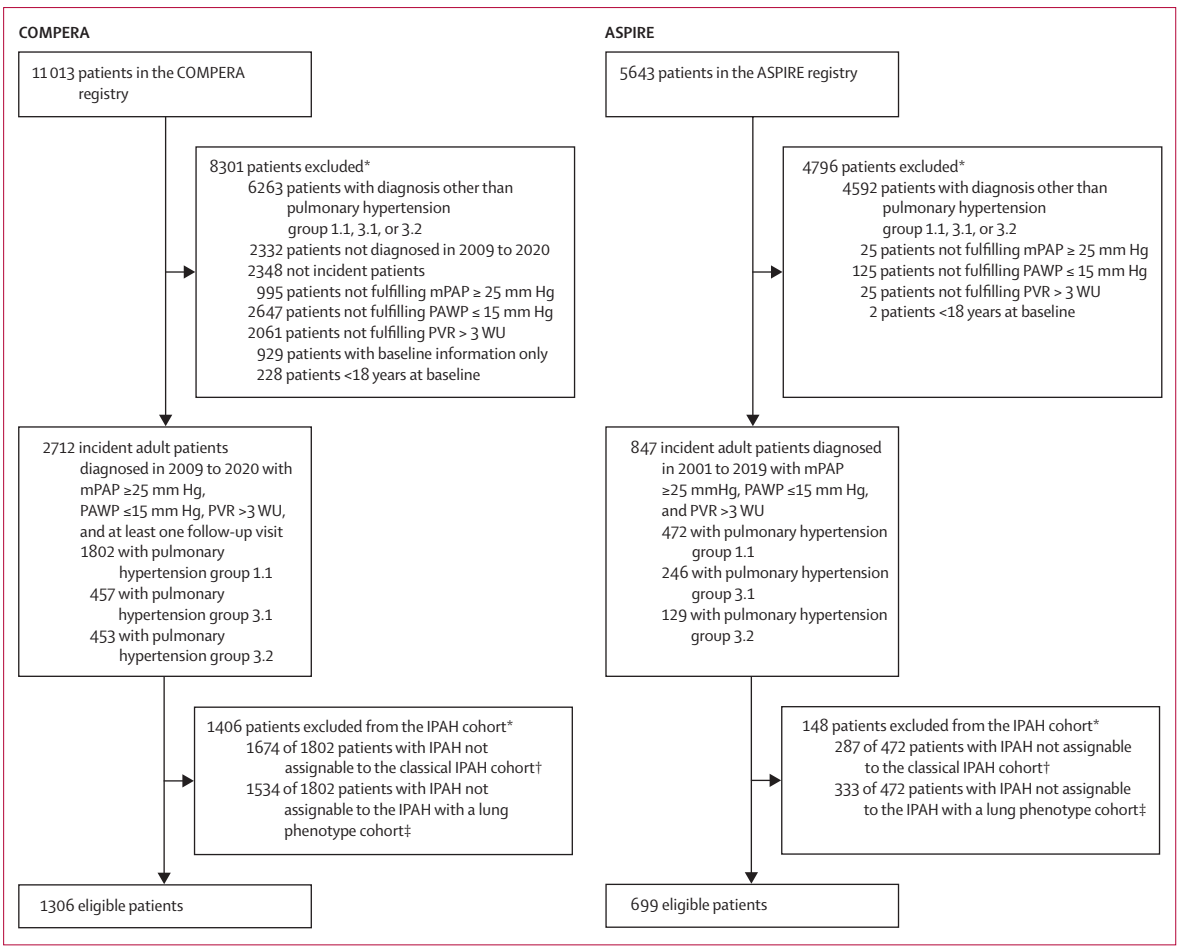

Figure 1: **Patient selection in COMPERA and ASPIRE**
ASPIRE=Assessing the Spectrum of Pulmonary Hypertension Identified at a Referral Centre. BMI=body-mass index. COMPERA=Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension. DLCO=low diffusion capacity for carbon monoxide. IPAH=idiopathic pulmonary arterial hypertension. mPAP=mean pulmonary arterial pressure. PAWP=pulmonary artery wedge pressure. PVR=pulmonary vascular resistance. WU=wood units. *More than one reason for exclusion could apply. †Classical IPAH defined by the absence of risk factors for left heart disease (BMI≥ 30 kg/m², hypertension, diabetes, and coronary heart disease), and a DLCO ≥45%. ‡Diagnosed with IPAH and a lung phenotype cohort defined by a smoking history (ie, current or former smoker) and a DLCO <45% of the predicted value.

Unit, a pulmonary hypertension centre with a referral population of 15–20 million, based in Sheffield UK, from 2001 onwards. During their assessment, patients undergo systematic evaluation including multimodality imaging and right heart catheterisation, in accordance to annually audited national standards of care. Ethical approval was granted by the Institutional Review Board and approved by the National Research Ethics Service (16/YH/0352). Analyses were conducted in accordance with General Data Protection Regulation.

Patient selection

From COMPERA, patients were selected to form three cohorts: (1) patients with classical IPAH (pulmonary hypertension group 1.1), defined by the absence of risk factors for left heart disease (BMI ≥30 kg/m², hypertension, diabetes, and coronary heart disease), and a DLCO of 45% or more; (2) patients diagnosed with IPAH and a lung phenotype, defined by a smoking history and a DLCO of less than 45% of the predicted value; and (3) patients classified by their physicians as group 3 pulmonary hypertension with the underlying conditions being either chronic obstructive pulmonary disease (COPD; pulmonary hypertension group 3.1) or interstitial lung disease (pulmonary hypertension group 3.2). The same selection criteria were used for ASPIRE, except for risk factors for left heart disease not being considered as these data were not available.

The DLCO cut-off value of less than 45% versus 45% or more was derived from previous studies that have determined the prognostic value of this threshold.[7,8,10,12]

For all cohorts, further inclusion criteria were participants aged 18 years or more, pulmonary hypertension diagnosis made between Jan 1, 2009, and Dec 31, 2020, in COMPERA, and between Feb 1, 2001, and Jan 31, 2019, in ASPIRE, and data from right heart

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For more on **COMPERA** see www.COMPERA.org

	Classical IPAH	Classical IPAH vs IPAH with a lung phenotype p value	IPAH with a lung phenotype	IPAH with a lung phenotype *vs* group 3.1 or 3.2 pulmonary hypertension p value	Group 3.1 or 3.2 pulmonary hypertension
COMPERA					
Number of patients	128	..	268	..	910
Age, years	45 (32–60)	<0·0001	72 (65–78)	0·89	71 (65–77)
Sex					
Female	99 (77%)	<0·0001	95 (35%)	0·71	336 (37%)
Male	29 (23%)	..	173 (65%)	..	574 (63%)
Body-mass index, kg/m^2	24 (22–27)	<0·0001	27 (24–32)	0·0002	26 (23–29)
WHO functional class	..	<0·0001	..	0·055	..
I	2 (2%)	..	0	..	0
II	30 (24%)	..	16 (6%)	..	32 (4%)
III	85 (67%)	..	184 (73%)	..	612 (71%)
IV	10 (8%)	..	51 (20%)	..	223 (26%)
6-minute walking distance, m	410 (320–476)	<0·0001	234 (167–310)	0·93	238 (159–318)
NT-proBNP, ng/L	1027 (360–2058)	0·0002	1871 (583–4348)	0·042	1423 (462–3380)
Brain natriuretic peptide, ng/L	127 (73–249)	0·11	304 (120–441)	0·004**2**	120 (59–276)
Pulmonary function					
TLC, % predicted	98 (87–110)	0·0011	93 (79–103)	<0·0001	85 (67–100)
FVC, % predicted	92 (78–103)	<0·0001	80 (66–94)	<0·0001	68 (53–84)
FEV_1, % predicted	85 (74–96)	<0·0001	71 (60–85)	<0·0001	59 (44–74)
FEV_1/FVC, %	80 (76–85)	<0·0001	71 (63–79)	0·0003	68 (52–81)
DLCO, % predicted	69 (59–76)	<0·0001	30 (24–36)	0·77	26 (20–35)
PaO_2, mm Hg	78 (71–84)	<0·0001	56 (50–63)	0·79	57 (49–64)
$PaCO_2$, mm Hg	33 (30–35)	<0·0001	35 (31–39)	<0·0001	37 (33–43)
Smoking history	..	<0·0001	..	<0·0001	..
Ever smoked	40 (34%)	..	268 (100%)	..	212 (81%)
Never smoked	76 (66%)	..	0	..	50 (19%)
Number of pack years	14 (10–30)	<0·0001	40 (21–50)	0·17	40 (30–60)
Comorbid conditions					
Body-mass index ≥30 kg/m^2	0	<0·0001	86 (32%)	0·0023	194 (23%)
Hypertension	0	<0·0001	183 (70%)	0·53	506 (68%)
Coronary heart disease	0	<0·0001	110 (42%)	0·17	270 (37%)
Diabetes	0	<0·0001	94 (36%)	0·011	206 (27%)
Atrial fibrillation	7 (6%)	0·033	36 (14%)	0·58	106 (12%)
Haemodynamics					
RAP, mm Hg	6 (4–9)	0·13	7 (5–10)	0·0011	6 (4–9)
mPAP, mm Hg	48 (40–57)	0·0016	43 (36–51)	<0·0001	39 (33–46)
PAWP, mm Hg	8 (5–10)	0·0003	10 (7–12)	0·0148	9 (6–11)
Cardiac index, L/min/m2	2·1 (1·7–2·7)	0·68	2·0 (1·6–2·4)	0·051	2·1 (1·8–2·6)
PVR, wood units	10·9 (7·8–15·6)	0·0005	8·7 (6·5–12·0)	<0·0001	7·4 (5·9–10·1)
SvO2, %	66 (59–70)	0·0011	62 (55–66)	<0·0001	65 (59–57)
Risk (4-strata model)*	..	<0·0001	..	0·97	..
Low	16 (12%)	..	5 (2%)	..	16 (2%)
Intermediate-low	42 (33%)	..	34 (13%)	..	108 (12%)
Intermediate-high	57 (45%)	..	139 (52%)	..	463 (52%)
High	13 (10%)	..	88 (33%)	..	311 (35%)
Pulmonary hypertension medications					
CCB	26 (20%)	<0·0001	10 (4%)	0·032	13 (1%)
ERA	56 (44%)	0·0007	70 (26%)	<0·0001	59 (6%)
PDE5i	82 (64%)	<0·0001	223 (83%)	<0·0001	852 (94%)

(Table 1 continues on next page)

	Classical IPAH	Classical IPAH vs IPAH with a lung phenotype p value	IPAH with a lung phenotype	IPAH with a lung phenotype *vs* group 3.1 or 3.2 pulmonary hypertension p value	Group 3.1 or 3.2 pulmonary hypertension
(Continued from previous page)					
sGCs	11 (9%)	0·22	13 (5%)	0·0052	15 (2%)
PPA	7 (5%)	0·17	6 (2%)	0·34	11 (1%)
Pulmonary hypertension therapy type	..	<0·0001	..	<0·0001	..
Monotherapy	81 (63%)	..	220 (82%)	..	871 (96%)
Combination therapy	47 (37%)	..	48 (18%)	..	37 (4%)
ASPIRE					
Number of patients	185	..	139	..	375
Age, years	52 (38–64)	<0·0001	71 (65–76)	0·049	69 (63–74)
Sex					
Female	133 (72%)	0·0009	75 (54%)	0·0032	148 (39%)
Male	52 (28%)	..	64 (46%)	..	227 (61%)
Body-mass index, kg/m^2	28 (25–34)	0·43	28 (25–31)	0·056	27 (23–31)
WHO functional class	..	<0·0001	..	0·94	..
I	0	..	0	..	0
II	47 (25%)	..	10 (7%)	..	29 (8%)
III	119 (64%)	..	80 (58%)	..	208 (56%)
IV	19 (10%)	..	49 (35%)	..	135 (36%)
Incremental shuttle walk distance , m	260 (140–400)	<0·0001	90 (30–150)	0·20	70 (30–140)
Pulmonary function					
FVC, % predicted	97 (84–110)	0·0114	103 (91–112)	<0·0001	82 (62–102)
FEV_1, % predicted	87 (75–97)	0·26	88 (74–99)	<0·0001	62 (44–80)
FEV_1/FVC, %	75 (69–80)	<0·0001	70 (63–76)	<0·0001	63 (48–76)
DLCO, % predicted	62 (52–73)	<0·0001	27 (22–34)	0·050	25 (19–32)
Smoking history	..	<0·0001	..	..	..
Ever	76 (45%)	..	139 (100%)	..	..
Never	92 (55%)	..	0	..	..
Pack years	20 (10–30)	0·0022	30 (20–40)	..	..
Haemodynamics					
RAP, mm Hg	9 (7–14)	0·33	10 (7–14)	0·0002	8 (5–12)
mPAP, mm Hg	54 (46–64)	<0·0001	49 (43–56)	<0·0001	41 (34–49)
PAWP, mm Hg	10 (8–12)	0·64	10 (8–13)	0·37	11 (8–13)
Cardiac index, L/min/m^2	2·3 (1·8–2·9)	<0·0001	2·0 (1·6–2·4)	<0·0001	2·6 (2·0–3·1)
PVR, wood units	10·5 (7·2–14·8)	0·50	11·1 (7·8–14·6)	<0·0001	6·5 (4·2–9·9)
SvO_2, %	64 (58–69)	<0·0001	58 (53–66)	<0·0001	66 (60–71)
Treatment†	..	0·0004	..	<0·0001	..
None	2 (1%)	..	2 (1%)	..	180 (48%)
CCB	17 (10%)	..	0	..	1 (0%)
Oral monotherapy	40 (24%)	..	43 (31%)	..	165 (44%)
Oral combination	79 (47%)	..	72 (52%)	..	22 (6%)
PPA ± oral therapy	29 (17%)	..	21 (15%)	..	7 (2%)

Data are n, n (%), and median (IQR). Percentages were calculated based on available data at baseline (appendix pp 2–5). IPAH=idiopathic pulmonary arterial hypertension. NT-proBNP=N-terminal fragment of pro-brain natriuretic peptide. TLC=total lung capacity. FVC=forced vital capacity. FEV_1=forced expiratory volume in 1 s. DLCO=diffusion capacity of the lung for carbon monoxide. PaO_2=partial pressure of oxygen in arterial blood. $PaCO_2$=partial pressure of carbon dioxide in arterial blood. RAP=right atrial pressure. mPAP=mean pulmonary arterial pressure. PAWP=pulmonary arterial wedge pressure. PVR=pulmonary vascular resistance. SvO_2=mixed-venous oxygen saturation. CCB=calcium channel blocker. ERA endothelin receptor antagonists. PDE5i=phosphodiesterase-5 inhibitors. sGCs=stimulator of soluble guanylate cyclase. PPA=prostacyclin pathway agents. *Risk was determined as published elsewhere.[14] †Oral monotherapy includes PDE5i or ERA or SGCs; oral combination includes ERA in combination with PDE5i or SCGs; PPA with or without oral therapy includes prostanoids either alone or in combination with PDE5i or sGCs with or without ERA.

Table 1: **Patient characteristics at baseline in COMPERA and ASPIRE**

catheterisation available at baseline showing precapillary pulmonary hypertension defined by mean pulmonary arterial pressure (mPAP) of 25 mm Hg or more, pulmonary artery wedge pressure of 15 mm Hg or less, and pulmonary vascular resistance (PVR) of more than 3 wood units. Furthermore, only incident patients with

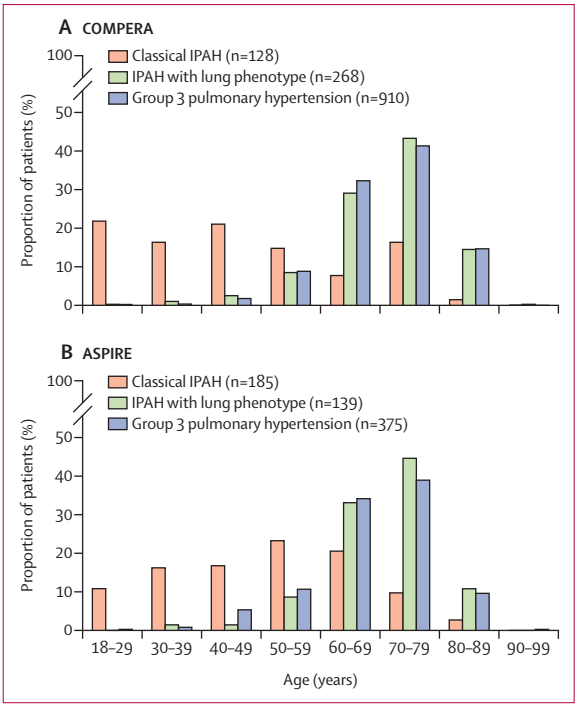

Figure 2: **Grouped bar plots showing age distribution of patients classified as classical IPAH, IPAH with a lung phenotype, and group 3 pulmonary hypertension in COMPERA (A) and ASPIRE (B)**
ASPIRE=Assessing the Spectrum of Pulmonary Hypertension Identified at a Referral Centre. COMPERA=Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension. IPAH=idiopathic pulmonary arterial hypertension.

at least one follow-up documentation were considered for COMPERA and only incident patients were considered for ASPIRE.

Imaging

Chest CT data were available only from ASPIRE. CT scans were evaluated by experienced radiologists for the presence of fibrotic or emphysematous changes, which were graded as absent, mild, moderate, or severe as previously described.[8,13]

Statistical analysis

All analyses from COMPERA and ASPIRE were performed separately and the data were not combined. This was a post-hoc analysis of prospectively collected data. Analyses were performed using R software major version 4. Categorical data are presented as number and percentage, continuous data as median and IQR. First follow-up was defined as the first assessment within 3 to 12 months after treatment initiation. Vital status was ascertained by on-site visits or phone calls to the patients or their caregivers. Patients who underwent lung transplantation and patients who were lost to follow-up were censored at the date of the last contact.

The focus of the present study was the identification of similarities and differences between patients diagnosed with IPAH who present with a lung phenotype and group 3 pulmonary hypertension. To compare the cohort of patients with IPAH and a lung phenotype with each of the two other cohorts, two-sample Welch t-tests or Wilcoxon rank sum tests were used for continuous data. Categorical data were compared by Pearson's χ^2 test or by Fisher's exact test. Response to therapy in COMPERA only was determined by changes from baseline to first follow-up in WHO functional class, 6-minute walking distance (6MWD), N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP), and mortality risk using the European Society of Cardiology and European Respiratory Society 4-strata model.[14] Survival estimates from the time of enrolment were done by Kaplan-Meier analyses, log-rank test, and Cox proportional hazard regression models to adjust for age and sex. A p value of 0·05 or less was considered statistically significant.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From COMPERA, 1306 patients fulfilled the eligibility criteria and were included in the analysis: 128 patients with classical IPAH, 268 patients with IPAH and a lung phenotype, and 910 patients with group 3 pulmonary hypertension. From ASPIRE, 699 patients fulfilled the eligibility criteria and were included in the analysis: 185 patients with classical IPAH, 139 patients with IPAH and a lung phenotype, and 375 patients with group 3 pulmonary hypertension (figure 1; table 1). The number of missing values for each variable is shown in the appendix (pp 2–5). Histograms showing the age distribution of the cohorts are shown in figure 2. The baseline characteristics of patients with IPAH who were excluded from the analyses are shown in the appendix (pp 6–9).

Patients with classical IPAH were mostly young with a median age of 45 years (IQR 32–60) in COMPERA and 52 years (IQR 38–64) in ASPIRE (although some patients were older than 70 as shown in figure 2), and predominantly female. About a third of patients with classical IPAH had a smoking history with a median of 14 pack years (IQR 10–30) in COMPERA and 20 pack years (IQR 10–30) in ASPIRE. Lung function was preserved while the DLCO was mildly reduced, and blood gas analyses (data available from COMPERA only) showed a near-normal PaO_2 and a low $PaCO_2$. Haemodynamic assessment at time of diagnosis showed severe pre-capillary pulmonary hypertension (mPAP 48 mm Hg [IQR 40–57] in COMPERA and 54 mm Hg [46–64] in ASPIRE) and most had a moderately impaired exercise capacity.

Compared with patients with classical IPAH, patients with IPAH and a lung phenotype were older (median age

	Classical IPAH (n=185)	Classical IPAH *vs* IPAH with a lung phenotype p value	IPAH with a lung phenotype (n=139)	IPAH with a lung phenotype *vs* group 3.1 or 3.2 pulmonary hypertension p value	Group 3.1 or 3.2 pulmonary hypertension (n=375)
CT available	109 (59%)	0·59	86 (62%)	0·48	219 (58%)
CT fibrosis, any present	9 (8%)	<0·0001	26 (30%)	0·0093	102 (47%)
CT fibrosis by severity	..	<0·0001	..	<0·0001	..
None	100 (93%)	..	60 (71%)	..	117 (57%)
Mild	6 (6%)	..	21 (25%)	..	21 (10%)
Moderate	1 (1%)	..	4 (5%)	..	33 (16%)
Severe	0	..	0	..	36 (17%)
CT emphysema, any present	15 (14%)	<0·0001	42 (49%)	0·070	132 (60%)
CT emphysema by severity	..	<0·0001	..	<0·0001	..
None	94 (89%)	..	44 (52%)	..	87 (41%)
Mild	11 (10%)	..	22 (26%)	..	21 (10%)
Moderate	1 (1%)	..	16 (19%)	..	62 (30%)
Severe	0	..	3 (4%)	..	40 (19%)

Data are n (%). Statistical comparisons were made by Pearson's χ^2 test or Fisher's exact test. Percentages for fibrosis and emphysema severity were calculated for those patients who had their severity score available in their original report (appendix pp 4–5). IPAH=idiopathic pulmonary arterial hypertension.

Table 2 **Lung parenchymal abnormalities on chest CT (ASPIRE)**

of about 70 years) and more often male. Per the inclusion criteria, all patients were smokers, and the median tobacco exposure was 40 pack years (IQR 21–50) in COMPERA and 30 pack years (IQR 20–40) in ASPIRE. Forced vital capacity (FVC) and forced expiratory volume in 1s (FEV_1) were mostly normal. However, the DLCO was severely reduced (30% of the predicted value [IQR 24–36] in COMPERA and 27% [IQR 22–34] in ASPIRE), and the patients were more hypoxaemic than patients with a classical phenotype (data available from COMPERA only). These patients also had severe pulmonary hypertension with a mPAP of 43 mm Hg (IQR 36–51) in COMPERA and 49 mm Hg (43–56 mm Hg) in ASPIRE. Hence, mPAP was slightly less elevated in patients with IPAH and a lung phenotype than in patients with classical IPAH, but the severity of haemodynamic impairment in both groups was comparable from a clinical perspective. Still, exercise capacity was much lower in patients with IPAH and a lung phenotype than in patients with classical IPAH.

Patients with group 3 pulmonary hypertension had a similar age to patients with IPAH and a lung phenotype and had nearly the same age distribution as well as a comparable male to female ratio (figure 2). 212 (81%) of 262 with available data had a smoking history with a median of 40 pack years (IQR 30–60; data available for COMPERA only). FVC and FEV_1 were lower than in patients with IPAH and a lung phenotype, but most patients did not have severely impaired pulmonary function, except for a very low DLCO (26% of the predicted value [IQR 20–35] in COMPERA and 25% [IQR 19–32] in ASPIRE). Blood gas analyses showed marked hypoxaemia (data available from COMPERA only), comparable to patients with IPAH and a lung phenotype. mPAP and PVR were lower than in the other cohorts but still much elevated compared with reference range. The degree of exercise limitation was similar to patients with IPAH and a lung phenotype.

Data on chest CT studies were available from ASPIRE. In classical IPAH, of the 109 patients with available data fibrotic changes were found in nine (8%) patients and emphysematous changes were found in 15 (14%) patients. In IPAH and a lung phenotype, of the 86 patients with available data fibrotic changes were found in 26 (30%) patients and emphysematous changes were found in 42 (49%) patients. In group 3 pulmonary hypertension, of the 219 patients with available data fibrotic changes were found in 102 (47%) patients and emphysematous changes were found in 132 (60%) patients (table 2).

In COMPERA the first follow-up visit took place 4·7 months (IQR 3·5–6·6) after baseline. Functional class, 6MWD, NT-proBNP and mortality risk at baseline and first follow-up are shown in figure 3. In patients with classical IPAH, functional class improved by at least one class in 54 (53·5%) of 101 patients with available data; the median change in 6MWD was 62·5 m (IQR 16·5 to 115·5; p=0·0015 for classical IPAH *vs* IPAH and a lung phenotype, and p=0·64 for IPAH and a lung phenotype *vs* group 3 pulmonary hypertension); NT-proBNP changed by –58·1% (IQR –85·2 to 6.0), and risk improved by at least one category in 75 (63·6%) of 118 patients. In patients with IPAH and a lung phenotype, functional class improved by at least one class in 52 (26·3%) of 198 patients with available data; the change in 6MWD was 24·5 m (IQR –10·0 to 76.8); NT-proBNP changed by –27·2% (IQR –64·4 to 17·9), and risk improved by at least one category in 75 (32·2%) of 233 patients. In patients with group 3 pulmonary hypertension, functional class improved by at least one class in 141 (21·5%) of 655 patients with available data (p<0·0001 for classical IPAH *vs* IPAH

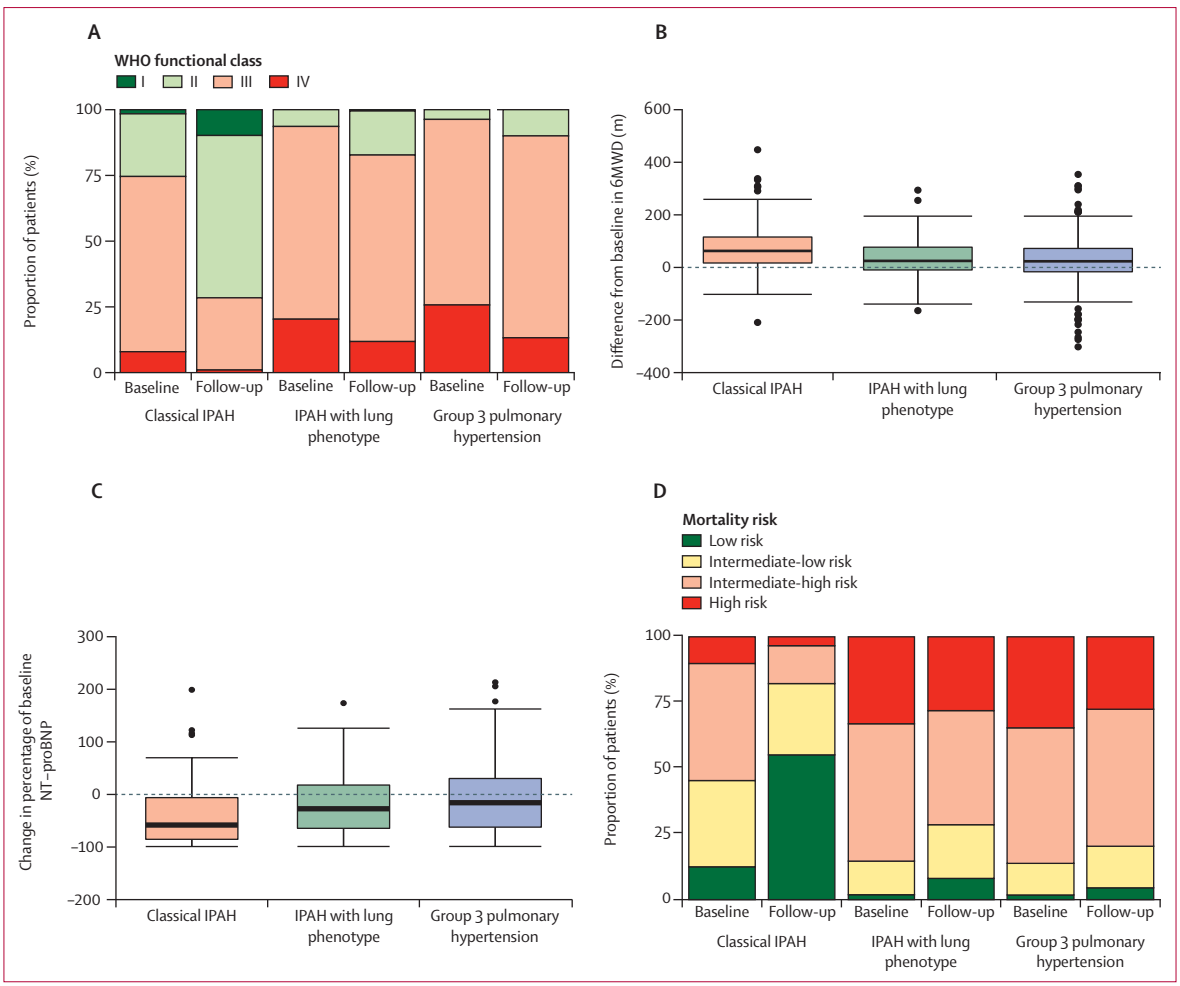

Figure 3: **Baseline and first follow-up measurement for functional class (A), 6MWD (B), NT-proBNP (C), and mortality risk (D) in COMPERA in patients with classical IPAH, IPAH with a lung phenotype, and patients with group 3 pulmonary hypertension**

(A) Bar graphs of WHO functional class at baseline and first follow-up after treatment initiation. (B) Box plots depicting the changes in 6MWD from baseline to first follow-up. (C) Box plots depicting the changes in NT-proBNP from baseline to first follow-up. (D) Bar graphs of mortality risk assessed by the European Society of Cardiology and European Respiratory Society 4-strata model at baseline and first follow-up after treatment initiation. COMPERA=Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension. IPAH=idiopathic pulmonary arterial hypertension. 6MWD=6-minute walking distance. NT-proBNP=N-terminal fragment of pro-brain natriuretic peptide.

and a lung phenotype, and p=0·194 for IPAH and a lung phenotype *vs* group 3 pulmonary hypertension); the change in 6MWD was 23·0 m (IQR –17·0 to 72·0); NT-proBNP changed by –15·7% (IQR –62·1 to 30·4; p=0·0043 for classical IPAH *vs* IPAH and a lung phenotype, and p=0·14 for IPAH and a lung phenotype *vs* group 3 pulmonary hypertension), and risk improved by at least one category in 208 (28·7%) of 726 patients (p<0·0001 for classical IPAH *vs* IPAH and a lung phenotype, and p=0·343 for IPAH and a lung phenotype *vs* group 3 pulmonary hypertension). Hence, in all categories, patients with classical IPAH improved most, whereas there were fewer and quantitatively similar changes in the two other cohorts.

In COMPERA, the median observation time was 3·9 years (IQR 1·8–6·6) for patients with classical IPAH, 2·0 years (IQR 1·2–3·4) for patients with IPAH and a lung phenotype, and 1·7 years (IQR 0·7–3·3) for patients with group 3 pulmonary hypertension. In the cohort of 128 patients with classical IPAH, 23 (18%) patients died, five (4%) underwent lung transplantation, and eight (6%) were lost to follow up. For the 268 patients with IPAH and a lung phenotype 138 (52%) patients died, five (2%) underwent lung transplantation, and 13 (5%) were lost to follow up. Among the 910 patients with group 3 pulmonary hypertension, 583 (64%) died, 22 (2%) underwent lung transplantation, and 46 (5%) were lost to follow-up.

In ASPIRE, the median observation time was 4·5 years (IQR 2·1–7·8) for patients with classical IPAH, 1·7 years (IQR 0·9–2·8) for patients with IPAH and a lung phenotype, and 1·4 years (IQR 0·6–3·1) for patients with group 3 pulmonary hypertension. No patients were lost to follow-up. In the cohort of 185 patients with classical IPAH, 42 (23%) patients died and seven (4%) underwent

lung transplantation. Of the 139 patients with IPAH and a lung phenotype 90 (65%) died, and none underwent lung transplantation. Among the 375 patients with group 3 pulmonary hypertension, 286 (76%) died and five (1%) underwent lung transplantation.

In both registries, the survival rates of patients with idiopathic PAH with a lung phenotype and of patients with group 3 pulmonary hypertension were comparable and both much inferior to the survival rate of patients with classical IPAH (figure 4).

In COMPERA, the Kaplan-Meier estimated survival rates of patients with classical IPAH was 95% at 1 year, 90% at 3 years, and 84% at 5 years. In patients with IPAH and a lung phenotype the estimated survival was 89% at 1 year, 49% at 3 years, and 31% at 5 years. In patients with group 3 pulmonary hypertension, the survival rates were 78% at 1 year, 43% at 3 years, and 26% at 5 years. The unadjusted survival rates differed significantly between patients with classical IPAH and IPAH with a lung phenotype (p<0·0001) and between patients with IPAH with a lung phenotype and patients with group 3 pulmonary hypertension (p=0·016; figure 4A). When adjusted for age and sex, the risk of death remained much higher for patients with IPAH and a lung phenotype than for patients with classical IPAH (hazard ratio [HR] 3·48 [95% CI 2·04–5·95], p<0·0001). The survival difference between patients with IPAH and a lung phenotype and patients with group 3 pulmonary hypertension was smaller albeit still statistically significant (HR 0·79 [95% CI 0·66–0·96], p=0·015).

In ASPIRE, the Kaplan-Meier estimated survival rates of patients with classical IPAH was 98% at 1 year, 91% at 3 years, and 80% at 5 years. In patients with IPAH and a lung phenotype, survival was 79% at 1 year, 35% at 3 years, and 21% at 5 years. In patients with group 3 pulmonary hypertension, survival rates were 64% at 1 year, 32% at 3 years, and 18% at 5 years. The unadjusted survival rates differed significantly between patients with classical IPAH and IPAH with a lung phenotype (p<0·0001) and between patients with IPAH with a lung phenotype and patients with group 3 pulmonary hypertension (p=0·045; figure 4B). When adjusted for age and sex, the risk of death remained much higher for patients with IPAH and a lung phenotype than for patients with classical IPAH (HR 3·61 [95% CI 2·35–5·54]). The survival difference between patients with IPAH and a lung phenotype and patients with group 3 pulmonary hypertension was smaller but still statistically significant (HR 0·74 [95% CI 0·58–0·94], p=0·010).

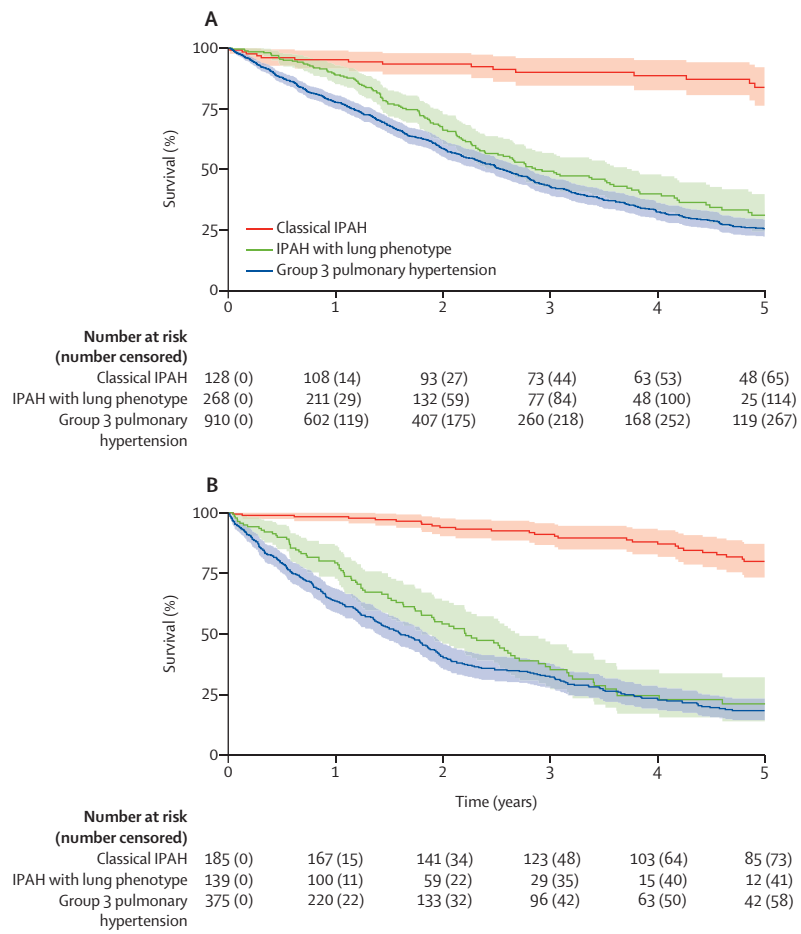

Figure 4: **Kaplan-Meier survival estimates for patients classified as classical IPAH, IPAH with a lung phenotype, and group 3 pulmonary hypertension in COMPERA (A) and ASPIRE (B)**
ASPIRE=Assessing the Spectrum of Pulmonary Hypertension Identified at a Referral Centre. COMPERA=Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension. IPAH=idiopathic pulmonary arterial hypertension.

Discussion

The key finding of this analysis was that patients diagnosed with IPAH and a lung phenotype defined by a smoking history and a low DLCO had little in common with classical IPAH patients, except for severe pre-capillary pulmonary hypertension, having similar baseline characteristics, treatment response, and survival as patients with group 3 pulmonary hypertension. These findings highlight a problem of the current diagnostic classification of patients with a low DLCO and no or mild parenchymal lung disease, which are classified as IPAH according to current guidelines, when in fact they phenotypically resemble patients with group 3 pulmonary hypertension.

In the present cohorts, patients categorised as classical IPAH resembled those originally described as primary pulmonary hypertension—ie, predominantly young, otherwise healthy females.[3] In our study, these patients had around an 80% survival rate 5 years after diagnosis, which is about twice as high as in historical controls,[15] presumably owing to therapeutic advances. However, the classical form has become the least common phenotype of IPAH, at least in most European countries, where IPAH is now being diagnosed predominantly in older patients with comorbidities.[6,10] These older patients continue to have a

high mortality risk.[10] In older patients with comorbidities, the diagnostic classification can be challenging. This problem is illustrated by our cohorts of patients diagnosed with IPAH who presented with a lung phenotype. Most of these patients with a lung phenotype had normal or near-normal static and dynamic lung function parameters, and, where available, the majority had a mild degree of parenchymal involvement, but severe pre-capillary pulmonary hypertension. Hence, the diagnosis of IPAH was in accordance with current guidelines.[1,16]

When we compared patients with IPAH and a lung phenotype with patients classified as group 3 pulmonary hypertension (pulmonary hypertension associated with either COPD or interstitial lung disease, 81% of whom were smokers), we found striking similarities. Age distribution and male-to-female ratio were comparable as were functional class and 6MWD. The same was true for the prevalence of risk factors for left heart disease such as hypertension, coronary heart disease, diabetes, or obesity, which might have contributed to the development of pulmonary hypertension. Patients with IPAH and a lung phenotype and patients classified as group 3 pulmonary hypertension had a similar response to medical therapy—ie, comparable changes from baseline to first follow up in functional class, 6MWD, NT-proBNP, and mortality risk. Taken together, patients with IPAH and a lung phenotype resembled those of patients with group 3 pulmonary hypertension; however, they had little in common with classical IPAH, except for the presence of severe pre-capillary pulmonary hypertension. Nonetheless, a comparison of the baseline characteristics of patients with IPAH and a lung phenotype and patients with group 3 pulmonary hypertension showed differences in lung function, suggesting that these are not the same patient populations.

As in previous studies,[7,8,12] a DLCO of 45% or more or a DLCO of less than 45% of the predicted value discriminated between patients with classical IPAH and patients with IPAH and a lung phenotype. It is unknown whether the low DLCO in patients with IPAH and a lung phenotype is caused by parenchymal abnormalities or by a distinct pulmonary vasculopathy involving the loss of small pulmonary vessels, for which the term vanishing pulmonary capillary syndrome has been proposed.[17] In mice models, prolonged exposure to tobacco smoke causes endothelial cell apoptosis in pulmonary capillaries, which precedes the development of emphysema.[18] Most of the patients diagnosed with IPAH and a low DLCO are older individuals with a history of heavy smoking (which might also explain the male predominance of this phenotype). We therefore speculate that in these patients, smoking might have been a contributor to the development of pulmonary hypertension, or even its main cause. Additionally, it is possible that the pulmonary vasculopathy of patients with IPAH and a lung phenotype and patients with group 3 pulmonary hypertension is similar, yet distinct from classical IPAH.

Our findings have implications not only for the diagnostic classification but also for therapeutic considerations. We have insufficient data on the safety and efficacy of PAH drugs in patients diagnosed with IPAH who present with a lung phenotype. None of the pivotal trials of globally approved PAH drugs reported the DLCO of their participants.[19–27] This absence of data is particularly worrisome when considering a recent study showing that PAH drugs might further impair gas exchange in patients with a low DLCO.[28] Moreover, our data suggested that the response to therapy in patients with IPAH and a lung phenotype was reduced compared with patients with classical IPAH, but it is unclear if this was due to a distinct pulmonary vasculopathy, less aggressive therapy, or comorbidities leaving little room for functional improvement.

It is important to note that IPAH with a low DLCO might also be found in patients who have never smoked. Such patients might have various conditions such as unrecognised pulmonary veno-occlusive disease or connective tissue disease. A similar disease phenotype has been reported in patients who have been exposed to organic solvents,[29] and in some forms of heritable PAH.[30]

Limitations of the present study include its post-hoc nature, missing values, absence of imaging data in COMPERA, and heterogeneities between the two registries. We also acknowledge the possibility of a selection bias in group 3 pulmonary hypertension introduced by COMPERA including only patients who received treatment with drugs approved for PAH. Notably, ASPIRE included all consecutive patients diagnosed with pulmonary hypertension and did not restrict inclusion to patients who received treatment with medications approved for PAH, but the key findings were still comparable between COMPERA and ASPIRE, suggesting that the treatment bias introduced in COMPERA had no substantial effect on the overall results. Additionally, even though all patients were evaluated at referral centres, we cannot fully exclude the possibility that misclassification bias might have interfered with our analysis, especially as a small proportion of patients diagnosed as IPAH had more than mild lung function test or CT abnormalities. Furthermore, for the present analysis, patients with IPAH were highly selected to ensure a proper phenotypic characterisation, and the results might not be generalisable to patients with mixed phenotypes.

In conclusion, patients diagnosed with IPAH who present with a lung phenotype have much more features of group 3 pulmonary hypertension rather than classical IPAH. These observations challenge the current diagnostic classification of pulmonary hypertension, and we propose to add a phenotypic component to the classification of unexplained pre-capillary pulmonary hypertension taking into account smoking history, DLCO, chest CT findings, and risk factors for left heart disease. Additionally, further data are needed on the

safety and efficacy of PAH drugs in these patients, and future clinical trials on PAH should collect and report data on smoking status and DLCO of their participants. Finally, our observations support the hypothesis that there is a distinct smoking-related pulmonary vasculopathy, which needs to be further investigated.

Contributors

MMH, CP, DH, DP, and MHa designed the first part of the study (COMPERA). DGK, RC, RAL, and KD co-designed the second part of the study (ASPIRE). MMH, CP, and DH accessed and verified the COMPERA data. DGK, RC, RAL, and KD accessed and verified the ASPIRE data. CP and DH were responsible for the statistical analyses of the COMPERA database. KD and DGK were responsible for the statistical analyses of the ASPIRE data base. MMH takes responsibility for the integrity of all data. All authors collected and interpreted the data. MMH, CP, and MHa wrote the first draft of the manuscript. All authors critically reviewed and revised the manuscript and approved the final version for publication. All authors had full access to the study data and had final responsibility for the decision to submit for publication.

Declaration of interests

MMH received fees for lectures or consultations from Acceleron, Actelion, Bayer, GlaxoSmithKline, Janssen, MSD, and Pfizer. KD has received research funding from Janssen Pharmaceuticals, National Institute of Health Research (NIHR), UK and The Wellcome Trust, UK. RAL has received honoraria and research grants from Janssen Pharmaceuticals. KMO has received fees for lectures or consultations from Acceleron, Actelion, Bayer, GlaxoSmithKline, Janssen, MSD, Pfizer, and United Therapeutics. DH has received travel compensation from Shire. DP has received fees for consultations from Actelion, Amgen, Aspen, Bayer, Biogen, Boehringer Ingelheim, Daiichi Sankyo, MSD, Novartis, Sanofi-Genzyme, Takeda and Viatris. EG has received fees for lectures or consultations from Actelion, Bayer, GlaxoSmithKline, Janssen, MSD, Pfizer, and United Therapeutics. GS has received honoraria for lectures or consultancy for Actelion, Bayer, GlaxoSmithKline, Novartis, and Pfizer. 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Data sharing

Data collected for the COMPERA study, including deidentified individual patient data and a data dictionary defining each field in the set, will be available for 24 months after the Article publication for analysis to researchers who provide a methodologically sound and ethically approved proposal, to achieve aims in that proposal. The COMPERA Steering Committee will assess each proposal and decide within 3 months after submission. Related study documents will be made available (protocol, informed consent sheets, data collection form, statistical analysis plan, data management plan). A data access agreement needs to be signed before data sharing. Requests for data sharing should be submitted to the corresponding author. The ASPIRE registry is an ethically approved research database managed by Sheffield Teaching Hospitals NHS Foundation Trust (STH14169, REC 22/EE/0011). Deidentified data within the ASPIRE registry can be made available for analysis to researchers who

provide a methodologically sound proposal which fits within the aims of the ASPIRE registry. The ASPIRE data management committee will assess each proposal and decide within 3 months after submission. A data access agreement signed by the lead researcher and a data sharing agreement between Sheffield Teaching Hospitals and the recipient institution will be required before data are shared. Information and application forms can be found at https://bit.ly/aspire-registry.

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