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ORIGINAL CLINICAL SCIENCE

Idiopathic pulmonary arterial hypertension phenotypes determined by cluster analysis from the COMPERA registry

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The term idiopathic pulmonary arterial hypertension (IPAH) is used to categorize patients with precapillary pulmonary hypertension of unknown origin. There is considerable variability in the clinical presentation of these patients.

Using data from the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension, we performed a cluster analysis of 841 patients with IPAH based on age, sex, diffusion capacity of the lung for carbon monoxide (DLCO; <45% vs ≥45% predicted), smoking status, and presence of comorbidities (obesity, hypertension, coronary heart disease, and diabetes mellitus). A hierarchical agglomerative clustering algorithm was performed using Ward's minimum variance method. The clusters were analyzed in terms of baseline characteristics; survival; and response to pulmonary arterial hypertension (PAH) therapy, expressed as changes from baseline to follow-up in functional class, 6-minute walking distance, cardiac biomarkers, and risk.

Three clusters were identified: Cluster 1 ($n = 106$; 12.6%): median age 45 years, 76% females, no comorbidities, mostly never smokers, DLCO ≥45%; Cluster 2 ($n = 301$; 35.8%): median age 75 years, 98% females, frequent comorbidities, no smoking history, DLCO mostly ≥45%; and Cluster 3 ($n = 434$; 51.6%): median age 72 years, 72% males, frequent comorbidities, history of smoking, and low DLCO. Patients in Cluster 1 had a better response to PAH treatment than patients in the 2 other clusters. Survival over 5 years was 84.6% in Cluster 1, 59.2% in Cluster 2, and 42.2% in Cluster 3 (unadjusted $p < 0.001$ for comparison between all groups).

The population of patients diagnosed with IPAH is heterogenous. This cluster analysis identified distinct phenotypes, which differed in clinical presentation, response to therapy, and survival.

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Pulmonary arterial hypertension (PAH) consists of heterogenous conditions that share a similar pulmonary arterial vasculopathy and a common therapeutic approach. PAH can be associated with well-defined diseases such as connective tissue disease, HIV infection, liver disease, or congenital heart disease, but the most common form of PAH is idiopathic (IPAH). A diagnosis of IPAH is made once the presence of pre-capillary pulmonary hypertension (PH) has been determined by right heart catheterization and other forms of PH and PAH have been excluded.[1]

Originally, IPAH (formerly known as primary PH) was described as a disease affecting primarily younger females without typical risk factors for cardiopulmonary diseases.[2] Contemporary registries from developing countries have shown a similar pattern.[3,4] However, more recent registries from Europe and the US have demonstrated a change in the demographics of patients diagnosed with IPAH characterized by increasing age and an accompanying surge in cardiopulmonary comorbidities.[5−9]

Comprehensive phenotypic analysis of large cohorts of patients diagnosed with IPAH have not yet been performed. Here, we present data from a cluster analysis of patients diagnosed with IPAH who have been enrolled in the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA). Cluster analysis

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is a data-driven approach that groups subjects into so-called clusters such that the subjects in each cluster are more similar to each other than to those in other clusters. It belongs to the unsupervised statistical learning methods, which means that it can be applied when groups are not known in advance. Few cluster analyses have been performed in patients with PH, but these analyses did not incorporate risk factors for other cardiopulmonary diseases.[10–12]

The primary objective of this investigation was to identify clinical phenotypes of adult patients with IPAH from COMPERA. As secondary objectives, responses to medical therapy and survival were analyzed and compared in the obtained groups.

Methods

Database

Details of COMPERA (www.COMPERA.org; registered at Clinicaltrials.gov under the identifier NCT01347216) have been described previously.[7,13–15] In brief, COMPERA is an ongoing web-based PH registry launched in 2007 that collects baseline, follow-up, and outcome data from patients who receive targeted therapies for PH. Specialized centers from several European countries participate (Austria, Belgium, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Netherlands, Slovakia, Switzerland, United Kingdom), with about 80% of the enrolled patients coming from German PH centers.

Patients

Patients were selected from the COMPERA database using the following criteria: (1) treatment-naive patients newly diagnosed with IPAH between June 1, 2007 and November 11, 2019; (2) mean pulmonary arterial pressure (mPAP) ≥25 mm Hg, pulmonary arterial wedge pressure (PAWP) ≤15 mm Hg, and pulmonary vascular resistance (PVR) >240 dyn·s·cm^{-5} at the time of diagnosis; (3) complete data concerning the parameters selected for clustering (described later); and (4) at least 1 follow-up visit available. Patients with other forms of PH or PAH were excluded, as were patients with hereditary or drug-associated PAH and patients younger than 18 years at diagnosis.

Statistical analyses

Hierarchical agglomerative clustering was performed using Ward's minimum variance method as linkage criterion. For calculation of the pairwise dissimilarities between observations, Gower's formula was used, as it is able to deal with variables of mixed type. The number of clusters was determined to be 3 based on the clinical observations outlined in the introduction. Cluster analysis requires complete data of all patients. The baseline parameters considered in the cluster analysis were age (continuous), sex (dichotomous), smoking history (dichotomous; never vs current/former), diffusion capacity of the lung for carbon monoxide (DLCO) (dichotomous; <45% vs ≥45% of the predicted value),[16,17] and comorbidities (dichotomous; none vs at least 1 of the pre-defined comorbidities: arterial hypertension, coronary heart disease [here, the database just captured whether coronary heart disease was present or not, without further details], diabetes mellitus, and obesity defined by a body mass index [BMI] ≥30 kg/m^2). Secondary cluster analyses were performed with the same parameters but different cut-offs for the numbers of comorbidities, including modified Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension (AMBITION) trial criteria based on <3 vs ≥3 comorbidities.[18] The variables were selected based on their assumed association with disease phenotypes.

Continuous data are presented as mean ± SD or as median and first and third quartile (Q1, Q3), categorical data as number and percentage. Survival was evaluated using Kaplan-Meier analysis, log-rank test, and Cox proportional hazards regression models to adjust for age.

To compare the obtained clusters, Kruskal-Wallis tests and chi-square tests were applied for continuous and categorical data, respectively. If the p-value was < 0.05, Wilcoxon rank sum and chi-square tests were performed to compare the clusters pairwise. Because of the exploratory nature of this study, no adjustment for multiple testing was made.

Response to PAH therapy was determined by changes from baseline to first follow-up (>3 months after treatment initiation). For 6-minute walking distance (6MWD), the difference in meters between first follow-up and baseline measures were calculated. For brain natriuretic peptide (BNP) and N-terminal fragment of probrain natriuretic peptide (NT-proBNP), the change at follow-up in percent of baseline was considered. Changes in functional class (FC) and risk status were summarized in the categories better, stable, and worse, referring to the status at follow-up compared with baseline. Risk status was assessed by the Swedish/COMPERA approach using non-invasive data[15,19] using the cut-off values suggested by the current European Society of Cardiology/European Respiratory Society PH guidelines.[20,21]. All statistical analyses were performed using R version 3.5.2.

Results

Patients and clusters

A flow diagram showing patient selection from the COMPERA database is depicted in Figure 1. Of 2,276 patients with IPAH, 841 (37.0%) patients met the inclusion criteria and were eligible for this study. The baseline characteristics of selected and non-selected patients were similar (Supplementary Table S1, available online at www.jhltonline.org).

The characteristics of the patients in the 3 clusters are presented in Table 1. Cluster 1 consisted of 106 (12.6%) patients with a median age of 45 years and a female to male ratio of approximately 3:1. These patients had none of the pre-specified risk factors for left heart disease. About one third of the patients were former or current smokers with a median of 16 pack years. Lung function was largely normal, and all patients had a DLCO ≥45% of the predicted value.

Cluster 2 was formed of 301 (35.8%) patients. These patients were almost exclusively (98%) females with a median age of 75 years. None of these patients had a smoking history, but almost all (94%) had at least 1 of the pre-specified risk factors for left heart disease.

The largest cluster (Cluster 3; $n = 434$; 51.6%) was formed by predominantly (72%) male patients with a median age of 72 years. As in Cluster 2, most of the patients (91%) in Cluster 3 had risk factors for left heart disease. What discriminated the patients in Cluster 3 from those in Cluster 2 was the male predominance, the high proportion (79%) of patients with a smoking history (median: 33 pack

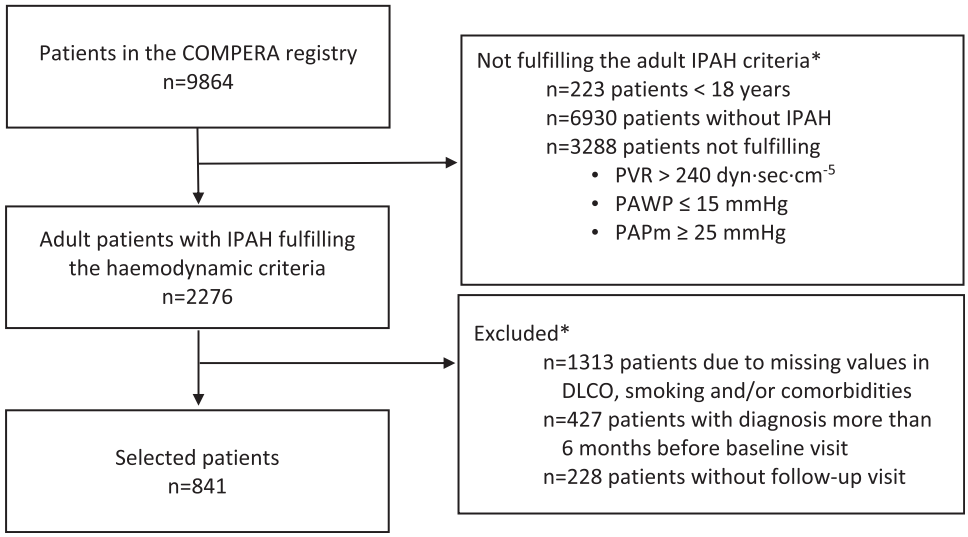

Figure 1 STROBE diagram showing patient selection for the analysis.

*Patients could have had more than 1 reason for not being eligible for this study. COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; DLCO, diffusion capacity of the lung for carbon monoxide; IPAH, idiopathic pulmonary arterial hypertension; PAPm, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; STROBE, STrengthening the Reporting of OBservational studies in Epidemiology.

years), and the large amount (53%) of patients with a DLCO <45% of the predicted value.

When the cluster analysis was repeated based on the presence of <3 vs ≥3 risk factors for left heart disease as done in the AMBITION study,[18,22] it was not possible to obtain distinct phenotypes. Even when we used <2 vs ≥2 risk factors for left heart disease as discriminators, cluster analysis did not discriminate well between phenotypes (Supplementary Tables S3 and S4, Supplementary Figures S1 and S2) online.

Clinical features at baseline

Besides the differences in age, sex, comorbidities, and smoking pattern described previously, there were distinct baseline features among the 3 clusters (Table 1 and Supplementary Table S2 online). All 3 clusters were characterized by severe pre-capillary PH. Pulmonary function expressed as total lung capacity (TLC), forced vital capacity (FVC), and forced expiratory volume in 1 second (FEV_1) was in the normal range in all 3 clusters but with the lowest numbers in Cluster 3; patients in this cluster also had lower arterial oxygen tension values than patients in the 2 other clusters.

The proportion of patients with a history of atrial fibrillation was 8%, 36%, and 25%, respectively, in Clusters 1, 2, and 3. When comparing baseline characteristics across clusters, patients with a history of atrial fibrillation were older and had a higher prevalence of comorbidities than patients without atrial fibrillation (Supplementary Table S5) online.

PAH therapy and treatment response

Table 2 shows PAH treatments according to clusters. Patients in Cluster 1 were treated predominantly with phospodiesterase-5 inhibitors and/or endothelin receptor antagonists. Combinations of PAH therapies were used in 38% of the patients within the first 3 months of diagnosis (between 2007 and 2014, the proportion of patents receiving initial combination therapy in this cluster was 26.5%; between 2015 and 2019, the corresponding figure was 49.0%). After 1 year, 63% of these patients were receiving combination therapies. Patients in Clusters 2 and 3 were predominantly treated with phospodiesterase-5 inhibitor monotherapy, both at baseline and at follow-up. Combinations of PAH drugs were used in 13% and 15% of the patients in Cluster 2 and Cluster 3, respectively, at baseline and in 28% and 39% of the patients in Cluster 2 and Cluster 3, respectively, at follow-up.

Treatment responses assessed by changes in 6MWD and BNP/NT-proBNP from baseline to follow-up are shown in Figure 2. The 6MWD increased by 85 ± 87 m in Cluster 1, by 20 ± 73 m in Cluster 2, and by 37 ± 78 m in Cluster 3.

BNP/NT-proBNP levels declined from baseline to follow-up by a median of 54% (interquartile range [IQR]: −11% to −80%) in Cluster 1, by 6% (IQR: −46% to +39%) in Cluster 2, and by 23% (IQR: -55 to +16%) in Cluster 3.

FC improved in 51% of patients in Cluster 1, remained stable in 48%, and worsened in 1%. In Cluster 2, FC improved in 33%, remained stable in 63%, and worsened in 4% of the patients. In Cluster 3, FC improved in 36%, remained stable in 60%, and worsened in 4% of the patients.

Risk, as assessed by the Swedish/COMPERA approach, improved substantially in Cluster 1 patients but to a much lesser extent in Cluster 2 and Cluster 3 patients (Figure 3).

Survival

Survival rates at 1, 3, and 5 years in Cluster 1 were 93.7%, 88.4%, and 84.6%, respectively; 93.5%, 75.7%, and 59.2%,

Table 1 Patient Characteristics at the Time of IPAH Diagnosis

Characteristic	Cluster 1 $n = 106$	Cluster 2 $n = 301$	Cluster 3 $n = 434$	p-value[a]	All $n = 846$
Age, years (median, Q1–Q3)	45 (31–61)	75 (68–80)	72 (64–78)	<0.001	72 (61–78)
Female sex, *n* (%)	80 (76)	296 (98)	121 (28)	<0.001	497 (59)
BMI, kg/m^2 (mean ± SD)	24.2 ± 3.2	30.7 ± 7.2	29.1 ± 5.9	<0.001	29.1 ± 6.5
Smoking habits					
Former/current smokers, *n* (%)	33 (31)	0 (0)	343 (79)	<0.001	376 (44)
Pack years (median, Q1–Q3)	16 (10–28)	—	33 (20–50)	<0.001	30 (15–50)
WHO FC				<0.001	
I/II, *n* (%)	20 (19)	20 (7)	25 (6)		65 (8)
III, *n* (%)	75 (72)	215 (72)	311 (76)		601 (74)
IV, *n* (%)	9 (9)	63 (21)	72 (18)		144 (18)
6MWD, m (mean ± SD)	386 ± 119	268 ± 114	276 ± 108	<0.001	287 ± 118
BNP, ng/l (median, Q1–Q3)	129 (81–259)	206 (92–299)	278 (112–468)	0.183	206 (101–371)
NT-proBNP, ng/l (median, Q1–Q3)	1,313 (524–2,480)	1,579 (676–3,520)	1,835 (634–3,592)	0.065	1,614 (631–3,460)
Hemodynamics					
RAP, mm Hg (mean ± SD)	7 ± 5	8 ± 5	8 ± 4	0.026	8 ± 5
mPAP, mm Hg (mean ± SD)	49 ± 14	40 ± 11	43 ± 11	<0.001	42 ± 12
PAWP, mm Hg (mean ± SD)	8 ± 3	10 ± 3	9 ± 4	<0.001	9 ± 3
CI, l/min/m^2 (mean ± SD)	2.1 ± 0.7	2.0 ± 0.6	2.1 ± 0.7	0.471	2.1 ± 0.7
PVR, dyn·s·cm^{-5} (mean ± SD)	948 ± 463	727 ± 398	730 ± 380	<0.001	756 ± 404
SvO_2, % (mean ± SD)	64 ± 10	64 ± 8	62 ± 8	<0.001	63 ± 8
Pulmonary function and blood gases					
TLC, % predicted (mean ± SD)	99 ± 16	93 ± 17	92 ± 17	<0.001	93 ± 17
FVC, % predicted (mean ± SD)	92 ± 17	83 ± 18	80 ± 20	<0.001	82 ± 20
FEV1, % predicted (mean ± SD)	87 ± 17	80 ± 19	75 ± 20	<0.001	78 ± 19
DLCO, % predicted (mean ± SD)	69 ± 15	56 ± 22	47 ± 21	<0.001	53 ± 22
DLCO <45% predicted, *n* (%)	0 (0)	101 (34)	231 (53)	<0.001	332 (40)
paO_2, mm Hg (mean ± SD)	77 ± 17	65 ± 11	61 ± 12	<0.001	65 ± 14
$paCO_2$, mm Hg (mean ± SD)	33 ± 4	36 ± 6	36 ± 7	<0.001	35 ± 6
Comorbidities					
Arterial hypertension, *n* (%)	0 (0)	251 (83)	320 (74)	<0.001	571 (68)
Coronary heart disease, *n* (%)	0 (0)	58 (19)	153 (35)	<0.001	211 (25)
Diabetes mellitus, *n* (%)	0 (0)	106 (35)	154 (36)	<0.001	260 (31)
BMI ≥30 kg/m^2, *n* (%)	0 (0)	149 (50)	170 (39)	<0.001	319 (38)
At least 1 comorbidity	0 (0)	283 (94)	396 (91)	<0.001	679 (81)
Number of comorbidities				<0.001	
0, *n* (%)	106 (100)	18 (6)	38 (9)		162 (19)
1, *n* (%)	0 (0)	93 (31)	138 (32)		231 (28)
2, *n* (%)	0 (0)	116 (38)	139 (32)		255 (30)
3, *n* (%)	0 (0)	57 (19)	95 (22)		152 (18)
4, *n* (%)	0 (0)	17 (6)	25 (6)		41 (5)
History of atrial fibrillation, *n* (%)	8 (8)	109 (36)	108 (25)	<0.001	225 (27)

6MWD, 6-minute walking distance; BMI, body mass index; BNP, brain natriuretic peptide; CI, cardiac index; DLCO, diffusion capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IPAH, idiopathic pulmonary arterial hypertension; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal fragment of probrain natriuretic peptide; $paCO_2$, arterial carbon dioxide tension; paO_2, arterial oxygen tension; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SvO_2, mixed-venous oxygen saturation; TLC, total lung capacity; WHO FC, World Health Organization Functional Class.

Categorical data are shown as *n* and % of the respective population. Continuous data are depicted as mean ± SD or median (Q1–Q3).

[a]Comparison of the 3 groups by Kruskal-Wallis test for continuous variables and chi-square test for binary variables. Detailed information on *p*-values between each group can be obtained from the online supplement.

respectively, in Cluster 2; and 90.0%, 61.9%, and 42.2%, respectively, in Cluster 3 (Figure 4). The unadjusted differences between the groups were statistically significant ($p < 0.0001$). When adjusted for age, the differences between Clusters 1 and 3 and Clusters 2 and 3 remained significant ($p = 0.005$ and $p < 0.001$, respectively), whereas the survival difference between Clusters 1 and 2 was no longer statistically significant.

A sensitivity analysis including only patients without a history of atrial fibrillation showed similar results (Supplementary Table S6 and Supplementary Figure S3).

Discussion

This study confirms that the population of patients diagnosed with IPAH is heterogeneous. Our cluster analysis

Table 2 PAH Therapies According to Clusters

Therapy	Cluster 1 $n = 106$	Cluster 2 $n = 306$	Cluster 3 $n = 434$	All $n = 846$
PAH medication within 3 months after diagnosis				
Calcium channel blocker monotherapy, *n* (%)	16 (16)	3 (1)	5 (1)	24 (3)
PDE5i or sGC stimulators, *n* (%)	76 (76)	257 (90)	358 (86)	691 (86)
ERA, *n* (%)	43 (43)	59 (21)	108 (26)	210 (26)
PCA, *n* (%)	5 (5)	7 (2)	6 (1)	18 (2)
Combination therapies, *n* (%)	38 (38)	38 (13)	63 (15)	139 (17)
PAH medication at 1 year after diagnosis				
Calcium channel blocker monotherapy, *n* (%)	17 (16)	3 (1)	5 (1)	25 (3)
PDE5i or sGC stimulators, *n* (%)	63 (81)	193 (86)	277 (86)	533 (85)
ERA, *n* (%)	50 (64)	74 (33)	144 (45)	268 (43)
PCA, *n* (%)	9 (12)	16 (7)	18 (6)	43 (7)
Combination therapies, *n* (%)	49 (63)	62 (28)	125 (39)	236 (38)

ERA, endothelin receptor antagonists; PAH, pulmonary arterial hypertension; PCA, prostacyclin analog (including prostacyclin receptor agonists); PDE5i, phosphodiesterase-5 inhibitor; sGC, soluble guanylate cyclase.

identified 3 distinct cohorts: (1) patients with a classical IPAH phenotype (Cluster 1) characterized by relatively young age, female predominance, absence of pre-defined risk factors for cardiopulmonary disease, and preserved DLCO; (2) patients with a heart failure with preserved ejection fraction (HFpEF)-like phenotype (Cluster 2), that is, mostly elderly women with abundant risk factors for left heart disease but without a history of smoking, most of them presenting with preserved DLCO; and (3) patients with a cardiopulmonary phenotype (Cluster 3), consisting of mostly elderly men with a history of smoking who presented with abundant risk factors for left heart disease but also with low DLCO. Patients in the 3 clusters not only differed in demographics and comorbidities but also showed a different response to PAH therapy and different survival rates. It remains unclear whether these differences were related to the pulmonary vascular disease itself or to other factors, such as different treatment strategies or comorbidities.

Patients with the classical IPAH phenotype formed only 12.5% of our cohort. This low number resulted from our strategy of identifying patients without pre-specified risk factors for left heart disease. About 30% of these patients had a history of tobacco smoking, which is in line with the proportion of smokers in Europe[23]. The median number of pack years was 16, making it unlikely that smoking had contributed in a clinically relevant manner to the pulmonary vasculopathy of these patients. Patients in Cluster 1 were slightly older but otherwise comparable to the US National Institutes of Health cohort of patients with primary PH described in 1987.[2] Compared with the other clusters, patients in Cluster 1 were younger and presented with higher levels of mPAP and PVR at baseline but showed the best response to medical therapy and had the highest (unadjusted) survival rates. However, when adjusted for age, the survival difference between Clusters 1 and 2 was no longer statistically significant.

Cluster 2 consisted almost exclusively of elderly women with a median age of 75 years who had no smoking history but multiple other risk factors for left heart disease. These patients presented with an HFpEF phenotype,[24,25] yet they fulfilled the diagnostic criteria of IPAH including the presence of pre-capillary PH with a PAWP of 10 ± 3 mm Hg. Still, it is likely that many of these patients pathogenetically had Group 2 PH, that is, PH because of left heart disease rather than classical IPAH. It is well known that PAWP at rest can be normal in these patients.[26,27] Data on hemodynamics during exercise or volume challenge that might provide additional diagnostic information[25]) were not available.

Attempting to distinguish between patients with IPAH with a classical phenotype and those with an HFpEF phenotype, the AMBITION study introduced an arbitrary cut-off of <3 vs ≥ 3 pre-specified comorbidities.[18,22] When applying this strategy to this cluster analysis, we lost the phenotypic discrimination between the clusters. Based on these data, we doubt that the AMBITION strategy is well suited to distinguish patients with a classical IPAH phenotype from those with a left heart disease phenotype. Our cluster analysis yielded a clean population of patients with classical IPAH only when we distinguished between patients with or without any risk factors for left heart disease. These observations may be considered when planning future clinical trials.

The third and largest (51.6%) cluster of patients was also the most complex; in terms of age, the patients were comparable to Cluster 2 (median age: 72 vs 75 years). The patients in Cluster 3 also had abundant risk factors for left heart disease. However, in contrast to the 2 other clusters, patients in Cluster 3 were predominantly male, and most of them had a history of smoking. Although lung function measured by TLC, FVC, and FEV_1 was normal, DLCO and arterial oxygen tension were lower than in the 2 other clusters. Similar to the patients in Cluster 2, patients in Cluster 3 fulfilled the current diagnostic criteria for IPAH. However, these patients appeared to have at least 2 additional components contributing to the development of PH, that is, an abundance of risk factors for left heart disease similar to Cluster 2 with an additional smoking-associated pulmonary vasculopathy.

The concept of a smoking-associated pulmonary vasculopathy is relatively new. In mice exposed to tobacco smoke,

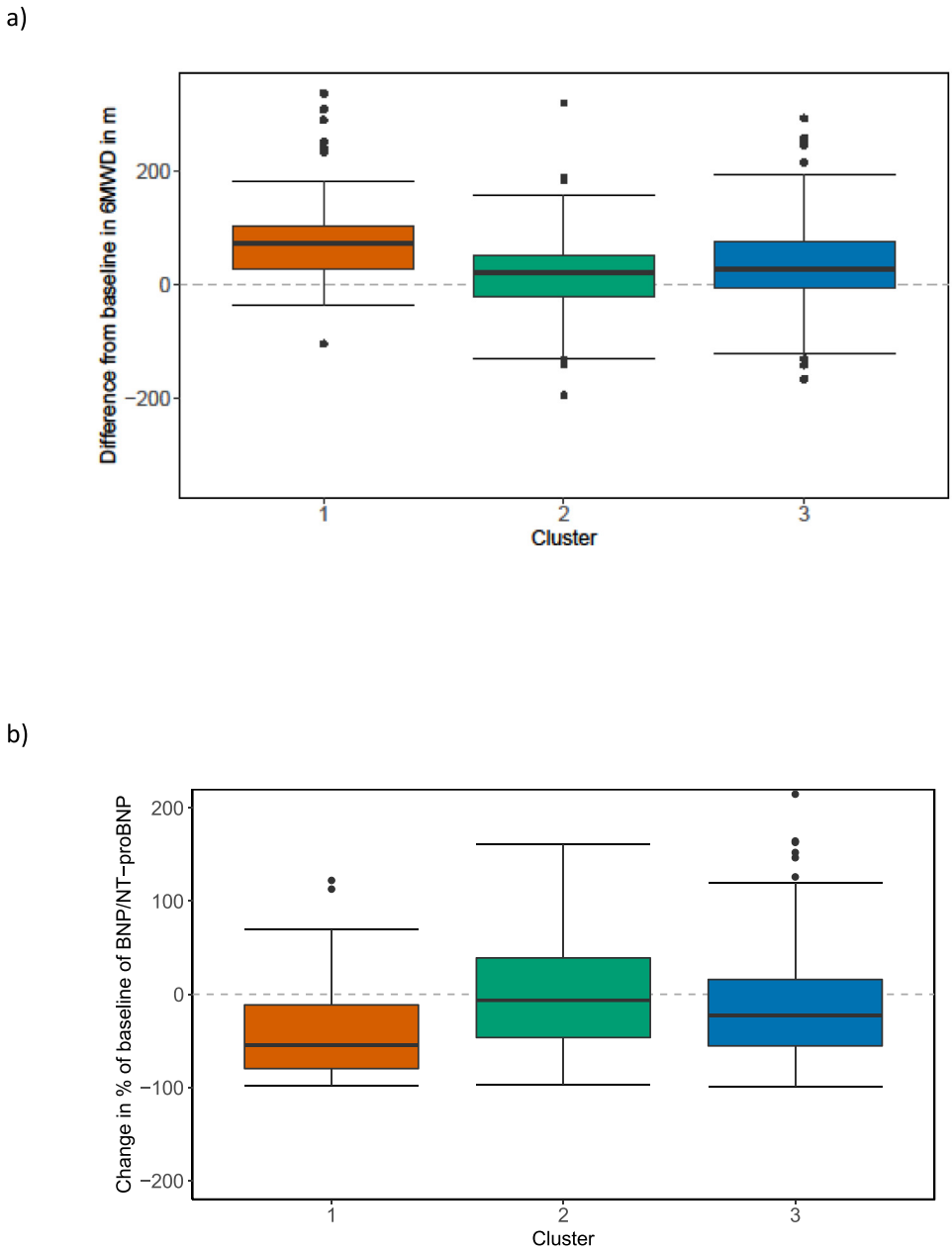

Figure 2 Changes from baseline to first follow-up in (a) 6MWD (difference in m) and (b) BNP/NT-proBNP (%) (20 outliers > 200% in Clusters 2 and 3 are not depicted). 6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; NT-proBNP, N-terminal fragment of probrain natriuretic peptide.

a loss of pulmonary capillaries because of apoptosis precedes the development of emphysematous changes.[28] It has been proposed that a similar pulmonary small vessel pathology may develop in patients with a history of smoking.[16, 29–31] Apparently, this pulmonary vasculopathy can develop in patients with or without clinical and radiological signs of parenchymal lung disease.[29] Patients in Cluster 3 had a particularly poor survival, which is consistent with previous reports on patients with IPAH and low DLCO.[16,29,31] Further studies are needed to delineate the mechanisms underlying the survival differences between the clusters.

PAH treatments varied between the clusters. Combinations of PAH drugs were used much more frequently in Cluster 1 than in the 2 other clusters. Patients receiving calcium channel blocker monotherapy were found almost exclusively in this cluster. Treatment response in terms of improving 6MWD, FC, BNP/NT-proBNP, and risk was seen in all clusters, but treatment effects were considerably more pronounced in Cluster 1 than in the 2 other clusters. It is unclear whether this was due to the more aggressive treatment approach or to a better responsiveness of these patients.

Our study has potential implications. First, it confirms and extends previous reports suggesting that there are different phenotypes among patients diagnosed with IPAH. Second, our data show that—at least in the participating European countries—most patients diagnosed with IPAH are phenotypically different from the patients originally described.[2] Third, while acknowledging that the different survival rates may reflect the impact of age and

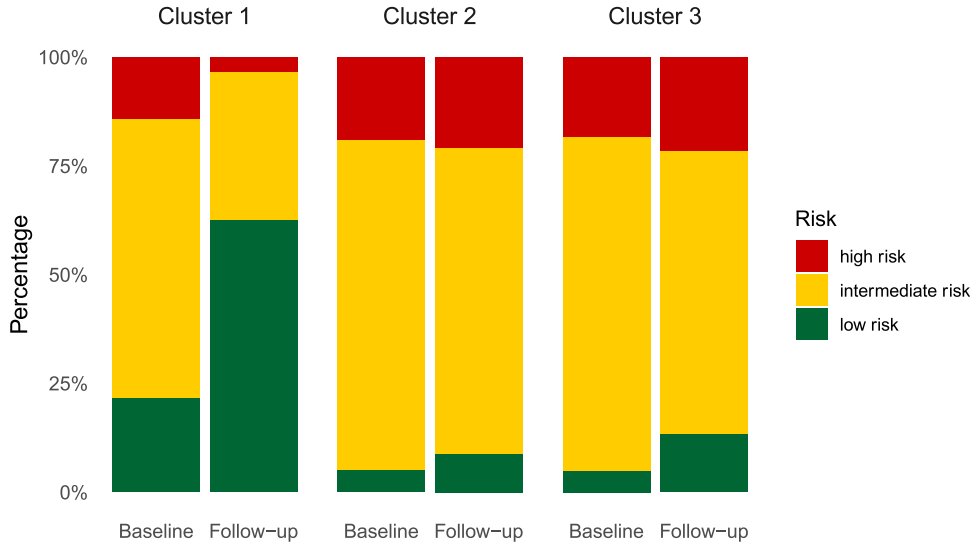

Figure 3 Risk as determined by the Swedish/COMPERA approach at baseline and follow-up in the 3 clusters. COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension.

comorbidities, our findings raise the hypothesis that distinct etiologies and different pathophysiological mechanisms contributed to the pulmonary vascular disease in the patients under study.

Our study has strengths and limitations. The main strength is the large cohort of eligible patients; further strengths are the real-world setting, the prospective and multicenter data acquisition, and the long follow-up period. It is uncertain whether all patients were correctly classified, but they all fulfilled the current diagnostic criteria for IPAH. Although COMPERA is a European registry with participation from 12 countries, about 80% of the patients were enrolled from Germany, generating potential bias, starting with the age and demographics of the patients. Given that the data were captured over a 12-year period, PAH treatments may not always reflect the contemporary approach, which explains the relatively infrequent use of combination therapy. Further limitations include the inherent weaknesses of registries such as missing values and a limited data set, making it difficult to obtain additional data on relevant variables such as comorbidities, echocardiography, or chest imaging. It is unknown if the patients with severely impaired DLCO had radiological signs of parenchymal lung disease. Still, pulmonary function measured by TLC, FVC, and FEV_1 was preserved in these patients, and a recent study by Lewis et al[30] has shown that patients with this phenotype may present with normal or near-normal chest computer tomography findings.[31]

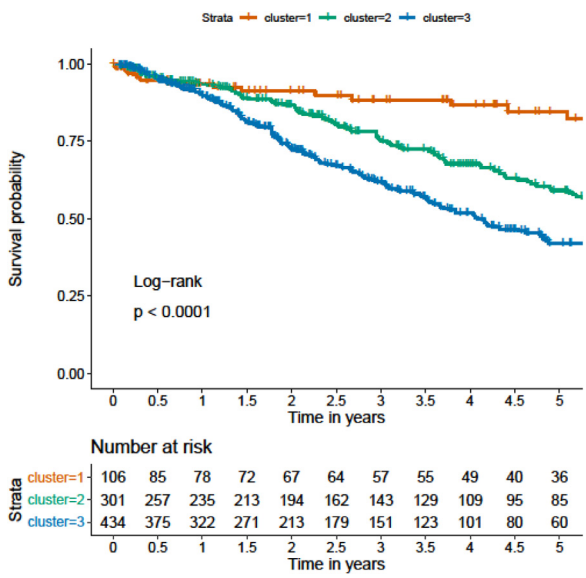

Figure 4 Kaplan-Meier survival estimates according to clusters.

Furthermore, some limitations related to the cluster approach require consideration. The methodological postulate of cluster analysis is not to have missing data. This criterion was met by only 37% of the patients with IPAH enrolled into COMPERA, which may have resulted in selection bias. In addition, although cluster analysis does not require an a priori hypothesis, the variables of interest have to be selected in advance, which implies a kind of assumption, in particular, as the number of variables considered in this cluster analysis was relatively low. With different variables, the segmentation might have been different.

In conclusion, our cluster analysis yielded 3 distinct IPAH phenotypes. The smallest cohort were patients with classical IPAH, that is, predominantly females of younger age without cardiovascular risk factors. The next largest cohort were older women without a history of smoking but with abundant risk factors for left heart disease. The largest cohort were older patients, predominantly males, most of whom had a history of smoking. Among the 3 clusters, patients with classical IPAH had the best survival, whereas the survival of the latter group of patients was particularly poor. It is likely that the pathogenetic mechanisms leading to PAH differ among these 3 cohorts, and our data indicate that the same may be true for the response to PAH therapy.

Disclosure statement

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.healun.2020.09.011.

References

1. Frost A, Badesch D, Gibbs JSR, et al. Diagnosis of pulmonary hypertension. Eur Respir J 2019;53:1801904.
2. Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension. A national prospective study. Ann Intern Med 1987;107:216-23.
3. Zhang R, Dai LZ, Xie WP, et al. Survival of Chinese patients with pulmonary arterial hypertension in the modern treatment era. Chest 2011;140:301-9.
4. Alves JL Jr, Gavilanes F, Jardim C, et al. Pulmonary arterial hypertension in the southern hemisphere: results from a registry of incident Brazilian cases. Chest 2015;147:495-501.
5. Ling Y, Johnson MK, Kiely DG, et al. Changing demographics, epidemiology, and survival of incident pulmonary arterial hypertension: results from the pulmonary hypertension registry of the United Kingdom and Ireland. Am J Respir Crit Care Med 2012;186:790-6.
6. Frost AE, Badesch DB, Barst RJ, et al. The changing picture of patients with pulmonary arterial hypertension in the United States: how REVEAL differs from historic and non-US contemporary registries. Chest 2011;139:128-37.
7. Hoeper MM, Huscher D, Ghofrani HA, et al. Elderly patients diagnosed with idiopathic pulmonary arterial hypertension: results from the COMPERA registry. Int J Cardiol 2013;168:871-80.
8. Hoeper MM, Huscher D, Pittrow D. Incidence and prevalence of pulmonary arterial hypertension in Germany. Int J Cardiol 2016;203:612-3.
9. Rådegran G, Kjellström B, Ekmehag B, et al. Characteristics and survival of adult Swedish PAH and CTEPH patients 2000-2014. Scand Cardiovasc J 2016;50:243-50.
10. Badagliacca R, Rischard F, Papa S, et al. Clinical implications of idiopathic pulmonary arterial hypertension phenotypes defined by cluster analysis. J Heart Lung Transplant 2020;39:310-20.
11. Parikh KS, Rao Y, Ahmad T, Shen K, Felker GM, Rajagopal S. Novel approach to classifying patients with pulmonary arterial hypertension using cluster analysis. Pulm Circ 2017;7:486-93.
12. Launay D, Montani D, Hassoun PM, et al. Clinical phenotypes and survival of pre-capillary pulmonary hypertension in systemic sclerosis. PLoS One 2018;13:e0197112.
13. Hoeper MM, Behr J, Held M, et al. Pulmonary hypertension in patients with chronic fibrosing idiopathic interstitial pneumonias. PLoS One 2015;10:e0141911.
14. Opitz CF, Hoeper MM, Gibbs JS, et al. Pre-capillary, combined, and post-capillary pulmonary hypertension: a pathophysiological continuum. J Am Coll Cardiol 2016;68:368-78.
15. Hoeper MM, Kramer T, Pan Z, et al. Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. Eur Respir J 2017;50:1700740.

16. Trip P, Nossent EJ, de Man FS, et al. Severely reduced diffusion capacity in idiopathic pulmonary arterial hypertension: patient characteristics and treatment responses. Eur Respir J 2013;42:1575-85.
17. Hoeper MM, Meyer K, Rademacher J, Fuge J, Welte T, Olsson KM. Diffusion capacity and mortality in patients with pulmonary hypertension due to heart failure with preserved ejection fraction. JACC Heart Fail 2016;4:441-9.
18. Galiè N, Barberà JA, Frost AE, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. N Engl J Med 2015;373:834-44.
19. Kylhammar D, Kjellström B, Hjalmarsson C, et al. A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension. Eur Heart J 2018;39:4175-81.
20. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J 2015;46:903-75.
21. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37:67-119.
22. McLaughlin VV, Vachiery JL, Oudiz RJ, et al. Patients with pulmonary arterial hypertension with and without cardiovascular risk factors: results from the AMBITION trial. J Heart Lung Transplant 2019;38:1286-95.
23. Statista. Global no.1 business data platform. Available at: www.statista.com .
24. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. Circulation 2018;138:861-70.
25. Vachiéry JL, Tedford RJ, Rosenkranz S, et al. Pulmonary hypertension due to left heart disease. Eur Respir J 2019;53:1801897.
26. Borlaug BA, Kane GC, Melenovsky V, Olson TP. Abnormal right ventricular-pulmonary artery coupling with exercise in heart failure with preserved ejection fraction. Eur Heart J 2016;37:3293-302.
27. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. Circ Heart Fail 2010;3:588-95.
28. Seimetz M, Parajuli N, Pichl A, et al. Inducible NOS inhibition reverses tobacco-smoke-induced emphysema and pulmonary hypertension in mice. Cell 2011;147:293-305.
29. Olsson KM, Fuge J, Meyer K, Welte T, Hoeper MM. More on idiopathic pulmonary arterial hypertension with a low diffusing capacity. Eur Respir J 2017;50:1700354.
30. Hoeper MM, Vonk-Noordegraaf A. Is there a vanishing pulmonary capillary syndrome? Lancet Respir Med 2017;5:676-8.
31. Lewis RA, Thompson AAR, Billings CG, et al. Mild parenchymal lung disease and/or low diffusion capacity impacts survival and treatment response in patients diagnosed with idiopathic pulmonary arterial hypertension. Eur Respir J 2020;55:2000041.