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Supplementary appendix

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Phenotyping of idiopathic pulmonary arterial hypertension: a registry analysis

Supplementary material

Content

Table S1a: Number of available data for each variable in COMPERA

	Classical IPAH n=128	IPAH with a pulmonary phenotype n=268	Group 3 PH n=910
Age, years	128 (100%)	268 (100%)	910 (100%)
Female	128 (100%)	268 (100%)	910 (100%)
BMI, kg/m^2	128 (100%)	268 (100%)	858 (94%)
WHO FC	126 (98%)	251 (94%)	867 (95%)
6MWD, m	111 (87%)	195 (73%)	662 (73%)
NT-proBNP, ng/L BNP, ng/L	98 (77%) 15 (12%)	197 (74%) 33 (12%)	532 (59%) 180 (20%)
Pulmonary function TLC, % pred FVC, % pred FEV_1, % pred FEV_1/FVC (%) DLCO, % pred PaO_2, mmHg $PaCO_2$, mmHg	 103 (81%) 113 (88%) 111 (87%) 102 (80%) 128 (100%) 105 (82%) 107 (84%)	 228 (85%) 235 (88%) 237 (88%) 222 (83%) 268 (100%) 225 (84%) 223 (83%)	 734 (81%) 884 (93%) 855 (94%) 724 (80%) 578 (64%) 828 (91%) 825 (91%)
Smoking history If ever: Pack years	116 (91%) 27 (68%)	268 (100%) 194 (72%)	262 (29%) 189 (89%)
Comorbid conditions BMI >30 kg/m^2 Hypertension Coronary heart disease Diabetes mellitus Atrial fibrillation	 128 (100%) 128 (100%) 128 (100%) 128 (100%) 119 (93%)	 268 (100%) 262 (98%) 262 (98%) 261 (97%) 257 (96%)	 858 (94%) 750 (82%) 731 (80%) 751 (83%) 853 (94%)
Haemodynamics RAP, mmHg mPAP, mmHg PAWP, mmHg CI, L/min/m^2 PVR, WU SvO_2, %	 113 (88%) 128 (100%) 128 (100%) 122 (95%) 128 (100%) 111 (87%)	 229 (85%) 268 (100%) 268 (100%) 252 (94%) 268 (100%) 216 (81%)	 837 (92%) 910 (100%) 910 (100%) 861 (95%) 910 (100%) 780 (86%)
Risk	128 (100%)	266 (99%)	898 (99%)

Medication	128 (100%)	266 (99%)	898 (99%)

Data are shown as n and % of the respective population.

Definition of abbreviations: BMI, body mass index; IPAH, idiopathic pulmonary arterial hypertension; PH, pulmonary hypertension; WHO FC, World Health Organization Functional Class; 6MWD, 6-minute walking distance; 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; RA, right atrial pressure; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; CI, cardiac index; PVR, pulmonary vascular resistance; SvO_2, mixed-venous oxygen saturation.

Table S1b: Number of available data for each variable in ASPIRE

	Classical IPAH (i) n=185	IPAH with a lung phenotype (ii) n=139	Group 3.1 or 3.2 PH n=375 (iii)
Age, years	185 (100%)	139 (100%)	375 (100%)
Female	185 (100%)	139 (100%)	375 (100%)
BMI, kg/m^2	178 (96%)	133 (96%)	358 (95%)
WHO FC	185 (100%)	139 (100%)	372 (99%)
ISWD, m	181 (98%)	121 (87%)	353 (94%)
Pulmonary function			
FEV_1, % pred	183 (99%)	139 (100%)	345 (92%)
FVC, % pred	183 (99%)	139 (100%)	344 (92%)
FEV_1/FVC (%)	183 (99%)	139 (100%)	345 (92%)
DLCO, % pred	185 (100%)	139 (100%)	302 (81%)
Smoking history	168 (91%)	139 (100%)	0 (0%)
If ever:			
Pack years	36 (47%)	97 (70%)	0 (0%)
Haemodynamics			
RAP, mmHg	183 (99%)	138 (99%)	373 (99%)
mPAP, mmHg	185 (100%)	139 (100%)	375 (100%)
PAWP, mmHg	185 (100%)	139 (100%)	375 (100%)
CI, L/min/m^2	178 (96%)	131 (94%)	368 (98%)
PVR, WU	185 (100%)	139 (100%)	375 (100%)
SvO_2, %	168 (91%)	125 (90%)	347 (93%)
Computed Tomography (CT)			
CT report available	109 (59%)	86 (62%)	219 (58%)
Fibrosis	109 (59%)	86 (62%)	219 (58%)
Fibrosis severity	107 (58%)	85 (61%)	207 (55%)
Emphysema	109 (59%)	86 (62%)	219 (58%)
Emphysema severity	106 (57%)	85 (61%)	210 (56%)
Medication	167 (90%)	138 (99%)	375 (100%)

Data are shown as n and % of the respective population.

Definition of abbreviations: BMI, body mass index; IPAH, idiopathic pulmonary arterial hypertension; PH, pulmonary hypertension; WHO FC, World Health Organization Functional Class; ISWD, incremental shuttle walk distance; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; DLCO, diffusion capacity of the lung for carbon monoxide; RA, right atrial pressure; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; CI, cardiac index; PVR, pulmonary vascular resistance; SvO_2, mixed-venous oxygen saturation.

Table S2a: COMPERA baseline characteristics of patients with IPAH excluded from the analysis (i.e., patients belonging neither to classical IPAH nor to the group of patients with IPAH and a lung phenotype)

	Excluded IPAH patients n=1,406
Age, years	72 [60, 78]
Female	880 (63%)
BMI, kg/m^2	28 [25, 33]
WHO FC I II III IV	 4 (0.3%) 189 (14%) 941 (71%) 197 (15%)
6MWD, m	300 [200, 376]
NT-proBNP, ng/L BNP, ng/L	1641 [615, 3674] 209 [102, 461]
Pulmonary function TLC, % pred FVC, % pred FEV_1, % pred DLCO, % pred PaO_2, mmHg $PaCO_2$, mmHg	 92 [80, 102] 80 [65, 93] 75 [62, 91] 54 [40, 71] 64 [57, 73] 36 [32, 40]
Smoking history Ever Never Pack years	 302 (35%) 566 (65%) 25 [14, 40]
Comorbid conditions BMI >30 kg/m^2 Hypertension Coronary heart disease Diabetes mellitus Atrial fibrillation	 538 (39%) 900 (74%) 355 (30%) 412 (34%) 303 (24%)
Haemodynamics RAP, mmHg mPAP, mmHg	 8 [5, 11] 42 [34, 51]

PAWP, mmHg	10 [7, 12]
CI, L/min/m^2	2·1 [1·7, 2·6]
PVR, WU	8·1 [5·7, 11·7]
SvO_2, %	63 [57, 68]
Risk (4-strata model)[a]	
Low	88 (6%)
Intermediate-low	241 (17%)
Intermediate-high	697 (50%)
High	365 (26%)
PH medications	
CCB	71 (5%)
ERA	413 (29%)
PDE5i	1103 (78%)
sGCs	54 (4%)
PPA	39 (3%)
Monotherapy	1149 (82%)
Combination therapy	257 (18%)

Categorical data are shown as n and % of the respective population. Continuous data are depicted as median [Q1, Q3].

Definition of abbreviations: BMI, body mass index; IPAH, idiopathic pulmonary arterial hypertension; PH, pulmonary hypertension; WHO FC, World Health Organization Functional Class; 6MWD, 6-minute walking distance; 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; RA, right atrial pressure; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; CI, cardiac index; 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.

62 **Table S2b: ASPIRE baseline characteristics of patients with IPAH excluded from the analysis**

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	Excluded IPAH patients n=148
Age, years	69 [60, 77]
Female	78 (53%)
BMI, kg/m^2	28.4 [24.3, 32.6]
WHO FC I II III IV	 0 (0%) 15 (10%) 80 (54%) 52 (35%)
ISWD, m	80 [20, 180]
Pulmonary function FVC, % pred FEV_1, % pred FEV_1 / FVC Ratio DLCO, % pred	 93 [75, 101] 78 [61, 90] 70 [62, 76] 30 [23, 36]
Smoking history Ever Never Pack years	 28 (33%) 56 (67%) 25 [20, 30]
Haemodynamics RAP, mmHg mPAP, mmHg PAWP, mmHg CI, L/min/m^2 PVR, WU SvO_2, %	 11.0 [8.0, 15.0] 50 [45, 58] 11.0 [8.0, 13.0] 2.1 [1.8, 2.7] 9.9 [7.4, 12.9] 61 [55, 66]
CT report available Fibrosis (any present) Fibrosis (by severity) None Mild Moderate Severe Emphysema (any present)	80 (54%) 28 (35%) 52 (68%) 22 (29%) 3 (3.9%) 0 (0%) 24 (30%)

Emphysema (by severity) None Mild Moderate Severe	 56 (71%) 10 (13%) 11 (14%) 2 (2.5%)
Treatment* None CCB Oral monotherapy Oral combination PPA ± oral therapy	 0 (0%) 1 (1%) 50 (36%) 65 (46%) 24 (17%)

Categorical data are shown as n and % of the respective population. Continuous data are depicted as median [Q1, Q3].

Definition of abbreviations: BMI, body mass index; IPAH, idiopathic pulmonary arterial hypertension; PH, pulmonary hypertension; WHO FC, World Health Organization Functional Class; ISWD, incremental shuttle walk distance; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; DLCO, diffusion capacity of the lung for carbon monoxide; RA, right atrial pressure; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; CI, cardiac index; PVR, pulmonary vascular resistance; SvO_2, mixed-venous oxygen saturation; CT, computed tomography; CCB, calcium channel blocker; ERA endothelin receptor antagonists; PDE5i, phosphodiesterase-5 inhibitors; sGCs, stimulator of soluble guanylate cyclase; PPA, prostacyclin pathway agents.

*Oral monotherapy includes PDE5i or ERA or SGCs; oral combination includes ERA in combination with PDE5i or SCGs; PPA +/- oral therapy includes prostanoids either alone or in combination with PDE5i or sGCs +/- ERA.