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Phenotyping of idiopathic pulmonary arterial hypertension: a registry analysis

Running Title: Phenotyping of IPAH

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Abstract

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.

Methods: We analysed data from two European pulmonary hypertension (PH) registries, COMPERA and ASPIRE, to identify patients diagnosed with IPAH and a lung phenotype defined by a DLCO <45% predicted and a smoking history. We compared these patients to classical IPAH, defined by the absence of cardiopulmonary co-morbidities and DLCO ≥45% predicted and patients with PH due to lung disease (group 3 PH).

Findings: The COMPERA and ASPIRE analysis included 128 and 185 patients with classical IPAH, 268 and 139 patients with IPAH and a lung phenotype, and 910 and 375 patients with PH due to lung disease, respectively. Most patients with IPAH and a lung phenotype had normal or near normal spirometry, a severe reduction in DLCO with the majority having normal or a mild degree of parenchymal lung involvement on chest computed tomography. Patients in COMPERA and ASPIRE with IPAH and a lung phenotype (median [Q1, Q3] age, 72 [65,78] years and 71 [65, 76] years) and patients with group 3 PH (median age, 71 [65, 77] and 69 [63, 74] years) were older than those with classical IPAH (median age, 45 [32, 60] and 52 [38, 64] years; p<0.0001). While 77% and 72% of patients with classical IPAH were female, patients with IPAH and a lung phenotype were more often male (65% and 46%), similar to group 3 PH (63% and 61%). Response to PAH therapies at first follow-up was available for COMPERA. In classical IPAH, IPAH with a lung phenotype and group 3 PH, improvements in WHO functional class were observed in 54%, 26% and 22% of the patients; mean improvements in 6 min walking distance were 83 m, 31 m, and 27 m, and median reductions in N-terminal-pro-brain-natriuretic-peptide were 58%, 27% and 16% (classical IPAH vs IPAH and a lung phenotype, all p<0.005; IPAH with a lung phenotype versus group 3 PH, all p>0.05). In both registries, survival of patients with IPAH and a lung phenotype (1-year, 89% and 79%; 5-years, 31% and 21%) and group 3 PH (1-year, 78% and 64%; 5-years, 26% and 18%) was worse than survival of patients with classical IPAH (1-year, 95% and 98%; 5-years, 84% and 80%; p<0.0001).

Interpretation: A cohort of patients meeting diagnostic criteria for IPAH suffer from a distinct, presumably smoking-related form of PH accompanied by a low DLCO and resemble

patients with PH due to lung disease rather than classical IPAH. These observations have pathogenetic, diagnostic, and therapeutic implications, which require further exploration.

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Introduction

The current clinical classification of pulmonary hypertension (PH) consists of 5 major groups: Group 1, pulmonary arterial hypertension (PAH); group 2, PH associated with left heart disease; group 3, PH associated with lung disease; group 4, chronic thromboembolic PH; and group 5, PH due to systemic or multifactorial conditions.[1,2] The criteria for the diagnosis and classification of PH have been outlined in recent guidelines,[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 US have demonstrated that IPAH is now more frequently diagnosed in elderly patients, many of whom have cardiac and/or pulmonary comorbidities.[4-6] In such patients, it is not always easy to distinguish IPAH from group 2 or group 3 PH. Several disease phenotypes have been reported, including a subtype of patients diagnosed with IPAH who present with a lung phenotype, mainly characterized 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 PH.[7-9]

In a recent cluster analysis from the *Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension* (COMPERA), a European PH registry, only 12.6% of 846 patients diagnosed with IPAH presented with the classical phenotype while 35.8% had a left heart phenotype and 51.6% a lung phenotype, respectively.[10] The high proportion of patients with a lung phenotype came as surprise. To further characterize 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 PH associated with lung disease, i.e., group 3 PH, focussing on demographics, disease characteristics at diagnosis, response to PH therapy, and survival. Data obtained from the *Assessing the Spectrum of Pulmonary hypertension Identified at a REferral centre* (ASPIRE) registry were utilized for independent validation.[12]

Methods

Databases

Details of COMPERA (www.COMPERA.org; registered at Clinicaltrials.gov under the identifier NCT01347216) have been reported previously.[5,10] COMPERA is an ongoing PH 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 PH. PH centres 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 Germany. COMPERA has been approved by the responsible ethics committee, and all patients provided written, informed consent prior to inclusion.

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

All analyses from COMPERA and ASPIRE were performed separately and the data were not combined. From COMPERA, patients were selected to form three cohorts: (i) patients with classical IPAH (PH group 1.1), defined by the absence of risk factors for left heart disease (body mass index (BMI) ≥ 30 kg/m^2, hypertension, diabetes mellitus, and coronary heart disease), and a DLCO ≥ 45%; (ii) patients diagnosed with IPAH and a lung phenotype, defined by a smoking history and a DLCO < 45% of the predicted value; and (iii) patients classified by their physicians as group 3 PH with the underlying conditions being either COPD (PH group 3.1) or ILD (PH 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 <45% versus ≥45% 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 age ≥18 years, PH diagnosis made between Jan 1st, 2009 and Dec 31st, 2020 in COMPERA, and between Feb 1st, 2001 and Jan 31st, 2019 in ASPIRE, and data from right heart catheterization available at baseline showing mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg, pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg, and pulmonary vascular resistance (PVR) > 3 WU. Furthermore, only incident patients with at least one follow-up documentation were considered for COMPERA and incident patients for ASPIRE.

Imaging

Chest computed tomography (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 analyses

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 first and third quartile [Q1, Q3]. 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 PH. 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 Chi-squared test or by Fisher's exact test. Response to therapy was determined by changes from baseline to first follow-up in WHO functional class (FC), 6-minute walking distance (6MWD), N-terminal fragment of pro-

brain natriuretic peptide (NT-proBNP), and mortality risk using the ESC/ERS 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.

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Results

Patient characteristics of the study cohorts

In COMPERA, a total of 128 patients with classical IPAH, 268 patients with IPAH and a lung phenotype, and 910 patients with group 3 PH fulfilled the eligibility criteria and were included in the present analysis. The corresponding numbers from ASPIRE were 185, 139, and 375. Patient selection is shown in Figures 1a and 1b. The patient characteristics at baseline are shown in Tables 1a and 1b. The number of missing values for each variable is shown in the supplementary tables S1a and S1b. Histograms showing the age distribution of the cohorts are depicted in Figures 2a and 2b. The baseline characteristics of patients with IPAH who were excluded from the analyses are shown in supplementary tables S2a and S2b.

Patients with classical IPAH were mostly young with a median age of 45 and 52 years, respectively (although some patients were in the seventies and eighties as shown in Figures 2a and 2b), and predominantly female. About one third of these patients had a smoking history with a median of 14 and 20 pack years. 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 PH and most had a moderately impaired exercise capacity.

Compared to patients with classical IPAH, patients with IPAH and a lung phenotype were older (mean age of about 70 years) and more often male. Per inclusion criteria, all patients

were smokers, and the median tobacco exposure was 40 (COMPERA) and 30 (ASPIRE) pack years. Forced vital capacity (FVC) and forced expiratory volume in 1s (FEV_1) were mostly normal. However, the DLCO was severely reduced (30% and 27% of the predicted value, respectively), and the patients were more hypoxaemic than patients with a classical phenotype. Severity of PH as determined by mPAP and PVR was comparable to patients with the classical phenotype, but exercise capacity was substantially lower.

Patients with group 3 PH 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 (Figures 2a and 2b). Eighty-one percent had a smoking history with a median of 40 pack years (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% and 25%, respectively, of the predicted value). Blood gas analyses showed marked hypoxaemia, comparable to patients with IPAH and a lung phenotype. mPAP and PVR were lower than in the other cohorts but still much elevated. The degree of exercise limitation was similar to patients with IPAH and a lung phenotype.

Imaging (ASPIRE data only)

The chest CT studies from ASPIRE showed absence of parenchymal lung disease in most patients with classical IPAH. The majority of patients with IPAH and a lung phenotype had minor parenchymal abnormalities on CT. In contrast, almost all patients with group 3 PH had parenchymal abnormalities, mostly moderate or severe. Details are shown in Table 2.

Changes from baseline to first follow-up (COMPERA data only)

The first follow-up visit took place 4·7 [3·5, 6·6] months after baseline. FC, 6MWD, NT-proBNP and risk at baseline and first follow-up are shown in Figures 3a-d. In all categories, patients with classical IPAH improved most, whereas there were less and quantitatively similar changes in the two other cohorts.

Survival

In COMPERA, the median observation time was 3·9 [1·8, 6·6] years for patients with classic IPAH, 2·0 [1·2, 3·4] years for patients with IPAH and a lung phenotype, and 1·7 [0·7, 3·3] years for patients with group 3 PH. In the cohort of patients with classic IPAH, 23 (18%) patients died, 5 (4%) underwent lung transplantation, and 8 (6%) were lost to follow-up. The corresponding numbers for patients with IPAH and a lung phenotype were 138 (52%), 5 (2%) and 13 (5%), respectively. Among the patients with group 3 PH, 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 [2·1, 7·8] years for patients with classic IPAH, 1·7 [0·9, 2·8] years for patients with IPAH and a lung phenotype, and 1·4 [0·6, 3·1] years for patients with group 3 PH. No patients were lost to follow-up. In the cohort of patients with classic IPAH, 42 (23%) patients died and 7 (4%) underwent lung transplantation. The corresponding numbers for patients with IPAH and a lung phenotype were 90 (65%) and 0 respectively. Among the patients with group 3 PH, 286 (76%) died and 5 (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 PH were comparable and both much inferior to the survival rate of patients with classical IPAH (Figures 4a and b).

In COMPERA, the Kaplan-Meier estimated survival rates of patients with classical IPAH at 1, 3 and 5 years were 95%, 90%, and 84%, respectively. In patients with IPAH and a lung phenotype, the corresponding numbers were 89%, 49%, and 31%. In patients with group 3 PH, the respective survival rates were 78%, 43%, and 26%. The unadjusted survival rates differed significantly between patients with classical IPAH and IPAH with a lung phenotype ($p<0·0001$) and between the latter group and patients with group 3 PH ($p=0·0159$; Figure 4a). When adjusted for age and sex, the risk of death remained lower for patients with classical IPAH than for patients with IPAH and a lung phenotype (HR 3·48; 95% confidence interval 2·04 to 5·95, $p<0·0001$). The survival difference between patients with IPAH and a lung phenotype and patients with group 3 PH was smaller albeit still statistically significant (HR 0·79; 95% confidence interval 0·66 to 0·96, $p=0·0150$).

In ASPIRE, the Kaplan-Meier estimated survival rates of patients with classical IPAH at 1, 3 and 5 years were 98%, 91%, and 80%, respectively. In patients with IPAH and a lung phenotype, the corresponding numbers were 79%, 35%, and 21%. In patients with group 3

PH, the respective survival rates were 64%, 32%, and 18%. The unadjusted survival rates differed significantly between patients with classical IPAH and IPAH with a lung phenotype ($p<0{\cdot}0001$) and between the latter group and patients with group 3 PH ($p=0{\cdot}0450$; 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% confidence interval 2·35 to 5·54). The survival difference between patients with IPAH and a lung phenotype and patients with group 3 PH was smaller but still statistically significant (HR 0·74; 95% confidence interval 0·58 to 0·94, $p=0{\cdot}010$).

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, with the exception of severe pre-capillary PH, having similar baseline characteristics, treatment response and survival as patients with group 3 PH. 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, while in fact they phenotypically resemble patients with group 3 PH.

In the present cohorts, patients categorized as classical IPAH resembled those initially described as primary pulmonary hypertension, i.e., predominantly young, otherwise healthy females [3]. These patients had 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 elderly patients with co-morbidities [6,10]. These patients continue to have a high mortality risk.[10] In these patients, 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 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 PH. 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 PH (PH associated with either COPD or ILD, 81% of whom were smokers as well), we found striking similarities. Age distribution and male-to-female ratio were comparable as were FC and 6MWD. The same was true for the prevalence of risk factors for left heart disease, which may have contributed to the development of PH. Patients with IPAH and a lung phenotype and patients classified as group 3 PH had a similar response to medical therapy, i.e., comparable changes from baseline to first follow-up in FC, 6MWD, NT-proBNP and mortality risk. Taken together, patients with IPAH and a lung phenotype resembled those of patients with group 3 PH, while they had little in common with classical IPAH, except for the presence of severe pre-capillary PH. Nonetheless, a comparison of the baseline characteristics of patients with IPAH and a lung phenotype and patients with group

3 PH showed differences in lung function, suggesting that these are not the same patient populations.

As in previous studies,[7,8,12] a DLCO ≥45% or <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 the latter group of patients 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 animal models, prolonged exposure to tobacco smoke causes endothelial cell apoptosis in pulmonary capillaries, which precedes the development of emphysema,[18] and most of the patients diagnosed with IPAH and a low DLCO are elderly individuals with a history of heavy smoking (which may also explain the male predominance of this phenotype). We therefore speculate that in these patients, smoking may have been a contributor to the development of PH, or even its main cause. In addition, it is possible that the pulmonary vasculopathy of patients with IPAH and a lung phenotype and patients with group 3 PH 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 lack of data is particularly worrisome when considering a recent study showing that PAH drugs may further impair gas exchange in patients with a low DLCO.[28] Moreover, the response to therapy in patients with IPAH and a lung phenotype was blunted compared to patients with classical IPAH, but it is unclear if this was due to a distinct pulmonary vasculopathy, less aggressive therapy, or co-morbidities leaving little room for functional improvement.

It is important to note that IPAH with a low DLCO may also be found in patients who have never smoked. Such patients may suffer from various conditions such as unrecognized 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 certain forms of heritable PAH.[30]

Limitations of the present study include its post-hoc nature, missing values, lack of imaging data in COMPERA, and heterogeneities between the two registries. We also acknowledge the possibility of a selection bias in group 3 PH introduced by COMPERA including only patients who received treatment with drugs approved for PAH. Notably, ASPIRE 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. In addition, even though all patients were evaluated at referral centres, we cannot fully exclude the possibility that misclassification bias may 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 characterization, and the results may not be generalizable to patients with mixed phenotypes.

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

Research in context

Evidence before the Subject

Idiopathic pulmonary arterial hypertension (IPAH), originally observed mainly in young, otherwise healthy individuals, is increasingly diagnosed in elderly patients with co-morbidities. Among these patients, a distinct lung phenotype is emerging, characterized 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 characterized. 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”, 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 suffering from pulmonary hypertension (PH) associated with lung disease including sex and age distribution, functional impairment at diagnosis, response to PH medications, and survival. At the same time, these patients have very little in common with patients who present with a classical IPAH phenotype, i.e., patients without cardiopulmonary co-morbidities and a DLCO ≥45% of the predicted value.

Implications of the available evidence

We expect our findings to lead to a re-classification of some forms of pulmonary hypertension. A better characterization 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.

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544 **Table 1a Patient characteristics at baseline in COMPERA**

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	Classical IPAH (i) n=128	P-value (i) vs. (ii)	IPAH with a lung phenotype (ii) n=268	P-value (ii) vs. (iii)	Group 3.1 or 3.2 PH n=910 (iii)
Age, years	45 [32, 60]	<0·0001	72 [65, 78]	0·89	71 [65, 77]
Female	99 (77%)	<0·0001	95 (35%)	0·71	336 (37%)
BMI, kg/m^2	24 [22, 27]	<0·0001	27 [24, 32]	0·0002	26 [23, 29]
WHO FC I II III IV	 2 (2%) 30 (24%) 85 (67%) 10 (8%)	<0·0001	 0 (0%) 16 (6%) 184 (73%) 51 (20%)	0·055	 0 (0%) 32 (4%) 612 (71%) 223 (26%)
6MWD, m	410 [320, 476]	<0·0001	234 [167, 310]	0·93	238 [159, 318]
NT-proBNP, ng/L BNP, ng/L	1,027 [360, 2,058] 127 [73, 249]	0·0002 0·11	1,871 [583, 4,348] 304 [120, 441]	0·042 0·004	1,423 [462, 3,380] 120 [59, 276]
Pulmonary function TLC, % pred FVC, % pred FEV_1, % pred FEV_1/FVC (%) DLCO, % pred PaO_2, mmHg $PaCO_2$, mmHg	 98 [87, 110] 92 [78, 103] 85 [74, 96] 80 [76, 85] 69 [59, 76] 78 [71, 84] 33 [30, 35]	 0·0011 <0·0001 <0·0001 <0.0001 <0·0001 <0·0001 <0·0001	 93 [79, 103] 80 [66, 94] 71 [60, 85] 71 [63, 79] 30 [24, 36] 56 [50, 63] 35 [31, 39]	 <0·0001 <0·0001 <0·0001 0.0003 0·77 0·79 <0·0001	 85 [67, 100] 68 [53, 84] 59 [44, 74] 68 [52, 81] 26 [20, 35] 57 [49, 64] 37 [33, 43]
Smoking history Ever Never Pack years	 40 (34%) 76 (66%) 14 [10, 30]	 <0·0001 <0·0001	 268 (100%) 0 (0%) 40 [21, 50]	 <0·0001 0·17	 212 (81%) 50 (19%) 40 (30, 60]
Comorbid conditions BMI >30 kg/m^2 Hypertension Coronary heart disease Diabetes mellitus Atrial fibrillation	 0 (0%) 0 (0%) 0 (0%) 0 (0%) 7 (6%)	 <0·0001 <0·0001 <0·0001 <0·0001 0·033	 86 (32%) 183 (70%) 110 (42%) 94 (36%) 36 (14%)	 0·002 0·53 0·17 0·011 0·58	 194 (23%) 506 (68%) 270 (37%) 206 (27%) 106 (12%)

Haemodynamics					
RAP, mmHg	6 [4, 9]	0·13	7 [5, 10]	0·0011	6 [4, 9]
mPAP, mmHg	48 [40, 57]	0·002	43 [36, 51]	<0·0001	39 [33, 46]
PAWP, mmHg	8 [5, 10]	0·0003	10 [7, 12]	0·0148	9 [6, 11]
CI, L/min/m^2	2·1 [1·7, 2·7]	0·68	2·0 [1·6, 2·4]	0·051	2·1 [1·8, 2·6]
PVR, WU	10·9 [7·8, 15·6]	0·0005	8·7 [6·5, 12·0]	<0·0001	7·4 [5·9, 10·1]
SvO_2, %	66 [59, 70]	0·0011	62 [55, 66]	<0·0001	65 [59, 57]
Risk (4-strata model)[a]					
Low	16 (12%)	<0·001	5 (2%)	0·97	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%)
PH 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%)
sGCs	11 (9%)	0·22	13 (5%)	0·005	15 (2%)
PPA	7 (5%)	0·17	6 (2%)	0·34	11 (1%)
Monotherapy	81 (63%)	<0·0001	220 (82%)	<0·0001	871 (96%)
Combination therapy	47 (37%)		48 (18%)		37 (4%)

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

[a]Risk was determined as published elsewhere[14]

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,

559 phosphodiesterase-5 inhibitors; sGCs, stimulator of soluble guanylate cyclase; PPA,
560 prostacyclin pathway agents.
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564 **Table 1b Patient characteristics at baseline in ASPIRE**

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	Classical IPAH (i) n=185	P-value (i) vs. (ii)	IPAH with a lung phenotype (ii) n=139	P-value (ii) vs. (iii)	Group 3.1 or 3.2 PH n=375 (iii)
Age, years	52 [38, 64]	<0.0001	71 [65, 76]	0.049	69 [63, 74]
Female	133 (72%)	0.0009	75 (54%)	0.0032	148 (39%)
BMI, kg/m^2	28 [25, 34]	0.43	28 [25, 31]	0.056	27 [23, 31]
WHO FC I II III IV	 0 (0%) 47 (25%) 119 (64%) 19 (10%)	<0.0001	 0 (0%) 10 (7%) 80 (58%) 49 (35%)	0.94	 0 (0%) 29 (8%) 208 (56%) 135 (36%)
ISWD, m	260 [140, 400]	<0.0001	90 [30, 150]	0.20	70 [30, 140]
Pulmonary function FVC, % pred FEV$_1$, % pred FEV$_1$/FVC (%) DLCO, % pred	 97 [84, 110] 87 [75, 97] 75 [69, 80] 62 [52, 73]	 0.0114 0.26 <0.0001 <0.0001	 103 [91, 112] 88 [74, 99] 70 [63, 76] 27 [22, 34]	 <0.0001 <0.0001 <0.0001 0.0498	 82 [62, 102] 62 [44, 80] 63 [48, 76] 25 [19, 32]
Smoking history Ever Never Pack years	 76 (45%) 92 (55%) 20 [10, 30]	 <0.0001 0.0022	 139 (100%) 0 (0%) 30.0 [20, 40]	 n/a	 n/a
Haemodynamics RAP, mmHg mPAP, mmHg PAWP, mmHg CI, L/min/m^2 PVR, WU SvO$_2$, %	 9 [7, 14] 54 [46, 64] 10 [8, 12] 2.3 [1.8, 2.9] 10.5 [7.2, 14.8] 64 [58, 69]	 0.33 <0.0001 0.64 <0.0001 0.50 <0.0001	 10 [7, 14] 49 [43, 56] 10 [8, 13] 2.0 [1.6, 2.4] 11.1 [7.8, 14.6] 58 [53, 66]	 0.0002 <0.0001 0.37 <0.0001 <0.0001 <0.0001	 8 [5, 12] 41 [34, 49] 11 [8, 13] 2.6 [2.0, 3.1] 6.5 [4.2, 9.9] 66 [60, 71]
Treatment* None CCB	 2 (1.1%) 17 (10%)		 2 (1.4%) 0 (0%)		 180 (48%) 1 (0.3%)

Oral monotherapy	40 (24%)	0.0004	43 (31%)	<0.0001	165 (44%)
Oral combination	79 (47%)		72 (52%)		22 (6%)
PPA ± oral therapy	29 (19%)		21 (15%)		7 (2%)

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; CCB, calcium channel blockers; 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.

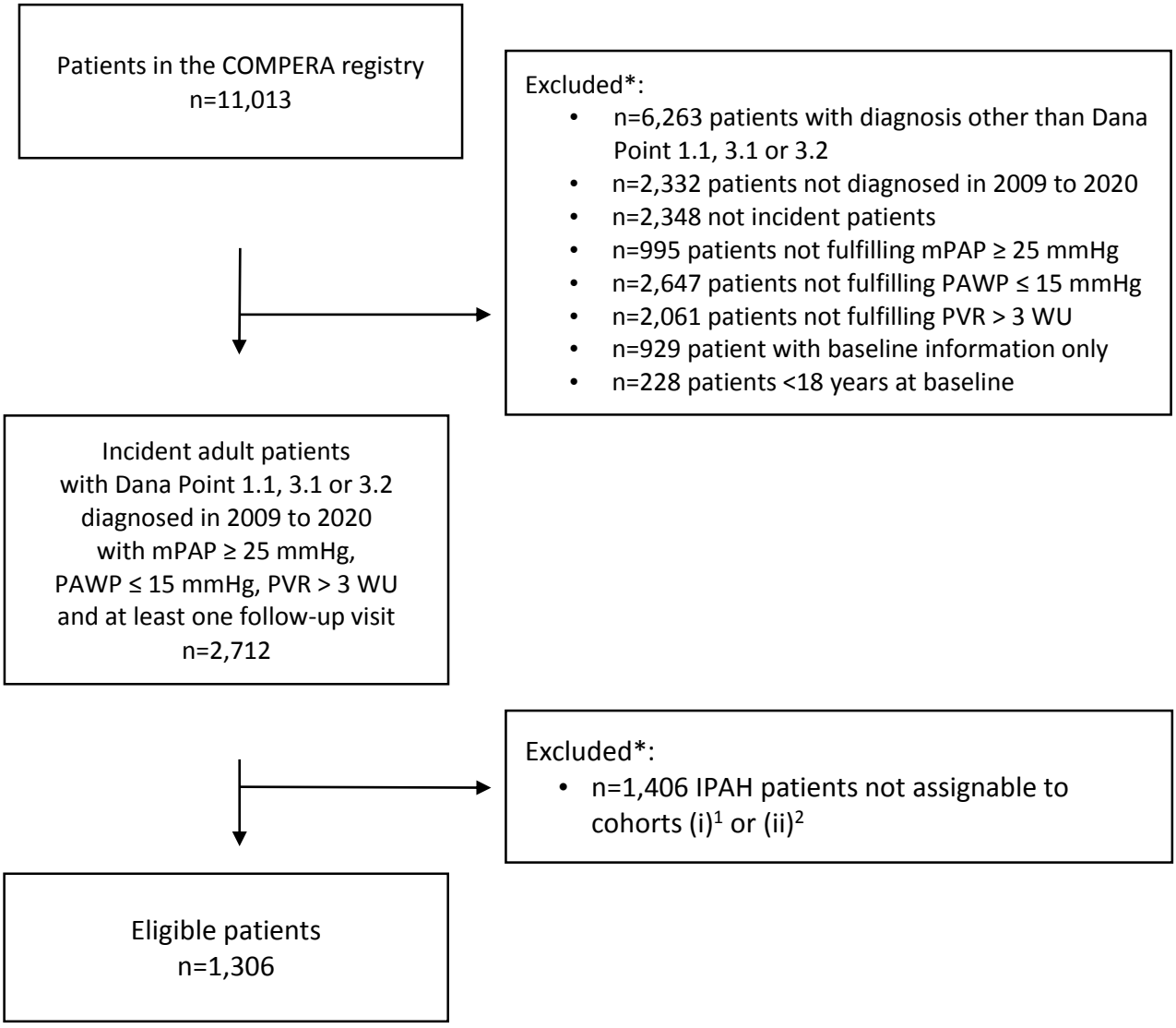
Table 2 Lung parenchymal abnormalities on chest computed tomography (ASPIRE)

	Classical IPAH (i) n=185	P-value (i) vs. (ii)	IPAH with a lung phenotype (ii) n=139	P-value (ii) vs. (iii)	Group 3.1 or 3.2 PH n=375 (iii)
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) None Mild Moderate Severe	 100 (93%) 6 (6%) 1 (1%) 0 (0%)	<0·0001	 60 (71%) 21 (25%) 4 (5%) 0 (0%)	<0·0001	 117 (57%) 21 (10%) 33 (16%) 36 (17%)
CT – Emphysema (any present)	15 (14%)	<0·0001	42 (49%)	0·07	132 (60%)
CT – Emphysema (by severity) None Mild Moderate Severe	 94 (89%) 11 (10%) 1 (1%) 0 (0%)	<0·0001	 44 (52%) 22 (26%) 16 (19%) 3 (4%)	<0·0001	 87 (41%) 21 (10%) 62 (30%) 40 (19%)

Data are shown as n (%). Statistical comparisons were made by Pearson's Chi-squared test or Fisher's exact test.

Figures

Figure 1a: STROBE diagram showing patient selection in COMPERA

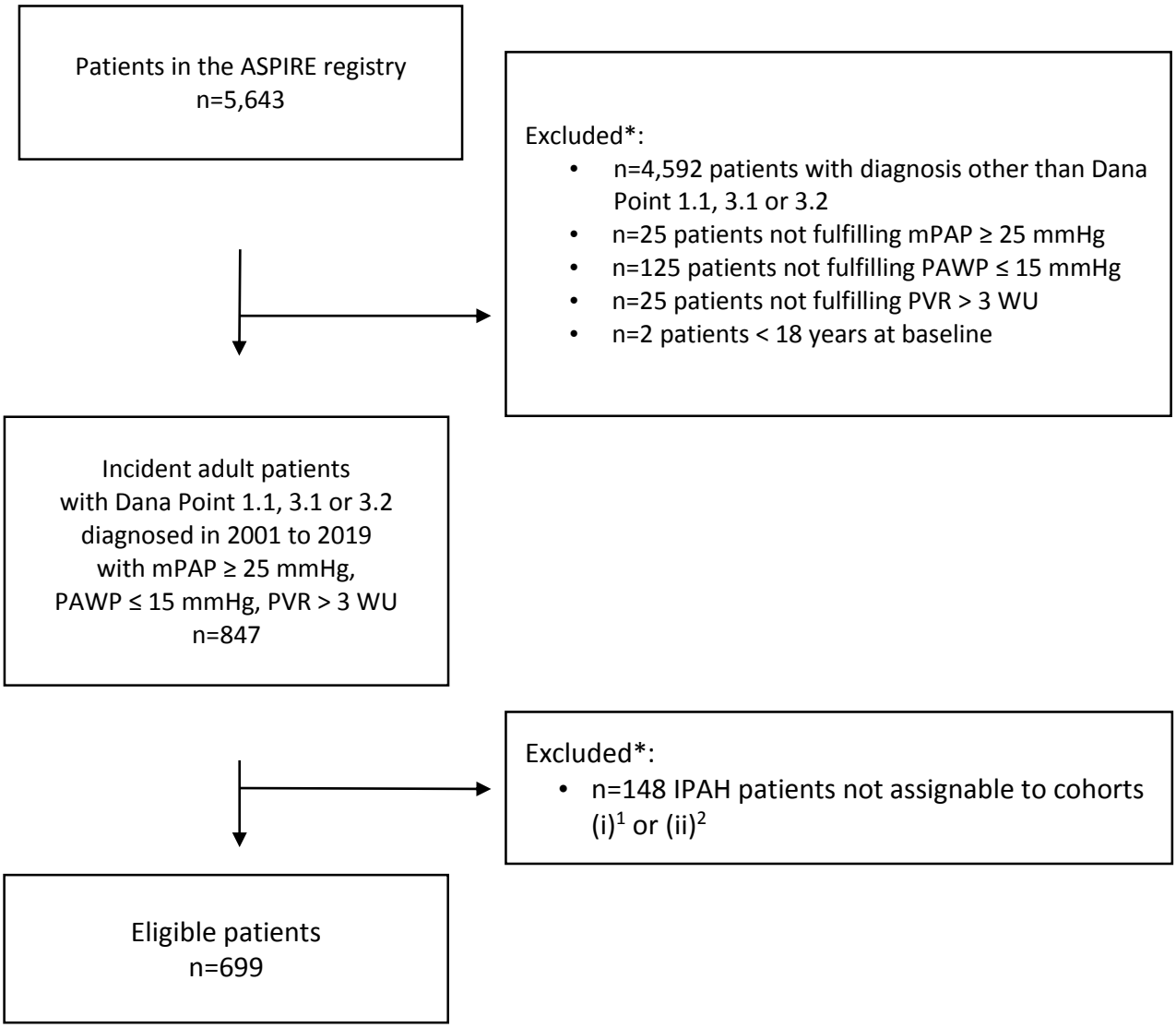


*more than one reason for exclusion could apply

[1] (i) Patients with classical IPAH, defined by the absence of risk factors for left heart disease (body mass index (BMI) ≥ 30 kg/m^2, hypertension, diabetes mellitus, and coronary heart disease), and a DLCO ≥ 45%

[2] (ii) Patients diagnosed with IPAH and a lung phenotype, defined by a smoking history (i.e., current or former smoker) and a DLCO < 45% of the predicted value

Figure 1b: STROBE diagram showing patient selection in ASPIRE



*more than one reason for exclusion could apply

[1] (i) Patients with classical IPAH and a DLCO ≥ 45%

[2] (ii) Patients diagnosed with IPAH and a lung phenotype, defined by a smoking history (i.e., current or former smoker) and a DLCO < 45% of the predicted value

Figure 2a: Grouped barplot showing age distribution of patients classified as classical IPAH, IPAH with a lung phenotype, and group 3 PH in COMPERA

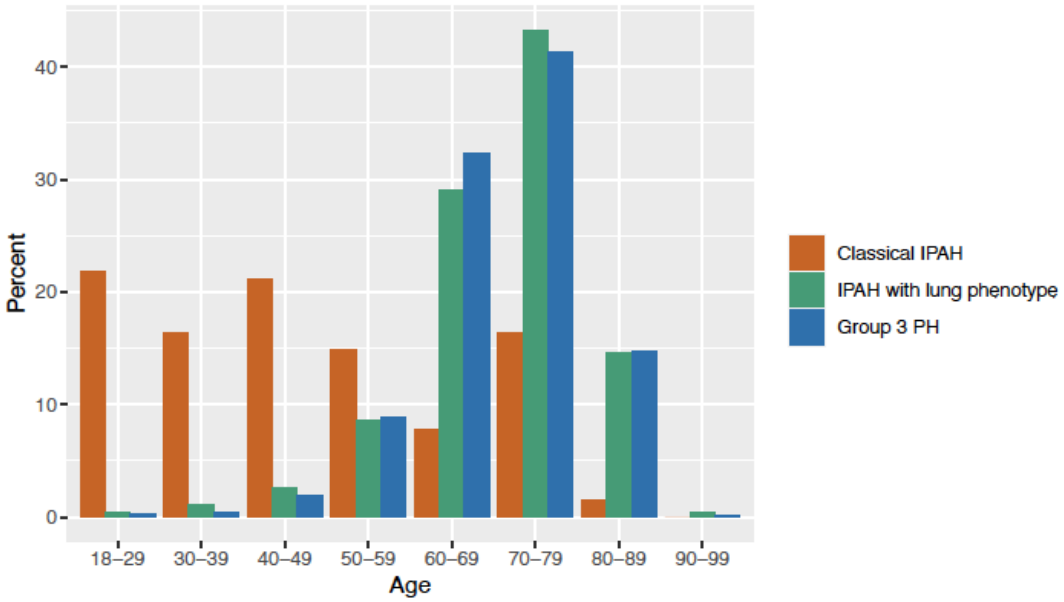


Figure 2b: Grouped barplot showing age distribution of patients classified as classical IPAH, IPAH with a lung phenotype, and group 3 PH in ASPIRE

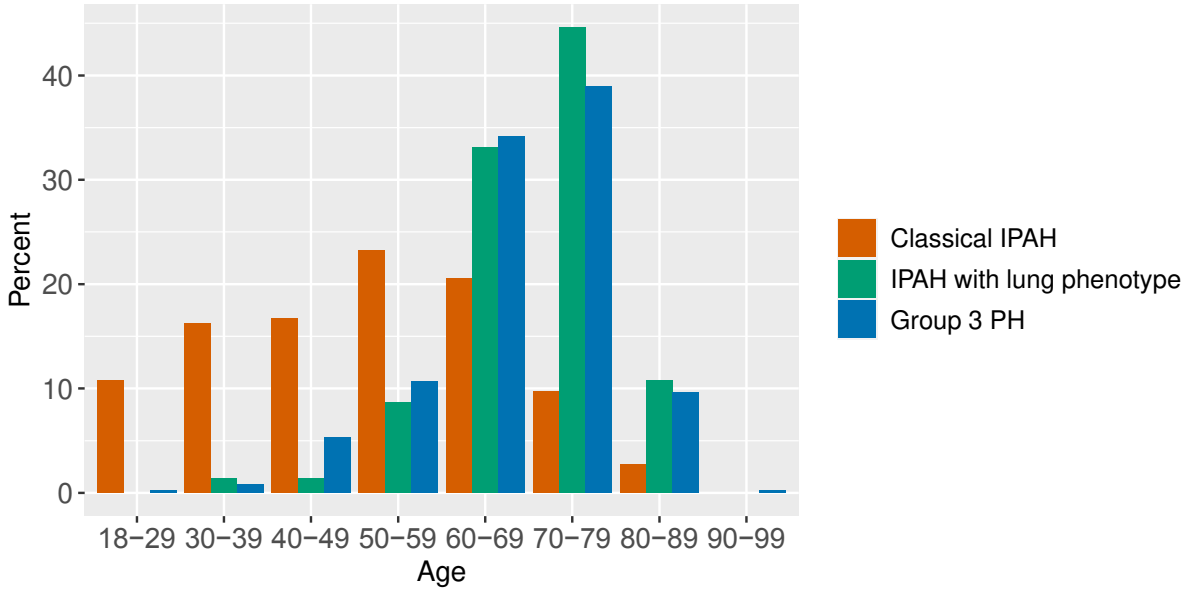
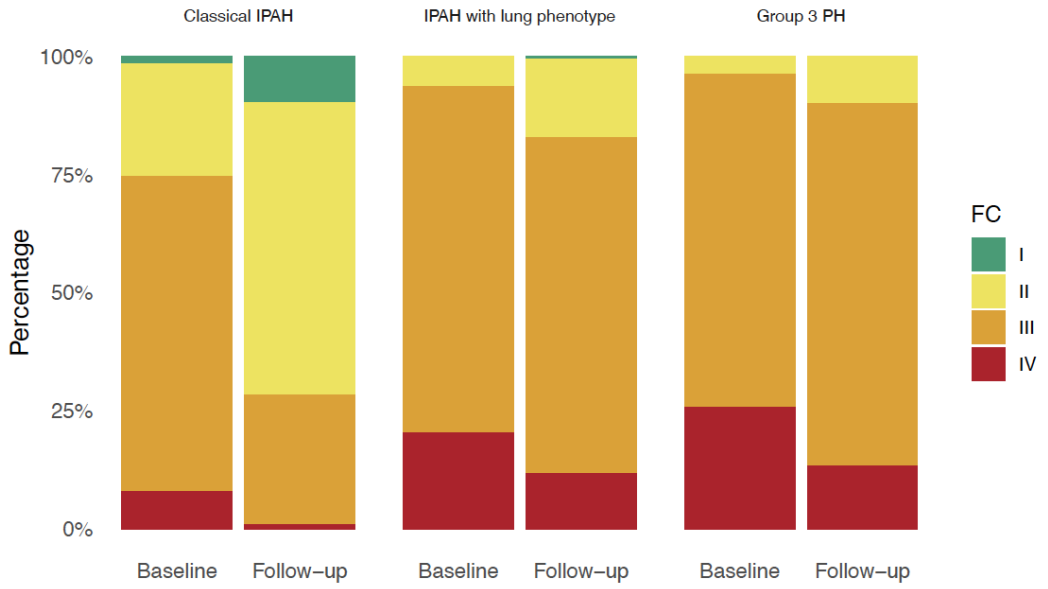


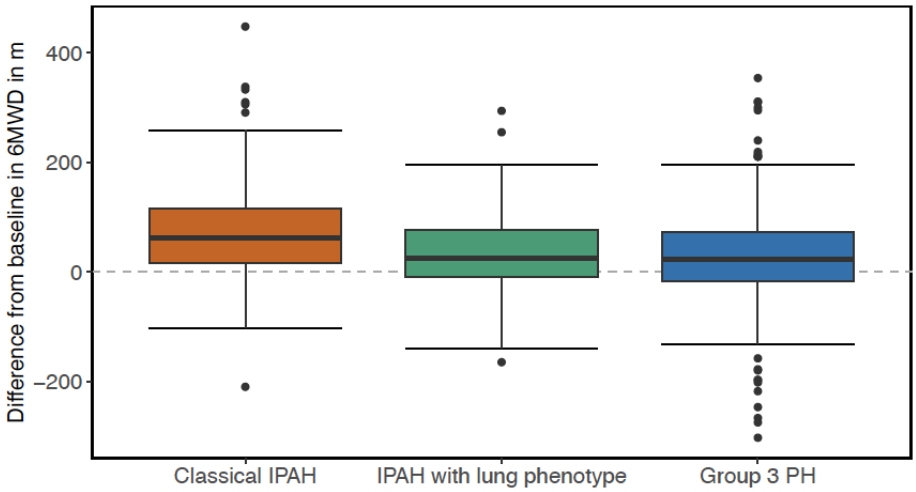
Figure 3a Baseline and first follow-up measurement for (a) functional class (FC), (b) 6-minute walking distance (6MWD), (c) N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP) and (d) mortality risk (as determined by the ESC/ERS 4-strata model) in COMPERA

a)



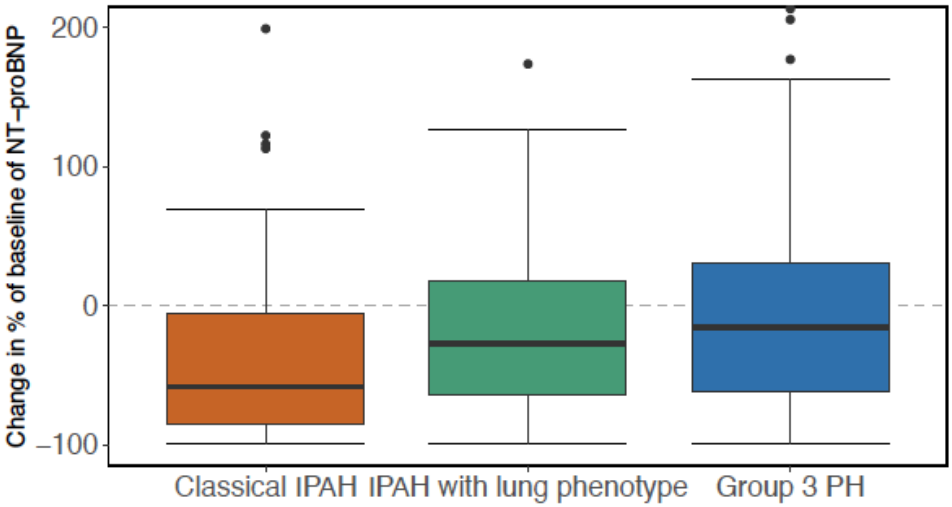
WHO FC improved from baseline to first follow-up in 54% of the patients with classical IPAH, 26% of patients with IPAH and a lung phenotype and 22% in patients with group 3 PH ($p<0{\cdot}0001$ for classical IPAH versus IPAH and a lung phenotype, and $p=0{\cdot}194$ for IPAH and a lung phenotype versus group 3 PH).

b)



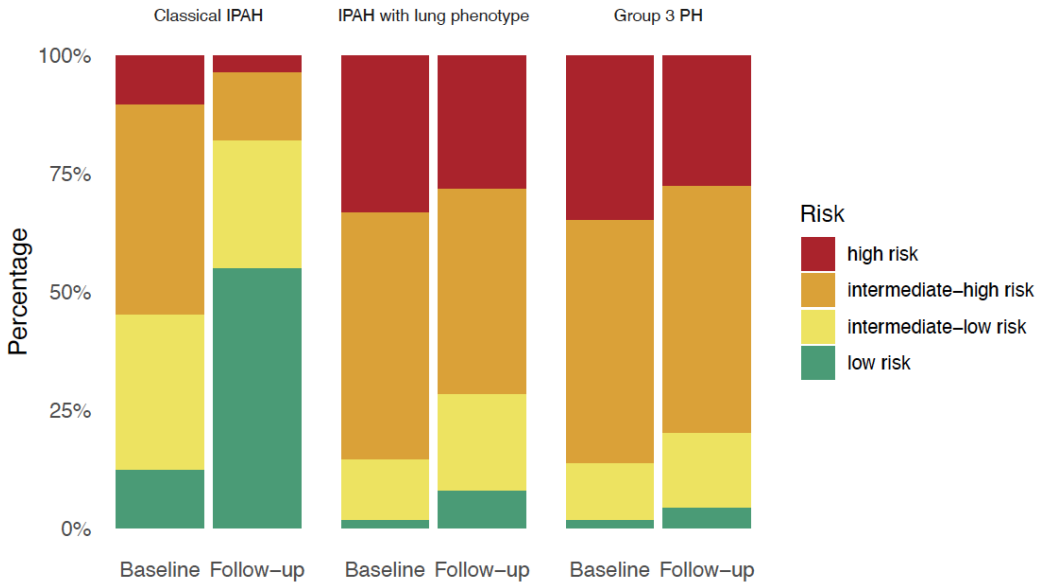
6MWD improved from baseline to first follow-up by 83 ± 111 m in patients with classical IPAH, by 31 ± 82 m of patients with IPAH and a lung phenotype, and by 27 ± 89 m in patients with group 3 PH (p=0·0015 for classical IPAH versus IPAH and a lung phenotype, and p=0·64 for IPAH and a lung phenotype versus group 3 PH).

c)



NT-proBNP decreased from baseline to first follow-up by 58 [-85, -6] % in patients with classical IPAH, by 27 [-64, 18] % of patients with IPAH and a lung phenotype, and by 16 [-62, 30] % in patients with group 3 PH (p=0·0043 for classical IPAH versus IPAH and a lung phenotype, and p=0·142 for IPAH and a lung phenotype versus group 3 PH).

d)



Risk improved from baseline to first follow-up in 64% of the patients with classical IPAH, 32% of patients with IPAH and a lung phenotype and 29% in patients with group 3 PH ($p<0{\cdot}0001$ for classical IPAH versus IPAH and a lung phenotype, and $p=0{\cdot}343$ for IPAH and a lung phenotype versus group 3 PH).

Figure 4a: Kaplan-Meier survival estimates for patients classified as classical IPAH, IPAH with a lung phenotype, and group 3 PH in COMPERA

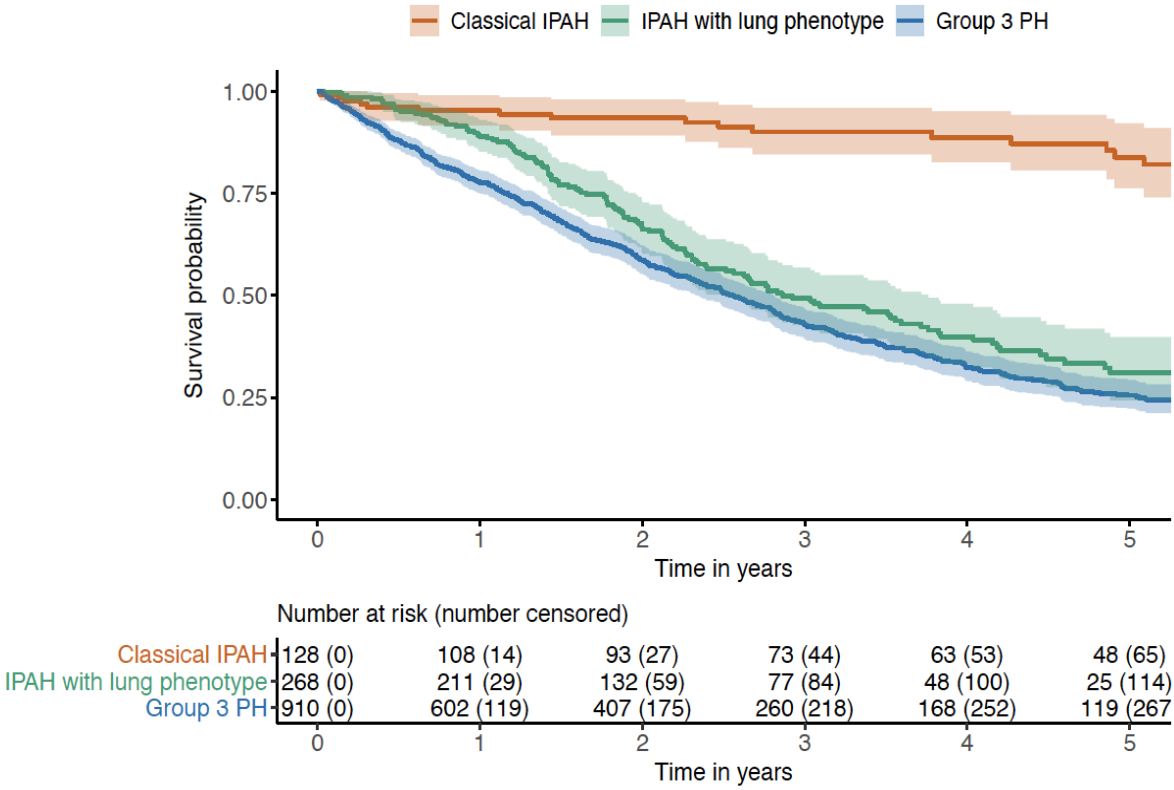
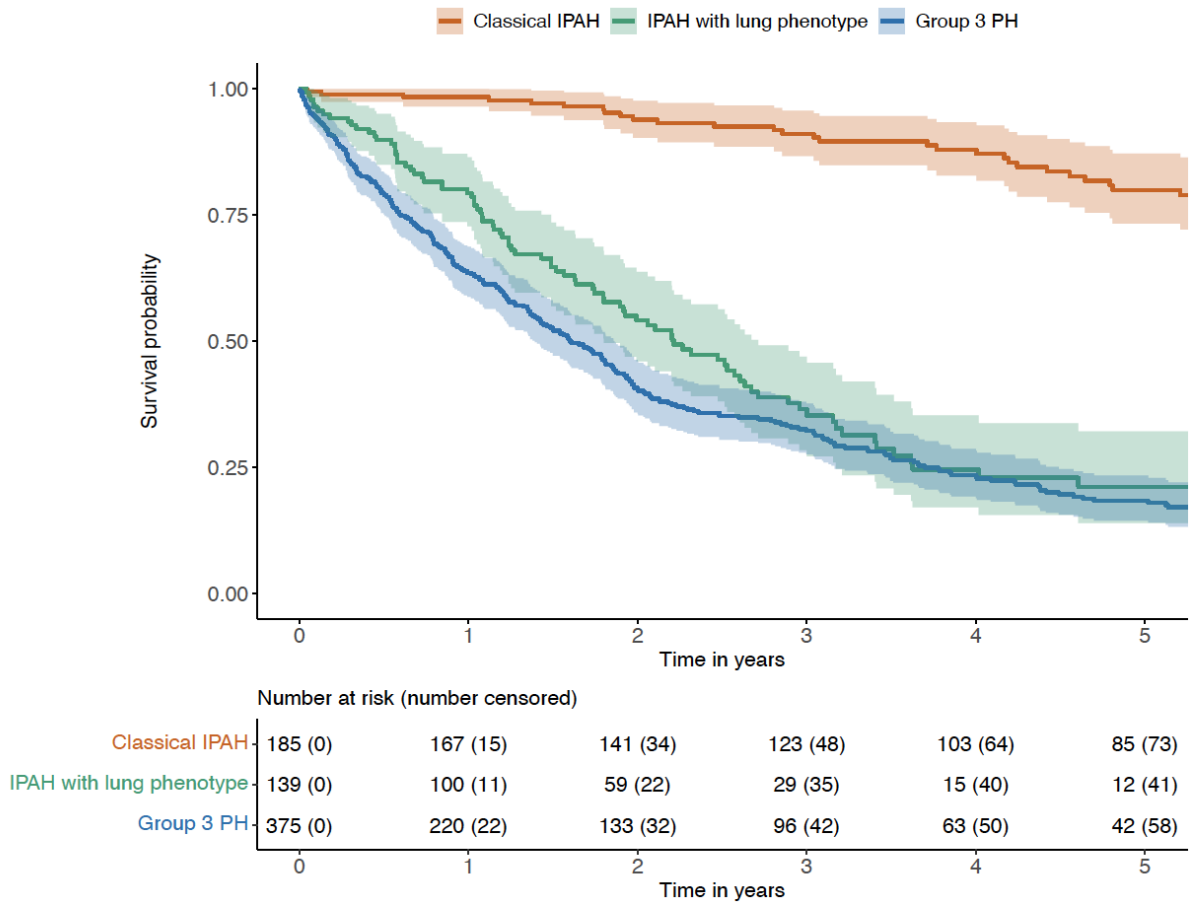


Figure 4b: Kaplan-Meier survival estimates for patients classified as classical IPAH, IPAH with a lung phenotype, and group 3 PH in ASPIRE



Contributors

MMH, CP, DH, DP, and MH designed the first part of the study (COMPERA). DGK, RC, RAL and KD co-designed the second part (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 data base. 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 MH 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.

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Strobe checklist

Figure 2a

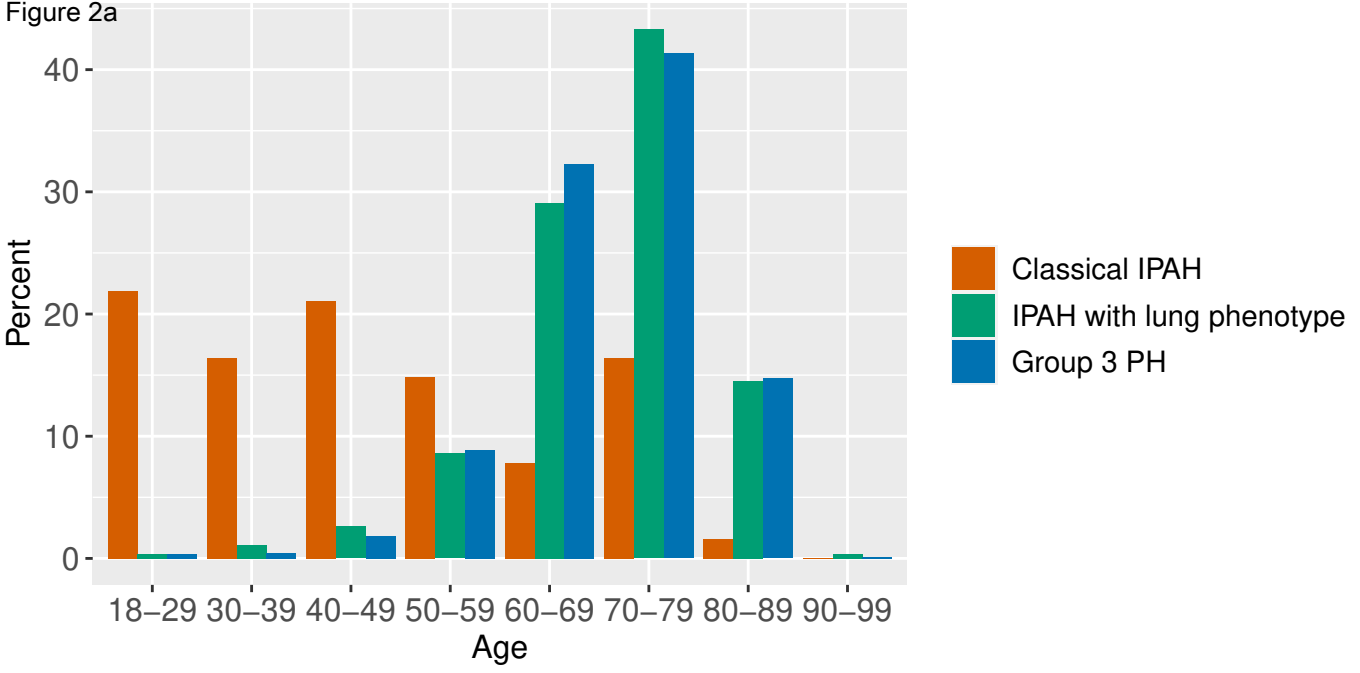

Percent
40
30
20
10
0
18–29
30–39
40–49
50–59
60–69
70–79
80–89
90–99
Age
Classical IPAH
IPAH with lung phenotype
Group 3 PH

Figure 2b

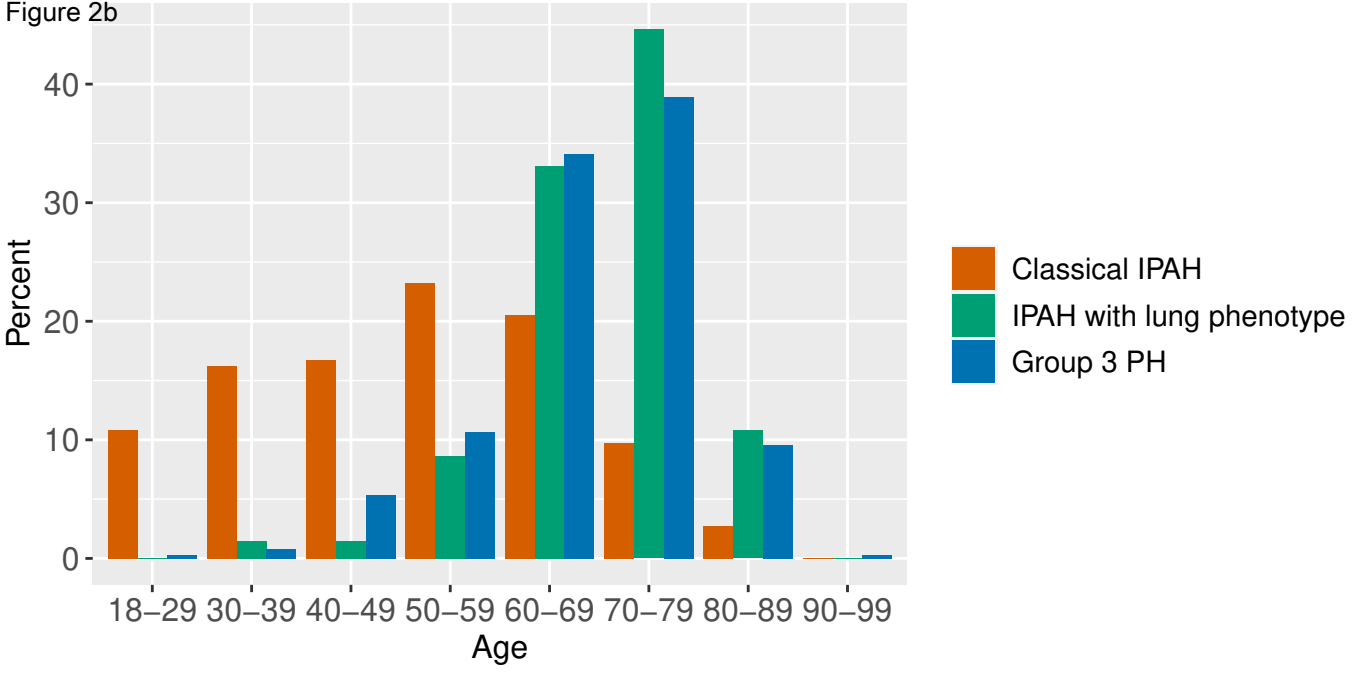

Percent
40
30
20
10
0
18–29
30–39
40–49
50–59
60–69
70–79
80–89
90–99
Age
Classical IPAH
IPAH with lung phenotype
Group 3 PH

Figure 3a

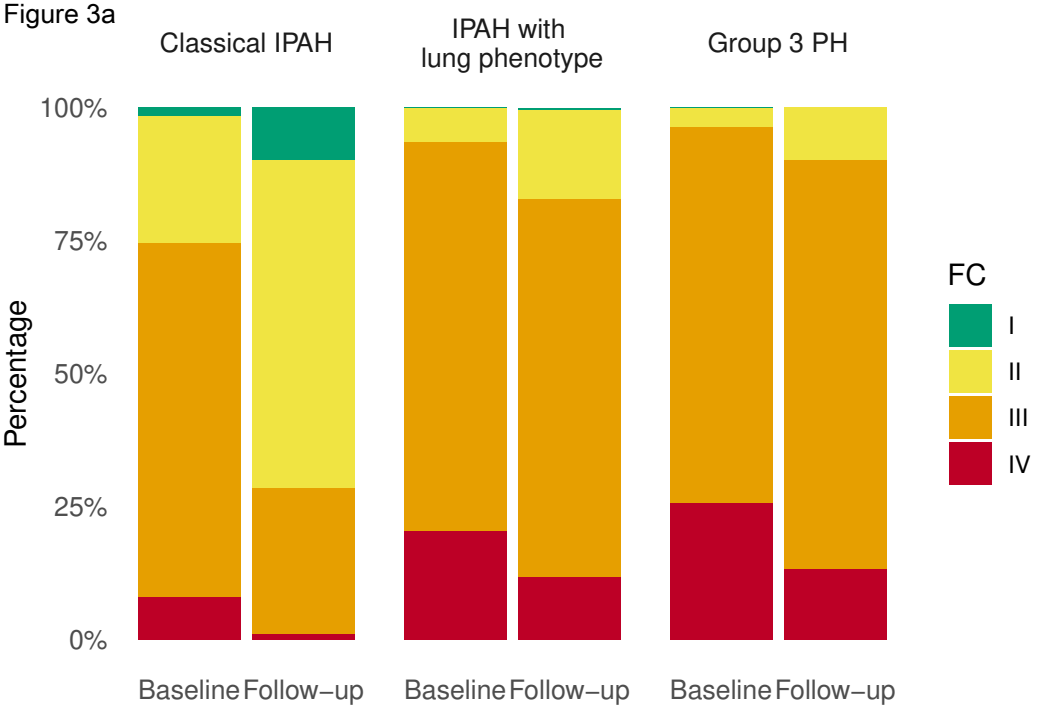

Classical IPAH
IPAH with lung phenotype
Group 3 PH
100%
75%
50%
25%
0%
Percentage
Baseline
Follow−up
Baseline
Follow−up
Baseline
Follow−up
FC
I
II
III
IV

Figure 3b

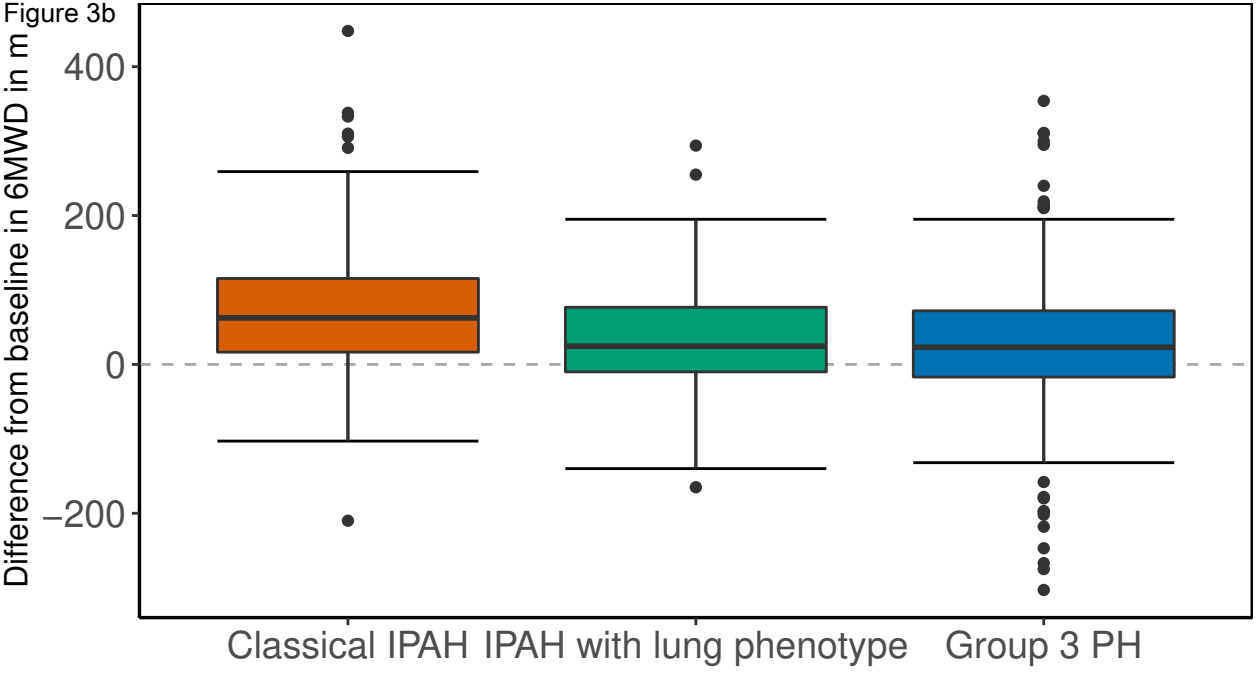

Difference from baseline in 6MWD in m
400
200
0
−200
Classical IPAH
IPAH with lung phenotype
Group 3 PH

Figure 3c

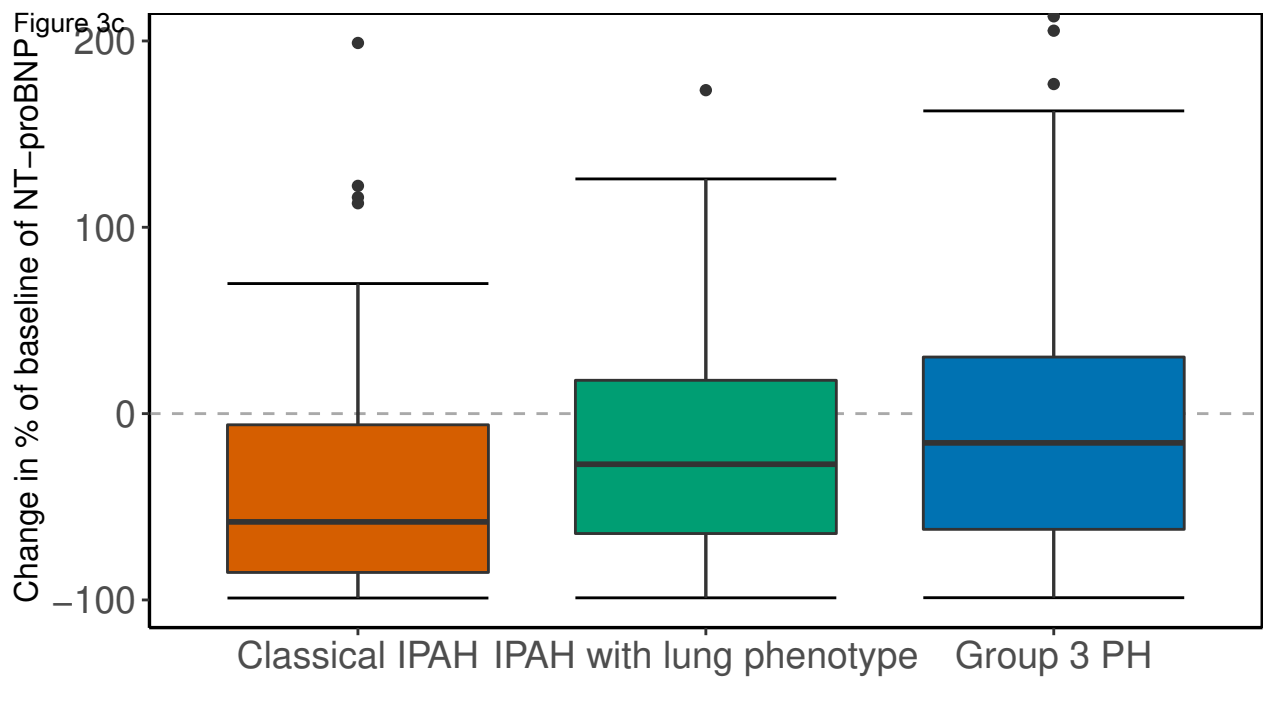

Change in % of baseline of NT−proBNP
200
100
0
−100
Classical IPAH
IPAH with lung phenotype
Group 3 PH

Figure 3d

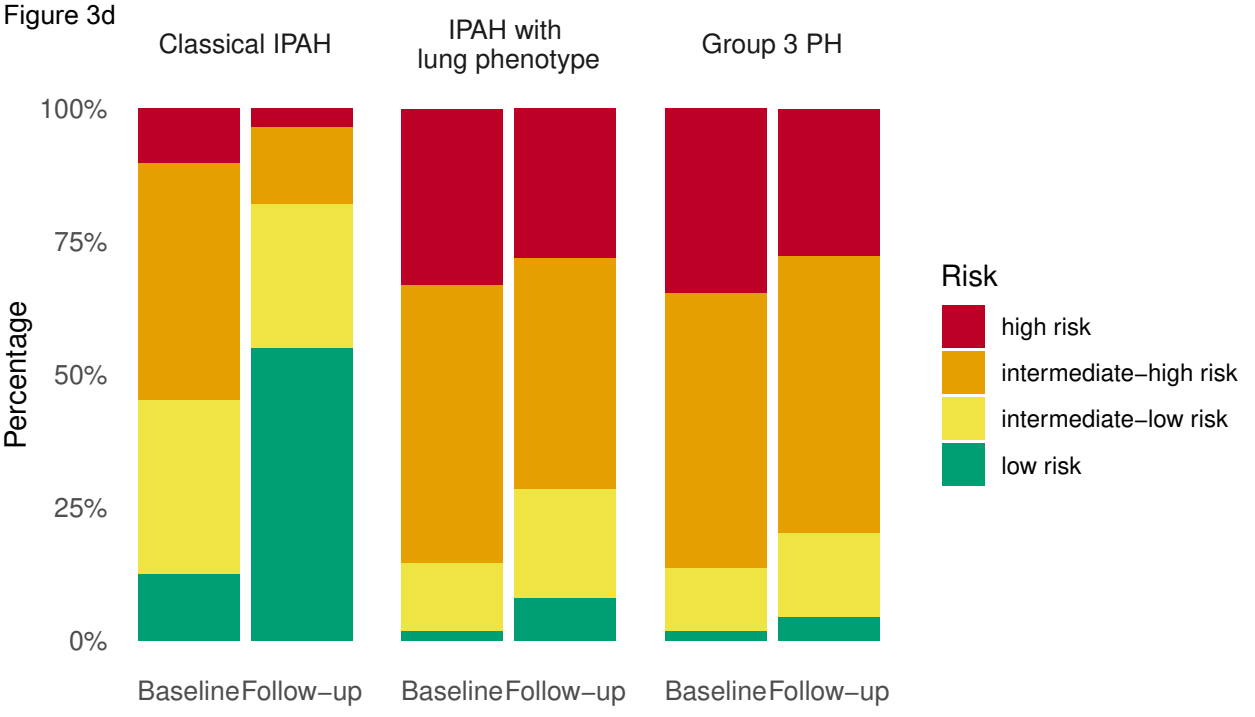

Classical IPAH
IPAH with lung phenotype
Group 3 PH
100%
75%
50%
25%
0%
Percentage
Baseline
Follow−up
Baseline
Follow−up
Baseline
Follow−up
Risk
high risk
intermediate−high risk
intermediate−low risk
low risk

Figure 4a

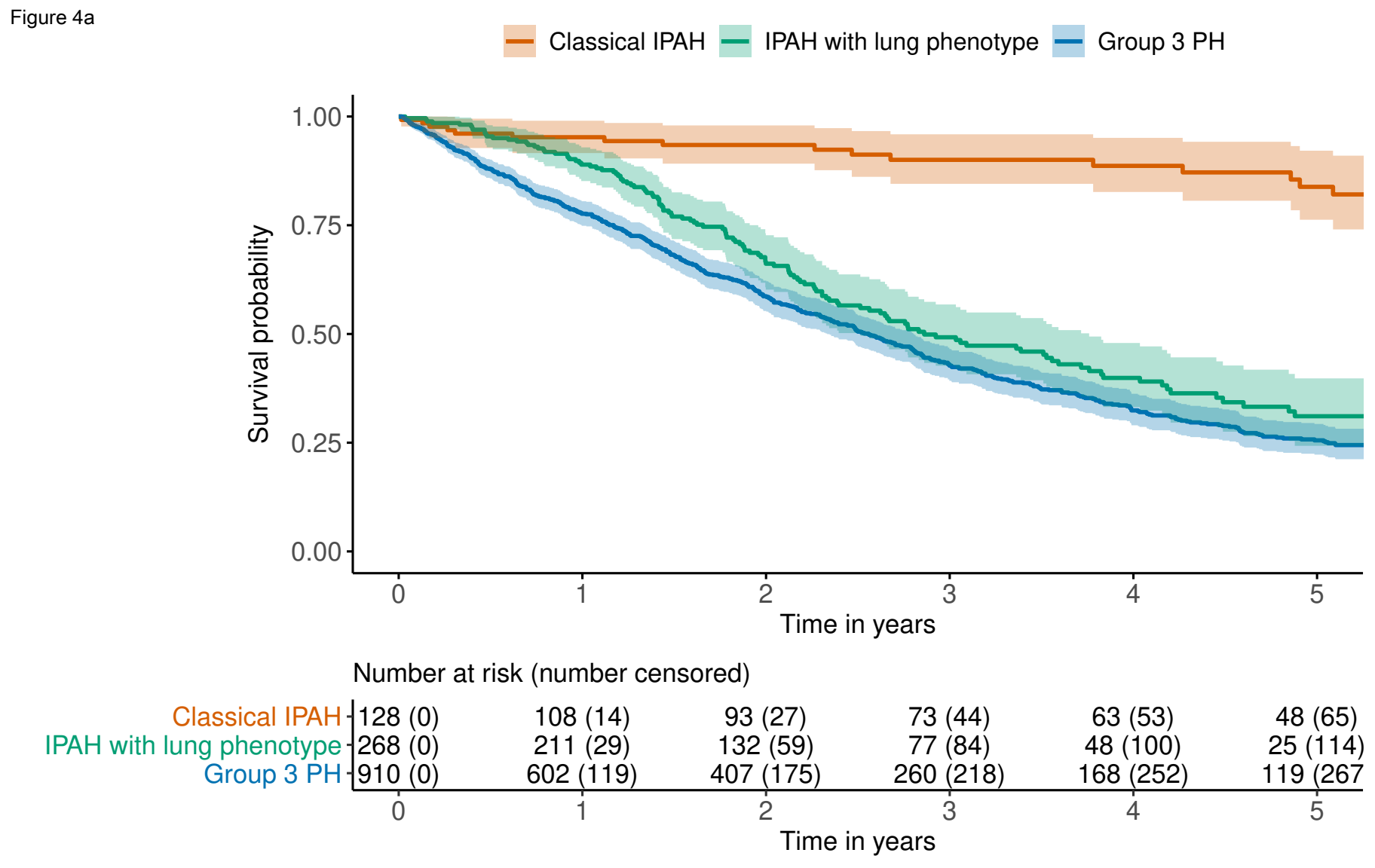
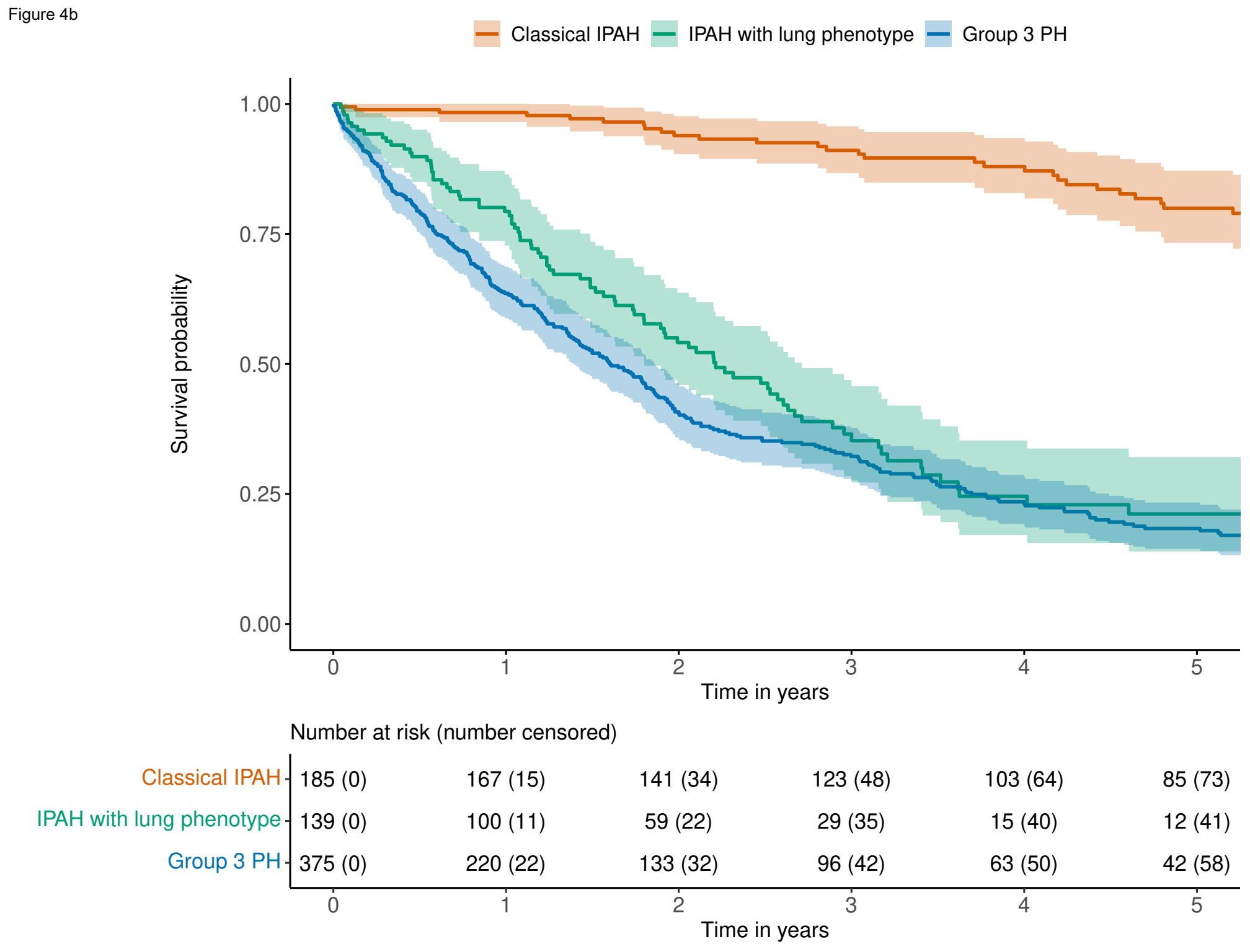

Classical IPAH
IPAH with lung phenotype
Group 3 PH
Survival probability
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
5
Time in years
Number at risk (number censored)
Classical IPAH 128 (0) 108 (14) 93 (27) 73 (44) 63 (53) 48 (65)
IPAH with lung phenotype 268 (0) 211 (29) 132 (59) 77 (84) 48 (100) 25 (114)
Group 3 PH 910 (0) 602 (119) 407 (175) 260 (218) 168 (252) 119 (267
0
1
2
3
4
5
Time in years

Figure 4b


Classical IPAH
IPAH with lung phenotype
Group 3 PH
Survival probability
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
5
Time in years
Number at risk (number censored)
Classical IPAH
IPAH with lung phenotype
Group 3 PH
185 (0)
167 (15)
141 (34)
123 (48)
103 (64)
85 (73)
139 (0)
100 (11)
59 (22)
29 (35)
15 (40)
12 (41)
375 (0)
220 (22)
133 (32)
96 (42)
63 (50)
42 (58)
0
1
2
3
4
5
Time in years