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Early View

Original research article

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External validation of a refined 4-strata risk assessment score from the French pulmonary hypertension Registry

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Take Home Message (250 characters): A 4-strata risk assessment method with low-, intermediate-low, intermediate-high, and high-risk categories was better at discriminating survival in pulmonary arterial hypertension than a 3-strata method with low-, intermediate-, and high-risk groups.

Abstract (250 words)

Introduction: Contemporary risk assessment tools categorize patients with pulmonary arterial hypertension (PAH) as low, intermediate, or high-risk. A minority of patients achieve low-risk status with most remaining intermediate-risk. Our aim was to validate a 4-strata risk assessment approach categorizing patients as low, intermediate-low, intermediate-high, or high risk, as proposed by the COMPERA Registry investigators.

Methods: We evaluated incident patients from the French PAH Registry and applied a 4-strata risk method at baseline and at first reassessment. We applied refined cut-points for 3 variables: World Health Organization functional class, 6-minute walk distance, and N-terminal pro-brain natriuretic peptide. We used Kaplan-Meier survival analyses and Cox proportional hazards regression to assess survival according to a 3-strata and 4-strata risk approach.

Results: At baseline (n=2879), the 4-strata approach identified 4 distinct risk groups and performed better than a 3-strata method for predicting mortality. The 4-strata model discrimination was higher than the 3-strata method when applied during follow-up and refined risk categories among subgroups with idiopathic PAH, connective tissue disease-associated PAH, congenital heart disease, and portopulmonary hypertension. Using the 4-strata approach, 53% of patients changed risk category from baseline compared to 39% of patients when applying the 3-strata approach. Those who achieved or maintained a low-risk status had the best survival, whereas there were more nuanced differences in survival for patients who were intermediate-low and intermediate-high.

Conclusions: The 4-strata risk assessment method refined risk prediction, especially within the intermediate risk category of patients, performed better at predicting survival and was more sensitive to change than the 3-strata approach.

Keywords: risk assessment, pulmonary arterial hypertension, prognosis

Introduction

In 2015, the European Society of Cardiology (ESC) and European Respiratory Society (ERS) guidelines proposed a multidimensional risk stratification tool to guide prognostication and treatment decisions for patients with pulmonary arterial hypertension (PAH)[1]. The 2015 ESC/ERS guidelines recommended categorization of patients into low (< 5% estimated risk of 1-year mortality), intermediate (5-10% estimated risk of 1-year mortality) and high risk (>10% estimated 1-year mortality) using clinical, exercise, imaging, and hemodynamic variables known to be associated with prognosis[1].

Shortly after the 2015 ESC/ERS guidelines, several Registry-based studies from Europe proposed methods of implementing this risk assessment proposal[2–5]. The Swedish Pulmonary Arterial Hypertension Register (SPAHR) and the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) group used an integer score method which assigned values of 1, 2, or 3 to each variable corresponding to their low-, intermediate-, or high-risk cut-points in the 2015 ESC/ERS guidelines risk table. They then calculated the average value for each patient[2, 3]. Similar to SPAHR/COMPERA, the French Pulmonary Hypertension (PH) Registry approach included clinical, exercise and invasive hemodynamic variables, but the French approach differed in methodology. Instead of an integer score, the French PH Registry method counted the number of variables meeting the low-risk criteria definition at baseline and first follow-up for World Health Organization (WHO)/New York Heart Association (NYHA) functional class (FC), 6-min walk distance (6MWD), right atrial pressure (RAP) and cardiac index (CI)[4, 5]. A simplified non-invasive French PH Registry approach using only 3 non-invasive low-risk variables (6-minute walk distance [6MWD] > 440 m, World Health Organization [WHO] functional class [FC] I or II, and NT-proBNP <

300 ng/L or BNP < 50 ng/L) can identify a truly low-risk group of patients with 1- and 5-year survival ≥95%[4, 6].

The SPAHR, COMPERA, and French PH Registry scores use overlapping variables and cut-points with the U.S. Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) score, which also includes non-modifiable prognostic factors such as disease etiology, age and sex[7]. The updated REVEAL 2.0 score classifies patients similarly into three categories (low, intermediate, and high-risk) with corresponding 1-year mortality estimates of 1.9%, 6.5%, and 25.8%[8]. These approaches have also been validated in post-hoc analyses of the PATENT-1 trial of riociguat in PAH[9, 10]. An abridged version of the REVEAL 2.0 Score, REVEAL 2.0 Lite, uses 6 modifiable variables and revised cut-points for non-invasive variables (WHO functional class, systolic blood pressure, heart rate, 6MWD and NT-proBNP/BNP)[11].

Still, advances in risk stratification are needed. Discrimination characteristics of the SPAHR/COMPERA, French PH Registry and REVEAL 2.0 scores are good but not excellent and could be further improved[8, 12, 13]. Furthermore, it remains uncertain what the best treatment strategy is for patients who remain in the intermediate-risk group using a 3-strata approach. In the European Registry studies, a minority of patients achieved a low-risk profile with initial PAH treatment and the majority of patients were in the intermediate risk category at baseline and during follow-up[2–4]. Thus, a more nuanced approach with more refined definition of intermediate risk patients may help better inform treatment decisions. To address this problem of the intermediate risk group, the SPAHR investigators suggested subdividing the intermediate risk group into intermediate-low risk and intermediate-high risk[14]. A 4-strata risk approach described by the COMPERA Registry investigators using revised scoring and cut-points for the 6MWD, WHO FC and NT-proBNP/BNP may better define risk groups[15]. The objective of this study was to validate this approach by assessing whether a 4-

strata risk assessment strategy is associated with survival among patients with PAH from the French PH Registry.

Methods

Study Design

This was a retrospective analysis of prospectively collected data in the French PH Registry (www.registre-htap.aphp.fr). Although French law does not require ethics committee approval or informed consent for retrospective data collection, the data were anonymized and compiled according to the requirements of the organization dedicated to privacy, information technology and civil rights in France ("CNIL"). The committee approved the methods used to collect and analyze data on May 24, 2003 (approval number 842063). The current study complied with the Declaration of Helsinki. The French PH Registry is part of the French Pulmonary Hypertension Reference Center (PulmoTension), funded by the French Ministry of Health.

Patient population

Data were collected using the web-based PAHTool® platform (Inovultus Ltd. Santa Maria da Feira, Portugal). We reviewed data from all incident patients with group 1 PAH who were enrolled in the French PH Registry between 01/01/2009 and 31/12/2020. Inclusion criteria were 1) adults (≥ 18 years old); 2) a right heart catheterization (RHC) demonstrating pre-capillary PAH, defined as mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg, pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg, and a pulmonary vascular resistance (PVR) > 3 Wood units. Patients were excluded if they had known pulmonary veno-occlusive disease, unrepaired congenital heart disease patients including those with Eisenmenger syndrome, or were missing data for WHO FC, 6MWD, and/or NT-proBNP/BNP at baseline.

Risk Stratification

Patients were classified using the 3-strata SPAHR/COMPERA approach (low, intermediate, high) as previously described[2, 3], as well as with a 4-strata using cut-points for WHO FC, 6MWD, NT-proBNP/BNP shown in **Table 1** based on cut-points derived and used in the COMPERA 2.0 analysis[15]. A score of 1 was assigned for low-risk, 2 for intermediate-low, 3 for intermediate-high, and 4 for high-risk values, then an average was calculated for each patient, rounded to the nearest integer. Thus, an average score of < 1.5 classified a patient as low risk, a score of 1.5-2.49 was intermediate-low risk, 2.5-3.49 was intermediate-high risk, and ≥3.5 was classified as high risk. We assessed overall survival according the 4-strata score at baseline and at the time of first follow-up within 3-24 months after diagnosis.

Statistical Analysis

Continuous data are represented as mean ± standard deviation (SD) or median (interquartile range [IQR] 25%-75%) according to data distribution. Categorical data are expressed as number (n) and percentage (%). The primary outcome was all-cause mortality. Survival time was calculated from the date of diagnostic RHC until death or last recorded clinical contact. Patients who underwent lung transplantation were censored on the date of transplantation. Survival analyses were performed using the Kaplan-Meier method with the log rank test. Cox proportional hazards regression was used to assess the association between risk category and survival, expressed as hazard ratios (HR) with 95% confidence interval (CI). We used the Harrell's C-statistic and Akaike information criteria (AIC) to compare model goodness of fit of the Cox model for discriminating overall and 1-year mortality for the 3-strata and 4-strata risk methods. We compared model performance using Harrell's C and Somers' D by randomly splitting the cohort into training and test sets[16]. Statistical significance was set at alpha ≤ 0.05. Statistical analysis was performed using SPSS Statistics version 26 (SPSS Inc, Chicago, IL) and STATA version 13.1 (StataCorp, College Station, TX).

Results

Patient characteristics

Among 4382 newly diagnosed patients with PAH enrolled in the French PH Registry between January 1, 2009 and December 31, 2020, 2879 patients met eligibility criteria and were included (**Figure 1**). There were 2082 patients with available data for a follow-up risk reassessment. Characteristics at baseline according to the 4 risk strata are shown in **Table 2**. The mean age was 61±15 years and 60% were female. Idiopathic PAH was the most frequent etiology (38%), followed by connective tissue disease (CTD)-associated PAH (27%). The median observation time was 2.25 years (IQR 0.71-4.57) and 1092 patients (38%) died during the follow-up period. The overall 1-, 3-, and 5-year survival in this cohort was 88%, 69%, and 52% respectively (**Supplementary Figure E1**).

Risk assessment at baseline

Using the 3-strata SPAHR/COMPERA risk assessment method, most patients (67%) were classified as intermediate risk at baseline, with 16% classified as low-risk and 16% classified as high-risk. Using the 4-strata approach, 12% were low-risk, 40% were intermediate-low risk, 33% were intermediate-high risk, and 15% were high-risk. Overall survival from diagnosis using the 3-strata and 4-strata risk scores is shown in **Figure 2**. There were significant differences in survival across risk groups using the 3-strata approach and using the 4-strata approach. Using the 4-risk strata at baseline, the low-risk group had an estimated 1-, 3-, and 5-year survival of 98%, 89%, 75%. For the intermediate-low risk group, 1-, 3-, and 5-year survival was 93%, 81%, 65%. For the intermediate-high risk group 1-, 3-, and 5-year survival was 86%, 63%, 44%. For the high-risk group, 1-, 3-, and 5-year survival was 75%, 45%, 31%.

In Cox proportional hazards regression models, there was an increasing risk of death for patients in the intermediate and high-risk groups compared to low-risk groups at baseline using both stratification methods (**Supplemental Table E1**). The 4-strata model discrimination for overall mortality was

slightly higher (Harrell's C-statistic 0.64, AIC 15238.4) than the 3-strata method (Harrell's C 0.61, AIC 15296.0) but this was not significantly different ($p>0.05$). The 4-strata model discrimination for 1-year mortality after diagnosis was also modestly but signicicantly higher compared to the 3-strata model (Harrell's C 0.67, AIC 4470.4 vs. Harrell's C 0.63, AIC 4500.9, $p<0.001$).

Risk assessment at follow-up

There were 2082 patients with complete data to calculate a 3-strata and 4-strata risk score at follow-up. The median duration between diagnosis and first reassessment for this analysis was 5.1 months (IQR 3.9-9.7). Using the 3-strata method, 39% were low-risk, 53% were intermediate risk, and 8% were high-risk at the time of first reassessment. Using the 4-strata method, 33% were classified as low-risk, 38% were intermediate-low risk, 23% were intermediate-high, and 6% were high-risk. Overall survival after first reassessment according to the 3-strata and 4-strata is shown in **Figure 2**. Using the 4-risk strata at first reassessment, the low-risk group had an estimated 1-, 3-, and 5-year survival of 97%, 89%, 81%. For the intermediate-low risk group, 1-, 3-, and 5-year survival was 94%, 75%, 57%. For the intermediate-high risk group 1-, 3-, and 5-year survival was 81%, 50%, 31%. For the high-risk group, 1-, 3-, and 5-year survival was 65, 28%, 13%.

In Cox regression models, there was increased risk of mortality after the first reassessment with increasing risk strata (**Supplemental Table E1**). Similar to the baseline risk assessment, the 4-strata discrimination for overall mortality after first reassessment was slightly but significantly higher compared to the 3-strata method (Harrell's C 0.70, AIC 9242.7 vs. Harrell's C 0.67, AIC 9299.3, $p<0.001$). The 4-strata model discrimination was also higher for 1-year mortality after the first reassessment compared to the 3-strata model (Harrell's C 0.73, AIC 2434.8, vs. Harrell's C 0.69, AIC 2466.0, $p=0.001$). Given that lung transplant may be a competing risk for death in eligible patients we

performed a competing risk analysis, which did not change the results at baseline or follow-up (data not shown).

Changes in 4-strata risk assessment

In the overall population (n=2879) we used Sankey diagrams to represent changes in risk category using the 3-strata and 4-strata methods (**Figure 3**). According to the 3-strata method, there was an increase in the proportion of patients in the low-risk category from baseline (16%) to follow-up (28%). Ten percent experienced early mortality or underwent lung transplantation before a full reassessment and 18% had no reassessment of risk available. Twenty-nine percent of patients changed risk categories (by improving or worsening) between baseline and follow-up with 10% remaining as stable low-risk, 31% as stable intermediate risk, and 3% remaining as high-risk. Few high-risk improved to the low-risk category.

Using the 4-strata method, the proportion of patients classified as low risk also improved from baseline (12%) to follow-up (24%). A higher proportion of patients changed risk category at follow-up when using the 4-strata method (39%) than with the 3-strata method (29%). Ten percent of patients worsened at least one category, 32% improved by at least one category, 10% were stable in the low-risk category, and 3% of patients were "stable" in the high-risk category. Of the intermediate-low risk patients at baseline, 39% changed risk categories, 39% stayed at intermediate-low risk, 6% experienced early death or transplant, and 15% had no follow-up available. . Of the patients who were at intermediate high-risk at baseline, approximately 48% changed risk categories, 25% remained intermediate-high risk, 10% experienced early death or transplant, and 18% had no follow-up available. The proportion of patients who were high risk and remained high risk was similar using the 3- or 4-strata approach. Among patients who were high-risk at baseline, 20% improved to low-risk or intermediate-low risk.

Survival was similar between patients who were stable in the low risk category and those who improved to low risk, whereas there were clear differences in long-term survival between those who ended up at intermediate-low risk compared to those who were intermediate-high risk at follow-up (**Figure 4**). Compared to patients who remained stable in the intermediate-low risk category or worsened from low to intermediate-low, survival was incrementally worse for those who improved to intermediate-low from higher risk groups and for those who improved to intermediate-high risk. Persistent high-risk status or worsening to high-risk was associated with the worst outcome. Survival according to the evolution in risk category is also shown for each baseline risk group in **Figure 5**.

4-Strata Risk Assessment in PAH Subgroups

Survival at baseline and follow-up according to the 4-strata method for the subgroups with idiopathic/heritable/drug-and toxin-induced PAH, CTD-PAH, systemic sclerosis (SSc)-associated PAHare presented in **Supplemental Figure E2** and for portopulmonary hypertension (PoPH) in **Supplemental Figure E3**. There were significant differences across risk groups using the 4-strata method for all subgroup populations (log rank rest < 0.01 for all comparisons). We also found an increase in the proportion of patients treated with initial dual combination therapy and fewer treated with monotherapy in the patients diagnosed in 2015 or later (**Supplemental Table E2**). Risk stratification models with 3 and 4-strata performed similarly in the pre-2015 and 2015-2020 groups (**Supplemental Table E3**). A sensitivity analysis excluding the 295 patients who died within 1 year of diagnosis did not change the overall results (**Supplemental Table E4**).

Discussion

In this large cohort of incident PAH patients from the French PH Registry, we evaluated a refined 4-strata risk assessment approach, based on new cut-points for 6MWD and NT-proBNP/BNP and compared this to a 3-strata risk assessment method previously proposed by the SPHAR/COMPERA Registry investigators. Our main findings were that: 1) few patients were low risk at baseline with either approach and less than 40% achieved the treatment goal of a low-risk profile during follow-up, regardless of which method was used; 2) using a 4-strata model identified distinct groups within the intermediate risk category, with an intermediate-low group that had <10% 1-year mortality, an intermediate-high risk group with a >10% 1-year mortality risk; 3) the 4-strata risk model had modestly higher discrimination for long-term mortality and 1-year mortality compared to the 3-strata model; 4) a greater proportion of patients changed risk category between baseline and follow-up when using the 4-strata approach compared to the 3-strata approach; 5) changes in risk category were associated with survival, with a more nuanced assessment of survival possible according to permutations of changes in the 4-strata risk method; 6) there were differences in survival across the 4 risk strata in all subgroups of patients with PAH. Our study confirms a recent analysis by the COMPERA investigators and provides new additional analyses to support the statistical validity of this approach. The 4-strata method was more sensitive in assessing changes in risk after initial treatment and was superior at discriminating long-term and short term (1-year) mortality, which will help patients and clinicians make better informed decisions about treatment.

Achieving or maintaining a low-risk profile is the therapeutic objective for patients with PAH[1, 17, 18]. Risk prediction is essential to inform patients about their prognosis and guides clinical decision making[1, 17]. There are several useful PAH risk assessment tools available, each with advantages and disadvantages. Importantly, objective multivariable risk scores are better at predicting a patient's risk than clinical gestalt which is why such tools are essential in modern clinical practice[19, 20]. We found

that by using a 4-strata approach with 3 variables, as proposed by the COMPERA and SPAHR investigators[14, 15], a greater proportion of patients changed their risk classification, although this alone does not necessarily indicate a better tool. The more important observation is that risk assessment using the 4-strata classification identified groups of patients in intermediate-low and intermediate-high risk categories who had clearly different outcomes. Also, the 4-strata method seemed to have higher discrimination of short and long-term outcomes compared to the 3-strata SPAHR/COMPERA approach. This indicates that a more nuanced categorization of risk can refine prediction of long-term survival using the 4-strata method. Our findings also highlight the importance of achieving a low-risk status regardless of where a patient starts, but also the prognostic relevance of unsatisfactory treatment responses and worsening risk status despite initial treatment.

Our cohort was larger than the recent COMPERA 2.0 cohort which derived the 4-strata approach, spanned a similar contemporary time period, and was comparable in terms of patient characteristics and hemodynamic severity. In validating the COMPERA 4-strata method, we confirm its simplicity and its utility in identifying a greater proportion of patients who changed risk over time. Our study also builds upon the COMPERA 2.0 analysis, with our statistical modelling demonstrating good discrimination for short and long-term survival using the 4-strata approach. The 4-strata method overlaps considerably with REVEAL 2.0 Lite, and indeed is based on the 6MWD and NT-proBNP cut-points proposed in REVEAL 2.0 Lite[11]. The COMPERA 2.0 approach uses 3 variables whereas REVEAL 2.0 Lite uses 6 variables (WHO FC, 6MWD, NT-proBNP/BNP, systolic blood pressure, heart rate, and renal function), and there is more granularity with 4 NT-proBNP groups with the COMPERA 2.0 4-strata approach as opposed to 3 NT-proBNP groups in REVEAL 2.0 Lite. These new cut-points for NT-proBNP were data-derived from the COMPERA 2.0 derivation study. In our study, the discrimination of the 4-strata model at follow-up was comparable to that reported for the 6-variable REVEAL 2.0 Lite score overall (C-Index 0.73) and when those variables that differ from the COMPERA 2.0 score

(systolic blood pressure, heart rate, and renal function) were missing (C-Index 0.72)[11]. Thus, our data indirectly support the REVEAL 2.0 Lite model and confirm the validity of the COMPERA 2.0 approach. Regardless of which method is used, a key message from all investigators and guidelines is to perform risk assessment on a regular and recurring basis.

One criticism of the 3-strata SPAHR/COMPERA risk assessment approach is that most patients remain at intermediate risk, which is potentially problematic in clinical practice. The treatment algorithm proposed in the 6th World Symposium on Pulmonary Hypertension recommends treatment escalation, which includes parenteral prostacyclin analogues or lung transplantation assessment for patients who remain at intermediate risk despite optimal therapy[12]. The management of low-risk patients and high-risk patients is relatively straightforward since low-risk patients are achieving treatment goals and high-risk patients clearly require more aggressive interventions such as parenteral therapies and/or lung transplantation referral, or should be provided with palliative care options if they are not candidates for these interventions. Refining risk within the intermediate risk category using the 4-strata approach will be valuable to clinicians and will better inform treatment decisions for this group, especially with respect to transplantation or parenteral prostanoids. For example, lung transplantation in general should be considered for patients with an estimated ≥50% mortality at 2-years[21]. Using the 3-strata method, the median survival time for patients who remained at intermediate risk at follow-up in our cohort was 4.3 (IQR 2.1-7.8) years, so referral for transplantation would be premature for most of these intermediate risk patients. Using the 4-strata method at follow-up, median survival was 5.8 years (IQR 3.0-9.6) for intermediate-low risk patients and 3 years (IQR 1.4-5.5) for intermediate-high risk patients. Therefore, lung transplantation assessment would certainly be reasonable for patients who remained at intermediate-high risk after initial therapy, but likely not reasonable for those intermediate-low risk patients. Another scenario in which the distinction between intermediate-low and intermediate-high may be clinically useful pertains to the addition of a third medication to a patient already on dual oral

therapy with a phosphodiesterase type-5 inhibitor and endothelin receptor antagonist. In places where oral selexipag or oral treprostinil are available, it might be more acceptable to an oral third agent for an intermediate-low risk patient, whereas a more compelling case can be made for adding a parenteral prostanoid for intermediate-high risk patients. These examples illustrate the value of refining risk within the intermediate-risk group of patients, with respect to clinical decision making.

A strength of this study was the large cohort size, which permitted validation of the risk assessment methods in several important subgroups such as idiopathic/heritable/drug-and-toxin induced PAH, CTD-PAH, SSc-PAH, and CHD-PAH, which often differ in terms of characteristics, treatment, and prognosis. The limitations of this study include the retrospective nature of the analysis and missing data for follow-up risk assessment for 28% of patients, due to early death or transplantation (10%) or lack of available follow-up data (18%). There may also have been changes in medical therapies after the first follow-up assessment and the impact of subsequent therapeutic decisions on long-term risk and long-term survival were not accounted for in this analysis, which is a limitation. While the 4-strata model performed well at discriminating outcomes, C-statistics in the range of 0.6-0.7 are considered good but not excellent. As most PAH risk scores have C-statistics in the range of 0.6-0.8[8, 12, 13], future studies should aim to improve the performance of risk prediction methods, ideally without sacrificing simplicity. We also noted that the 4-strata approach may be less useful in the subgroup with PoPH, with little difference between the intermediate-high- and high-risk strata (see **Supplemental Figure E3**). The optimal stratification method for patients with PoPH requires further study, as survival in this population is highly dependent on other factors, such as the presence of cirrhosis and severity of liver disease[22, 23]. Lastly, we included only patients with mPAP $\geq$ 25 mmHg, which was the accepted threshold for PAH at the time of this cohort. The applicability of our results to populations with PAH defined as mPAP > 20 mmHg according to the 6th World Symposium on Pulmonary Hypertension, requires further study[24].

In conclusion, our study supports the notion of a 4-strata risk assessment approach using revised cut-points for the 6MWD and NT-proBNP/BNP. The 4-strata approach better discriminated the risk of future mortality over the short and long term and appears to have greater sensitivity in identifying changes in risk. This approach enhanced the granularity of risk assessment, especially for intermediate risk patients, which will likely help clinicians evaluate more subtle treatment-related improvements and better identify patients who require more aggressive treatment. Further work is needed to determine which risk assessment method is most sensitive to change in the context of clinical trials.

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Tables

Table 1 – Proposed scoring for the COMPERA 2.0 4-strata risk assessment method

	Points Assigned			
Variable	**1**	**2**	**3**	**4**
WHO FC	I or II	-	III	IV
6MWD	>440 m	440-320 m	319-165 m	<165 m
BNP or	<50 ng/L	50-199 ng/L	200-800 ng/L	>800 ng/L
NT-proBNP	<300 ng/L	300-649 ng/L	650-1100 ng/L	>1100 ng/L

Abbreviations: WHO, World Health Organization; FC, functional class; 6MWD, 6 min walking distance, BNP, brain natriuretic peptide, NT-proBNP, N-terminal pro-brain natriuretic peptide

Table 2 – Baseline characteristics

Characteristic	**All Patients (n=2879)**	**Low Risk (n=340)**	**Intermediate -low Risk (n= 951)**	**Intermediate -high Risk (n= 1162)**	**High-Risk (n=426)**
Age, years	61±15	54±14	59±14	63±14	65±15
Female sex, n (%)	1737 (60)	181 (53)	562 (59)	720 (62)	274 (64)
BMI	27.2±6.5	26.1±4.9	27.4±6.2	27.6±7.0	26.6±6.7
Etiology of PAH, n (%)					
Idiopathic PAH	1094 (38)	99 (29)	323 (34)	483 (41.5)	189 (44)
Heritable PAH	137 (5)	23 (7)	45 (5)	56 (5)	13 (3)
Drug and toxin-induced	230 (8)	24 (7)	77 (8)	102 (9)	27 (6)
CTD	781 (27)	93 (27)	244 (25.5)	297 (25.5)	147 (35)
SSc	603 (21)	71 (21)	188 (20)	236 (20)	108 (25)
CHD	23 (1)	6 (2)	7 (0.5)	10 (1)	0
HIV	89 (3)	19 (6)	38 (4)	28 (2)	4 (1)
PoPH	525 (18)	76 (22)	217 (23)	186 (16)	46 (11)
Comorbidities, n (%)					
Obesity	654 (23)	56 (16)	221 (23)	284 (24)	93 (22)
Coronary heart disease	182 (6)	15 (4)	43 (5)	87 (7)	37 (9)
Diabetes mellitus	487 (17)	32 (9)	148 (16)	212 (18)	95 (22)
Arterial hypertension	1222 (42)	95 (28)	377 (40)	549 (47)	201 (47)
WHO FC, n (%)					
I-II	925 (32)	340 (100)	487 (51)	98 (8)	0

III	1541 (54)	0	456 (48)	925 (80)	160 (38)
IV	413 (14)	0	8 (1)	139 (12)	266 (62)
6MWD, m	300 (176-400)	466 (420-513)	367 (306-426)	248 (180-325)	0 (0-115)
NT-proBNP, ng/L	995(281-2726)	135 (78-247)	422 (161-858)	1573 (777-3020)	3597 (194-7074)
BNP, ng/L	207 (74-512)	35 (20-61)	108 (50-225)	360 (177-616)	880 (499-1286)
Hemodynamics					
RAP, mmHg	8 ± 5	6 ± 4	7 ± 5	9 ± 6	11 ± 7
PAPm, mmHg	45 ± 12	39 ± 12	43 ± 12	47 ± 12	49 ± 12
PAWP, mmHg	9 ± 4	9 ± 4	9 ± 4	9 ± 4	9 ± 4
CO, L/min	4.6 ± 1.6	5.6 ± 1.5	5.1 ± 1.6	4.3 ± 1.4	3.8 ± 1.2
CI, L/min/m2	2.6 ± 0.8	3.1 ± 0.8	2.8 ± 0.8	2.4 ± 0.7	2.2 ± 0.6
PVR, WU	8.8 ± 4.8	5.8 ± 2.9	7.4 ± 4.1	9.7 ± 4.8	11.6 ± 5.8
SvO2, %	63 ± 10	71 ± 7	66 ± 7	61 ± 9	56 ± 12
HR, bpm	79 ± 15	75 ± 14	76 ± 15	79 ± 16	84 ± 16
SVI, ml/m^2	35 ± 17	45 ± 30	39 ± 13	31 ± 10	26 ± 7
Initial Treatment Strategy, n (%)					
CCB only	167 (6)	37 (11)	59 (6)	62 (5)	9 (2)
Monotherapy	1397 (48)	193 (56.5)	530 (56)	531 (46)	143 (34)
Dual therapy	796 (28)	51 (15)	204 (21)	387 (33)	154 (36)
Triple therapy	79 (3)	1 (0.5)	14 (2)	35 (3)	29 (7)
None	440 (15)	58 (17)	144 (15)	147 (13)	91 (21)

Abbreviations: BMI – body mass index; PAH – pulmonary arterial hypertension; CTD – connective tissue disease; SSc – systemic sclerosis; CHD – congenital heart disease; HIV – human immunodeficiency virus; PoPH – portopulmonary hypertension; WHO FC – World Health Organization functional class; 6MWD – 6-minute walking distance; NT-proBNP – N-terminal pro-brain natriuretic peptide; BNP – brain natriuretic peptide; RAP – right atrial pressure; PAPm – mean pulmonary arterial pressure; PAWP – pulmonary artery wedge pressure; CO – cardiac output; CI – cardiac index; PVR – pulmonary vascular resistance; SvO2 – mixed venous oxygen saturation; HR – heart rate; SVI – stroke volume index; CCB – calcium channel blocker

Figure Legends

Figure 1 – Study Flow Diagram.

Abbreviations: PAH – pulmonary arterial hypertension; PVOD – pulmonary veno-occlusive disease; CHD – congenital heart disease; WHO FC – World Health Association functional class; 6MWD – 6-minute walking distance; BNP, brain natriuretic peptide; NTproBNP, N-terminal pro-brain natriuretic peptide

Figure 2 – Survival according to a 3-strata after diagnosis (A) and after first reassessment (B). Survival according the 4-strata risk assessment strategy after diagnosis (C) and after first reassessment (D).

Log rank test $p<0.001$ for all models.

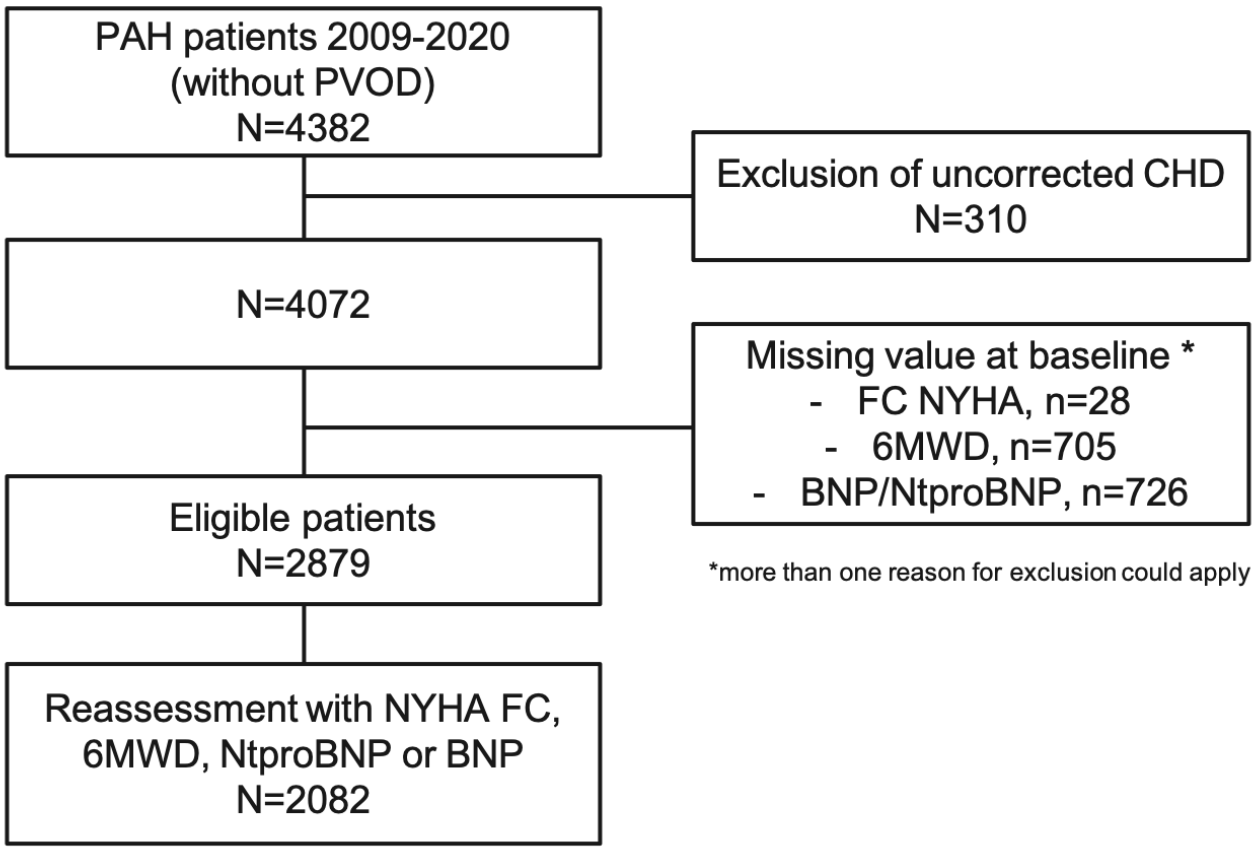
Figure 3 – Sankey diagrams showing changes in risk status using the 3-strata method (A) and 4-strata method (B). Sankey diagrams are a visualization technique to display flows. Each panel shows the flow of patients between risk strata (nodes) from baseline to first re-assessment. The width of each band is weighted to the proportion of patients who had a given risk trajectory.

Figure 4 – Overall survival according to changes in risk strata between baseline and first reassessment.

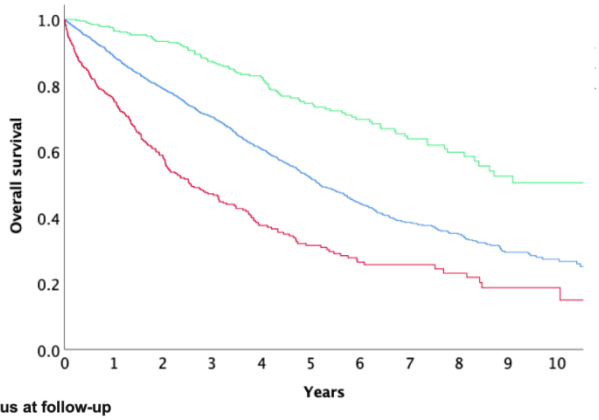
Log rank test $p<0.001$.

Figure 5 – Survival according to change in risk strata for patients who were low-risk at baseline (A), intermediate-low risk at baseline (B), intermediate-high at baseline (C), and high-risk at baseline (D).

Log-rank test $p<0.001$ for each panel.


PAH patients 2009-2020
(without PVOD)
N=4382
Exclusion of uncorrected CHD
N=310
N=4072
Missing value at baseline *
- FC NYHA, n=28
- 6MWD, n=705
- BNP/NtproBNP, n=726
Eligible patients
N=2879
*more than one reason for exclusion could apply
Reassessment with NYHA FC,
6MWD, NtproBNP or BNP
N=2082

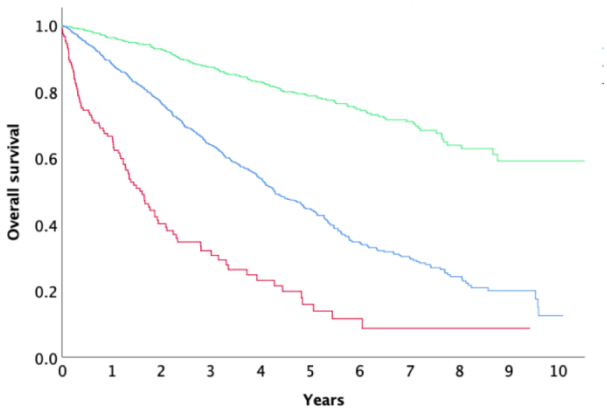
A



Risk status at follow-up

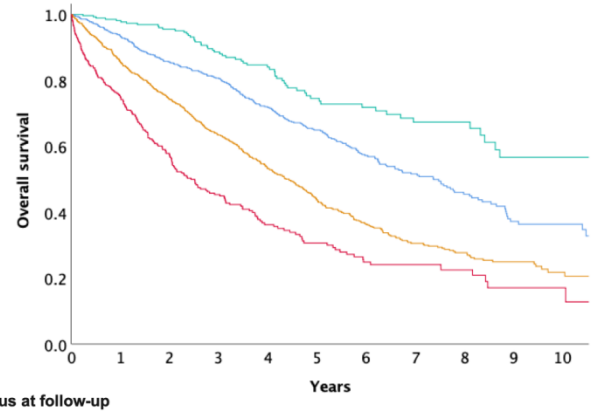
Low	471	336	281	234	178	133	106	80	50	26	10
Intermediate	1942	1303	1087	811	610	429	295	205	143	77	41
High	466	265	173	123	77	53	37	25	18	10	5

B



	816	618	511	408	322	252	178	114	62	21	3
	1109	790	597	416	297	199	121	78	38	14	1
	157	79	39	23	14	8	4	2	2	1	0

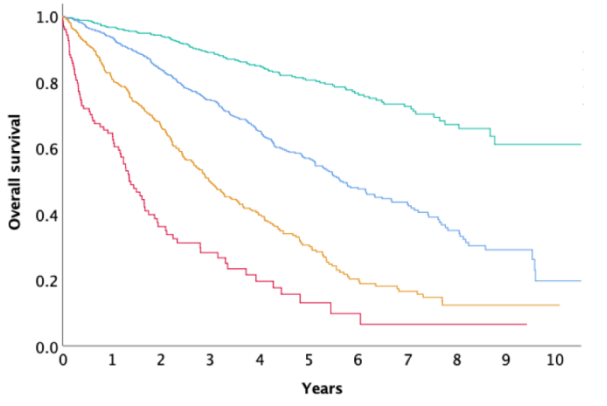
C



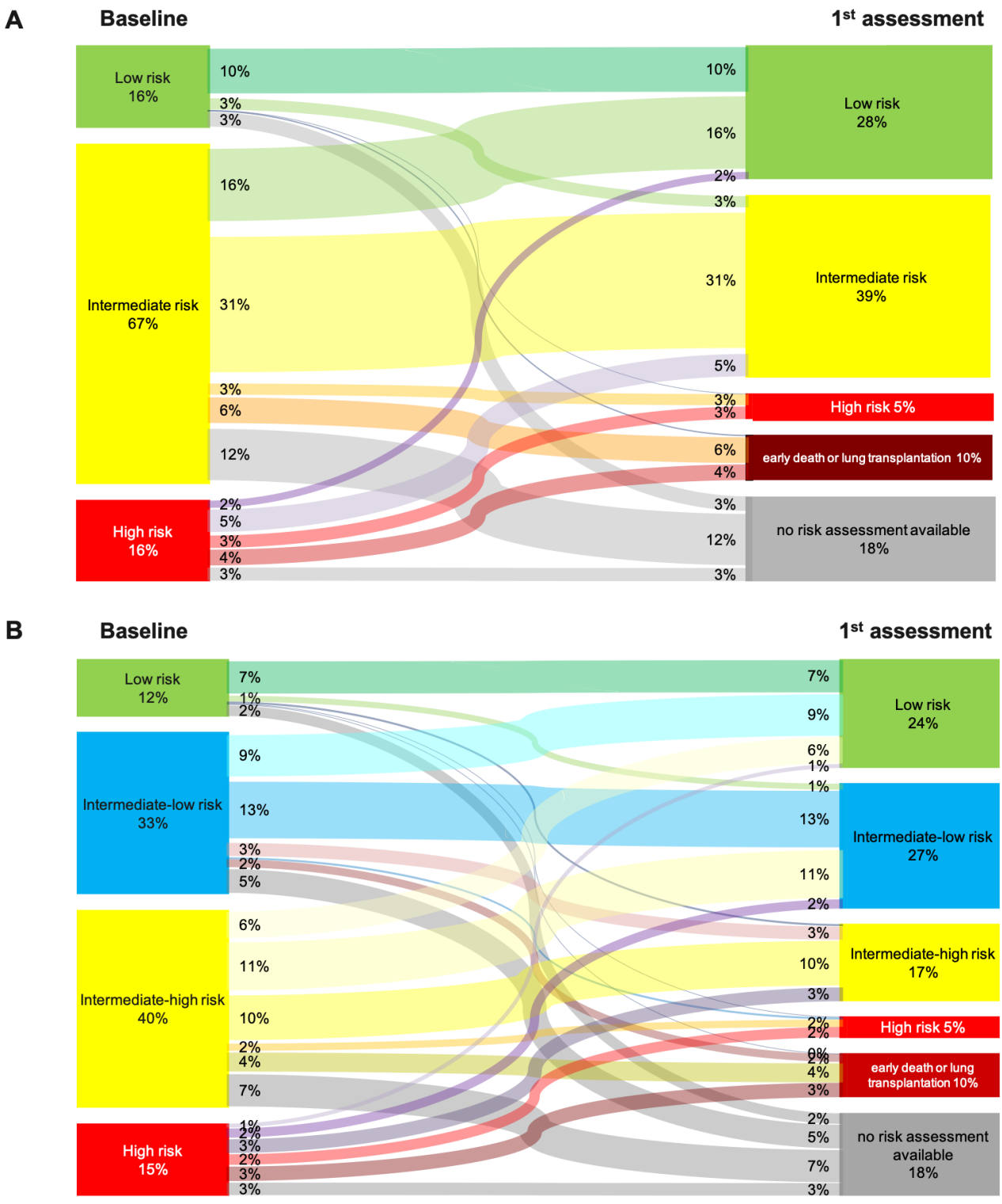
Risk status at follow-up

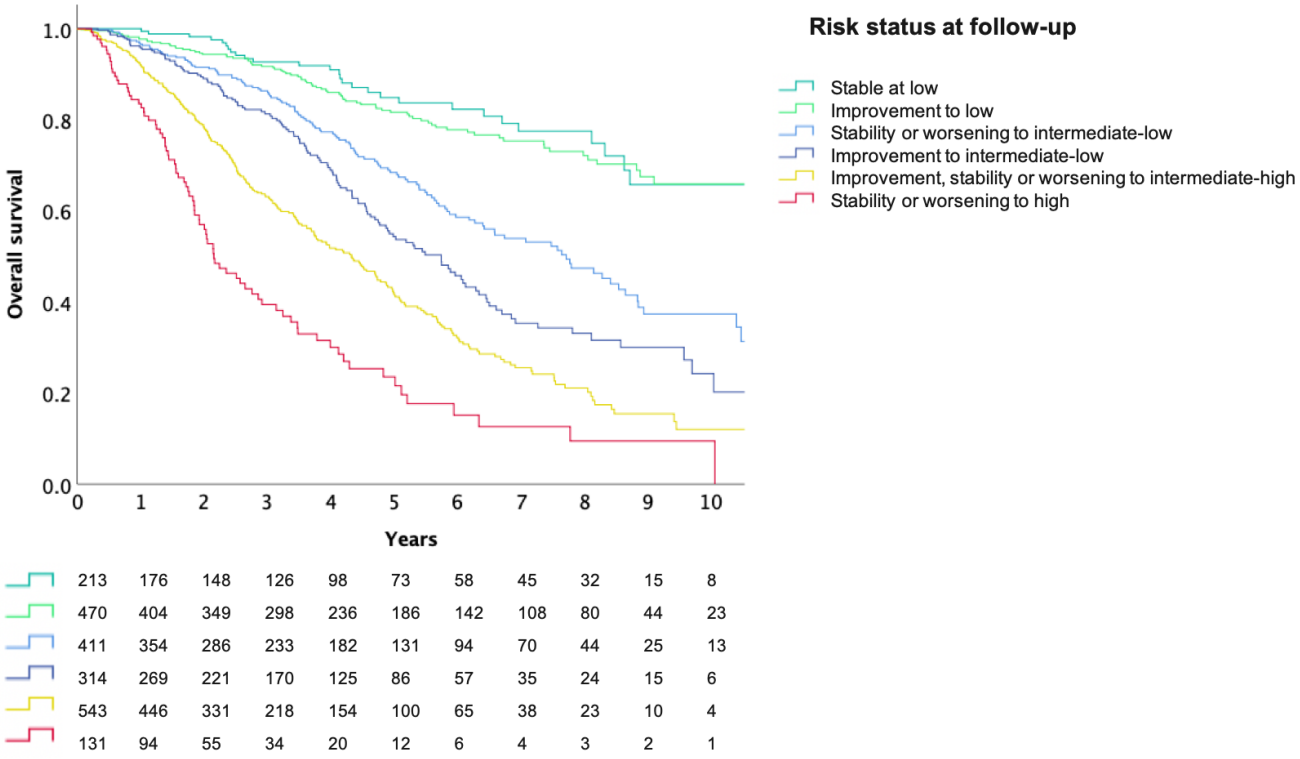
Low	340	243	205	169	126	88	71	56	38	18	8
Intermediate-low	1162	805	619	443	329	230	156	106	75	43	19
Intermediate-high	951	711	563	448	344	251	180	128	84	45	25
High	426	237	156	108	66	46	31	20	14	7	4

D

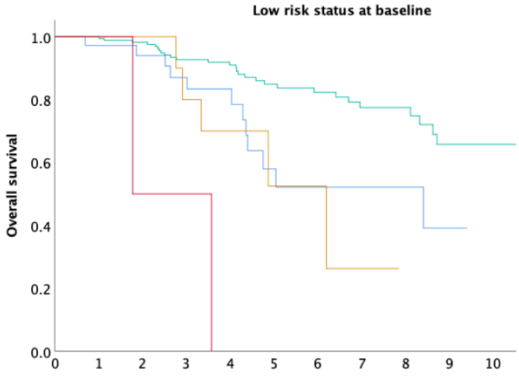


	683	521	440	356	280	217	151	100	54	17	2
	783	588	448	331	248	177	120	73	39	15	1
	483	316	229	142	95	60	29	20	7	3	1
	133	63	30	18	10	5	3	2	2	1	0


A
Baseline
1st assessment
Low risk 16%
Intermediate risk 67%
High risk 16%
10%
3%
3%
16%
31%
3%
6%
12%
2%
5%
3%
4%
3%
10%
16%
2%
3%
31%
5%
3%
3%
6%
4%
3%
12%
3%
Low risk 28%
Intermediate risk 39%
High risk 5%
early death or lung transplantation 10%
no risk assessment available 18%
B
Baseline
1st assessment
Low risk 12%
Intermediate-low risk 33%
Intermediate-high risk 40%
High risk 15%
7%
1%
2%
9%
13%
3%
2%
5%
6%
11%
10%
2%
4%
7%
1%
2%
3%
2%
3%
3%
7%
9%
6%
1%
1%
13%
11%
2%
3%
10%
3%
2%
2%
0%
2%
4%
3%
2%
5%
7%
3%
Low risk 24%
Intermediate-low risk 27%
Intermediate-high risk 17%
High risk 5%
early death or lung transplantation 10%
no risk assessment available 18%

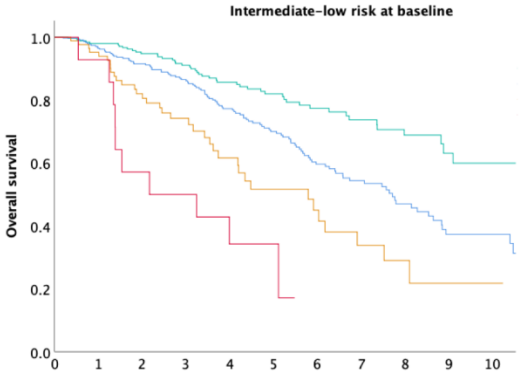

Risk status at follow-up
Stable at low
Improvement to low
Stability or worsening to intermediate-low
Improvement to intermediate-low
Improvement, stability or worsening to intermediate-high
Stability or worsening to high
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
6
7
8
9
10
Years
213 176 148 126 98 73 58 45 32 15 8
470 404 349 298 236 186 142 108 80 44 23
411 354 286 233 182 131 94 70 44 25 13
314 269 221 170 125 86 57 35 24 15 6
543 446 331 218 154 100 65 38 23 10 4
131 94 55 34 20 12 6 4 3 2 1

A



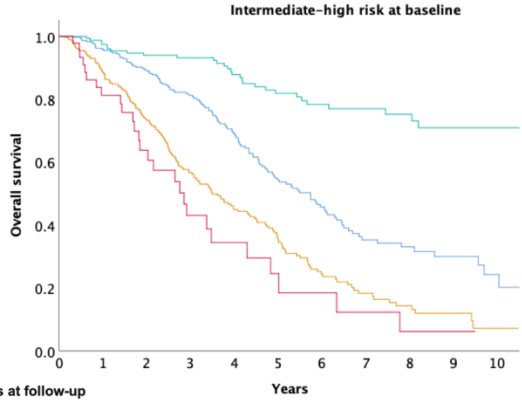
Risk status at follow-up											
Low	213	176	148	126	98	73	58	45	32	15	8
Intermediate-low	37	34	29	24	17	10	9	8	5	2	0
Intermediate-high	12	12	11	8	6	3	2	1	0	0	0
High	2	2	1	1	0	0	0	0	0	0	0

B



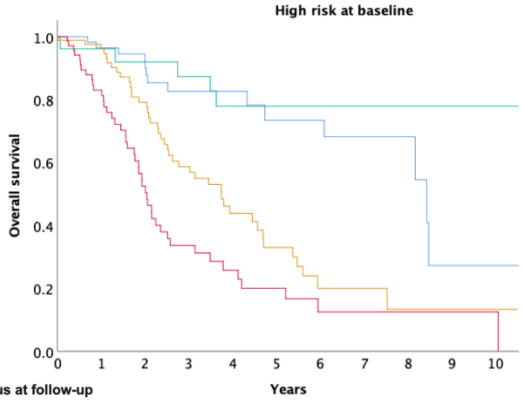
Risk status at follow-up											
Low	270	234	198	164	127	100	74	55	39	20	11
Intermediate-low	372	318	256	208	165	121	85	62	39	23	13
Intermediate-high	88	76	57	38	27	17	13	7	4	2	1
High	14	13	8	7	4	2	0	0	0	0	0

C



Risk status at follow-up											
Low	174	146	130	115	95	75	59	46	36	21	11
Intermediate-low	314	269	221	170	125	86	57	35	24	15	6
Intermediate-high	292	238	174	110	81	53	31	19	12	5	1
High	46	32	20	11	7	4	3	2	1	1	0

D



Risk status at follow-up											
Low	26	24	21	19	14	11	9	7	5	3	1
Intermediate-low	60	54	40	29	21	15	15	8	5	2	1
Intermediate-high	91	66	48	33	19	12	4	3	2	1	1
High	71	47	26	15	9	6	3	2	2	1	1

External validation of a refined 4-strata risk assessment score from the French pulmonary arterial hypertension registry

Athénaïs Boucly, Jason Weatherald, Laurent Savale, Pascal de Groote, Vincent Cottin, Grégoire Prévot, Ari Chaouat, François Picard, Delphine Horeau-Langlard, Arnaud Bourdin, Etienne-Marie Jutant, Antoine Beurnier, Mitja Jevnikar, Xavier Jaïs, Gérald Simonneau, David Montani, Olivier Sitbon, Marc Humbert

Online Supplemental Materials

Supplemental Table E1 – Cox proportional hazards regression models for overall survival at baseline and after 1st reassessment.

Baseline Risk Assessment	**Hazard Ratio**	**95% CI**	**1st Follow-up Risk Assessment**	**Hazard Ratio**	**95% CI**
3-Strata			3-Strata		
Low	-		Low	-	
Intermediate	2.24	1.81-2.78	Intermediate	3.39	2.80-4.10
High	4.24	3.34-5.39	High	8.95	6.83-11.73
4-Strata			4-Strata		
Low	-		Low	-	
Intermediate-low	1.82	1.37-2.42	Intermediate-low	2.65	2.11-3.17
Intermediate-high	3.20	2.44-4.19	Intermediate-high	5.65	4.50-7.11
High	5.19	3.88-6.94	High	11.08	8.23-14.92

Hazard ratios with reference to the low-risk group. Abbreviations: CI – confidence interval

Supplemental Table E2 – Initial treatment strategies for patients diagnosed in 2009-2014 compared to those diagnosed in 2015-2020

	2009-2014 (n=1401)	2015-2020 (n=1478)
CCB only	81 (6%)	86 (6%)
Monotherapy	808 (58%)	589 (40%)
Dual therapy	326 (23%)	470 (31.5%)
Triple Therapy	37 (3%)	42 (3%)
None	149 (10%)	291 (19%)

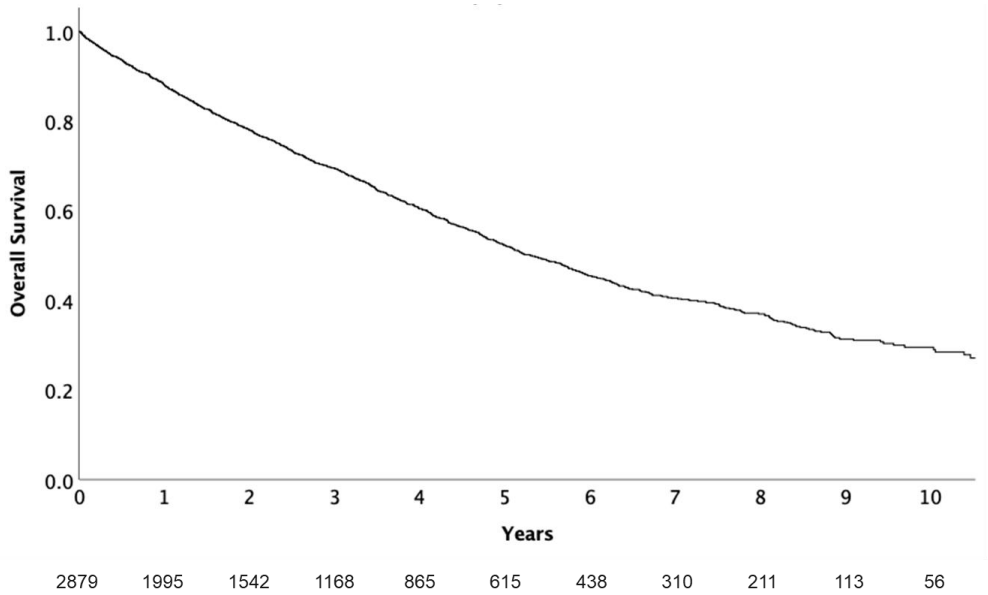
Supplemental Table E3 – Cox Proportional Hazards regression models for the 3 and 4-strata methods applied to patients diagnosed 2009-2014 and 2015-2020.

	2009-2014 (n=1401)			**2015-2020 (n=1478)**		
	Baseline			**Baseline**		
	HR	**95%CI**	**p**	**HR**	**95%CI**	**p**
3 Strata						
Low (Ref)	-			-		
Intermediate	2.41	1.85-3.12	<0.001	2.02	1.37-3.0	<0.001
High	4.12	3.06-5.56	<0.001	4.64	3.04-7.07	<0.001
4 Strata						
Low (Ref)	-			-		
Intermediate-low	1.78	1.27-2.49	0.001	2.02	1.18-3.45	0.01
Intermediate-high	3.16	2.29-4.37	<0.001	3.38	2.02-5.65	<0.001
High	4.71	3.31-6.71	<0.001	6.45	3.79-11.0	<0.001
	Follow-up			**Follow-up**		
	HR	**95%CI**	**p**	**HR**	**95%CI**	**p**
3 Strata						
Low (Ref)	-			-		
Intermediate	3.87	3.07-4.87	<0.001	2.32	1.66-3.24	<0.001
High	8.68	6.20-12.13	<0.01	6.56	4.26-10.1	<0.001
4 Strata						
Low (Ref)	-			-		
Intermediate-low	2.85	2.18-3.71	<0.001	1.96	1.30-2.98	0.001
Intermediate-high	6.33	4.81-8.32	<0.001	4.12	2.74-6.18	<0.001
High	9.99	6.94-14.37	<0.001	8.76	5.39-14.23	<0.001

Supplemental Table E4 – Cox Proportional Hazards regression models for the 3 and 4-strata methods after excluding 295 patients who died within 1 year of diagnosis (n=2584).

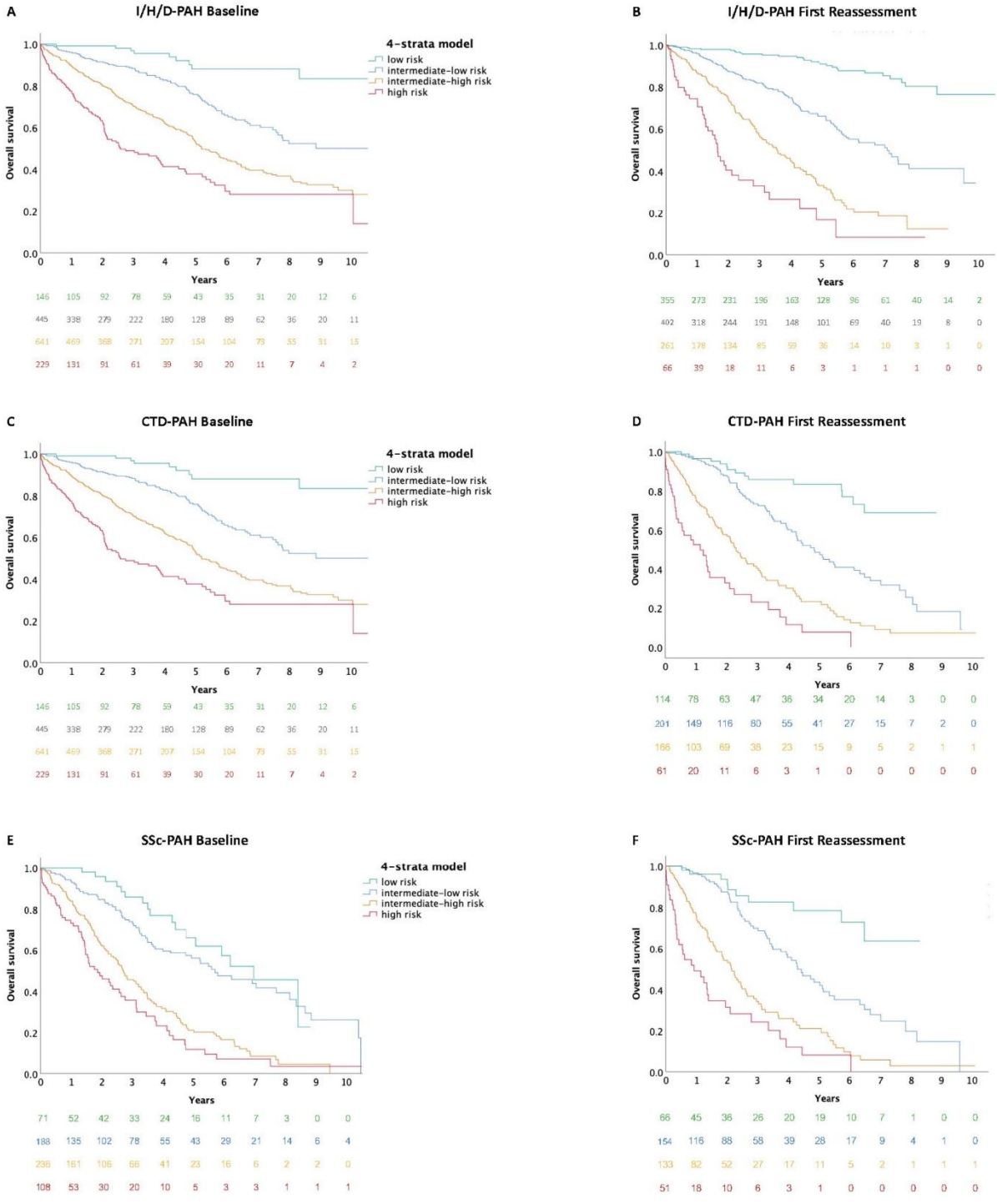
Baseline Risk Assessment	**Hazard Ratio**	**95% CI**	**Harrell's C**	**1st Follow-up Risk Assessment**	**Hazard Ratio**	**95% CI**	**Harrell's C**
3-Strata			0.59	3-Strata			0.65
Low	-			Low	-		
Intermediate	2.03	1.61-2.56		Intermediate	3.32	2.72-4.05	
High	3.30	2.51-4.34		High	7.61	5.68-10.19	
4-Strata			0.61	4-Strata			0.69
Low	-			Low	-		
Intermediate-low	1.65	1.22-2.22		Intermediate-low	2.57	2.03-3.24	
Intermediate-high	2.70	2.02-3.59		Intermediate-high	5.52	4.35-7.01	
High	3.85	2.79-5.31		High	9.22	6.71-12.67	

Supplemental Figure E1 – Overall survival for newly diagnosed pulmonary arterial hypertension patients from January 1, 2009 until December 31, 2020



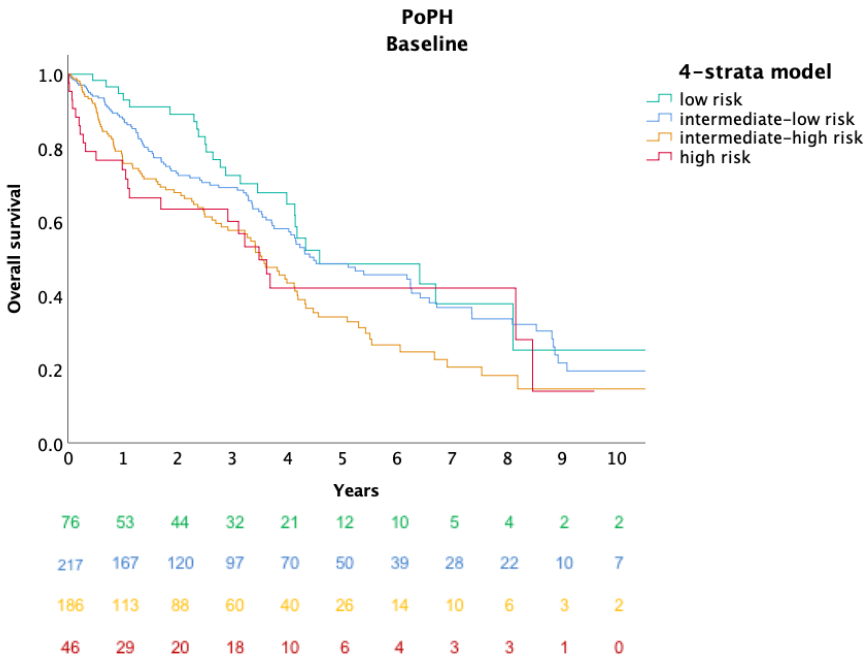
1 year: 88%
3 years: 69%
5 years: 52%
10 years: 29%

Supplemental Figure E2 - Risk stratification using the 4-strata model among patient subgroups. Those with idiopathic, heritable, and drug or toxin-induced PAH at baseline (A) and after first follow-up (B). Those with connective tissue disease-associated PAH at baseline (C) and after first follow-up (D). Those with systemic sclerosis-associated PAH at baseline (E) and after first follow-up (F). Log-rank test p<0.001 for each panel.



Supplemental Figure E3 – Survival by 4-strata risk groups for patients with portopulmonary hypertension after diagnosis (A) and after first reassessment (B). Log-rank test p=0.007 for (A) and p<0.001 for (B).

(A)



(B)