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Early View

Original article

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# Early risk prediction in idiopathic *versus* connective tissue disease-associated pulmonary arterial hypertension: call for a refined assessment


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Short title: Early risk assessment in CTD-PAH


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Take home message: ESC/ERS risk assessment accurately identifies low-risk patients but underestimates the one-year mortality rate of CTD-PAH and IPAH patients assessed as having intermediate risk at diagnosis.

## Abstract

Despite systematic screening and improved treatment strategies, the prognosis remains worse in patients with connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH) compared to patients with idiopathic/hereditary pulmonary arterial hypertension (IPAH). We aimed to investigate differences in clinical characteristics, outcome, and performance of the ESC/ERS risk stratification tool in these patient groups.

This retrospective analysis included incident patients with CTD-PAH (n=197, of which 64 had interstitial lung disease, ILD) or IPAH (n=305) enrolled in the Swedish PAH Register 2008-2019. Patients were classified as low, intermediate, or high risk at baseline, according to the "SPAHR-equation". One-year survival, stratified by type of PAH, was investigated by Cox proportional regression.

At baseline, CTD-PAH patients had lower diffusing capacity for carbon monoxide and lower haemoglobin, but, at the same time, lower N-terminal prohormone-brain natriuretic peptide, longer six minute walking distance, better hemodynamics, and more often a low-risk profile. No difference in age, WHO-FC, or renal function between groups was found. One-year survival rates were 75, 82 and 83%, in patients with CTD-PAH with ILD, CTD-PAH without ILD, and IPAH, respectively. The one-year mortality rates for low-, intermediate-, and high-risk groups in the whole cohort were 0, 18 and 34% ($p<0.001$), respectively. Corresponding percentages for CTD-PAH with ILD, CTD-PAH without ILD, and IPAH patients were: 0, 26, 67% ($p=0.008$); 0, 19, 39% ($p=0.004$); and 0, 16, 29% ($p=0.001$), respectively.

The ESC/ERS risk assessment tool accurately identified low-risk patients but underestimated the one-year mortality rate of CTD-PAH and IPAH patients assessed as having intermediate risk at diagnosis.

## Introduction

Pulmonary arterial hypertension (PAH) is a disease affecting the pulmonary circulation by vascular remodelling resulting from proliferation and migration of pulmonary arterial smooth muscle cells into peripheral non-muscular arteries, thickening of the intimal and/or medial layer of muscular arteries, and vaso-occlusive lesions [1]. Based on etiology, PAH is categorized as idiopathic or hereditary PAH (IPAH) and associated PAH (APAH), where PAH associated with connective tissue disease (CTD-PAH) is the second most prevalent type of PAH [2].

PAH is a serious complication in CTD and is associated with a highly unfavourable prognosis [3-6]. Despite improvement of functional parameters and survival rate by modern treatment, [7, 8] the outcome of patients with CTD-PAH, and especially of those with systemic sclerosis associated PAH (SSc-PAH), remains poor [9-11].

SSc, the most common underlying etiology in patients with CTD-PAH, is associated to complex vascular, pulmonary, and cardiac pathogenic effects; it may cause pre-capillary pulmonary hypertension (mediated through vascular and interstitial lung changes) [12], rarefication of pulmonary capillaries and/or veno-occlusive disease [13], as well as post-capillary pulmonary hypertension (due to systolic or diastolic dysfunction) [14, 15], resulting in distinct or combined phenotypes, with various prognosis.

The European Society of Cardiology (ESC) and the European Respiratory Society (ERS) advocate a goal-oriented treatment approach for patients with PAH [16, 17]. It is based on serial comprehensive risk assessments that aim to discriminate patients with low, intermediate or high risk of mortality [18-20].

Even though the clinical utility of the risk assessment tool in patients with SSc-PAH has been suggested by two previous publications [21, 22], it has not yet been validated in CTD-PAH, and comparative data on its prognostic value for survival in patients with/without interstitial lung disease (ILD) is lacking.

In a recent post hoc analysis [8] of patients with CTD-PAH included in the AMBITION study, two models of simplified risk assessment at baseline were shown to predict subsequent clinical failure events, but their predictive utility at follow-up (week 16) was limited.

The aim of the present study was to compare clinical characteristics, outcome, and one-year mortality prediction by the ESC/ERS risk stratification tool, according to the “SPAHR-equation” [20], in patients with incident CTD-PAH, with or without ILD, to those with IPAH.

## Methods

*Study population*

Adult, incident patients diagnosed with CTD-PAH or IPAH between January 2008 and March 2019 and recorded in the Swedish PAH Register (SPAHR) were included in the study. The PAH diagnosis was confirmed by right heart catheterization according to the European Society of Cardiology and European Respiratory Society (ESC/ERS) guidelines for the diagnosis and treatment of pulmonary hypertension effective at the time of diagnosis [16, 17, 23]. The date when the patients underwent the right heart catheterization was defined as *baseline*. Expert rheumatologists confirmed the CTD diagnosis.

The CTD-PAH group was categorized according to presence or absence of ILD. ILD is reported in SPAHR based on the diagnosis made in the clinics by routine investigations that include pulmonary function tests [collecting data on total lung capacity (TLC), forced vital capacity (FVC), diffusing capacity for carbon monoxide ($D_{LCO}$), forced expiratory volume in one second (FEV1)], and baseline high-resolution computed tomography of the chest.

Creatinine levels were used to estimate glomerular filtration rate (eGFR) according to the Modification of Diet in Renal Disease (MDRD) formula [24]. Body mass index (BMI) was calculated as weight (expressed in kilograms)/height$^2$ (expressed in meters).

*The Swedish PAH Register (SPAHR)*

SPAHR was launched in 2008 and it constitutes an open continuous register to which all Swedish PAH centres report their data, thereby enabling a high national coverage of >90% [25]. The register includes information on demographics, height and weight, comorbidities (hypertension, diabetes mellitus, atrial fibrillation, previous stroke, ischaemic heart disease, and thyroid disease, at time of diagnosis), PAH-specific treatments, World Health Organisation functional class (WHO-FC), 6-minute walking distance (6MWD), blood biochemistry, and data from echocardiography and right heart catheterization. SPAHR is approved by the National Board of Health and Welfare and the Swedish Data Protection Authority. All patients were informed about their participation in SPAHR and had the right to decline. The present study complies with the Declaration of Helsinki and was approved by the national ethics committee in Sweden (Dnr. 1002/15 and Dnr. 2019-01065).

*Risk assessment*

Risk assessment was based on specific variables, according to the risk assessment instrument from the ESC/ERS 2015 guidelines [17] and calculated by using the "SPAHR-equation" [20], which includes data on: WHO-FC, 6MWD, N-terminal prohormone-brain natriuretic peptide (NTproBNP), right atrial area, mean right atrial pressure, pericardial effusion, cardiac index (CI), and mixed venous oxygen saturation ($SvO_2$). Each variable was graded from 1 to 3 where 1 = 'Low risk', 2 = 'Intermediate risk', and 3 = 'High risk' and the sum of all grades was divided by the number of available variables for each patient rendering a mean grade. The mean grade was rounded off to the nearest integer, which was used to define the patient's risk group. Follow-ups performed after 6-18 months from baseline were included as 1-year follow-up. If multiple follow-ups were registered within the given time frame, the follow-up closest to 12 months was chosen.

*Statistics*

Baseline characteristics are reported as percentages for categorical variables and as mean ±SD or median (IQR), as appropriate, for continuous variables. $\chi^2$ -test was used to compare categorical variables; for continuous data, between-group differences were compared using Wilcoxon-Mann–Whitney *U* test. Risk group, age, sex, PAH-type, BMI, eGFR, and comorbidities were tested in univariate analyses and if the p-value was <0.15, they were used as covariates in the Cox proportional regression.

Cox proportional hazard analysis was used to calculate hazard ratios for 1-year mortality and only complete cases were included.

Survival was investigated using the Kaplan-Meier method and the log-rank test. Analyses were stratified by PAH type and/or risk group. Potential interaction effects between PAH type and risk group were assessed. Since there were no events among the low-risk patients during follow-up, this group could not be used as reference in the Cox proportional hazard analysis. Patients were censored at time of lung transplantation, upon death, or on 31$^{st}$ of January 2019.

Results are presented as the hazard ratio (HR) with 95% confidence intervals (CI). Change in risk group from baseline to follow-up in relation to PAH type was compared by the Wilcoxon signed-rank test.

P-values <0.05 were regarded as statistically significant (2-sided test). All statistical analyses were performed using SPSS Statistical Software Package, version 25.0 (SPSS Inc., Chicago, IL, USA).

## Results

The study included 502 patients with PAH (IPAH = 297, HPAH = 8, SSc-PAH = 161, other CTD-PAH = 36). ILD was reported in 64 CTD-PAH patients, of which 59 had SSc-PAH. Among patients with IPAH, 31 (10.2%) fulfilled the criteria as responders to an acute vaso-reactivity test [16, 17], and were treated with a high dose calcium channel blocker (CCB). PAH-specific treatment was initiated in 87% of patients with IPAH and in 89% of patients with CTD-PAH at baseline. For the remaining patients, first treatment recorded in SPAHR occurred later than three months after diagnosis. The median time from baseline to one-year follow-up was 10 months [IQR 6 months], with no difference between the IPAH and CTD-PAH groups.

*Baseline characteristics by PAH type*

The median age was 68 years in both groups, but women were more frequent among the CTD-PAH patients (78% *vs.* 57%, p<0.001). At baseline, patients with CTD-PAH had longer 6MWD, lower NTproBNP, lower mean pulmonary arterial pressure and pulmonary vascular resistance, and higher cardiac index, compared to patients with IPAH (Table 1). Lower $D_{LCO}$ was found among patients with CTD-PAH, whereas patients with IPAH more often had hypertension, diabetes, and higher BMI. Haemoglobin was significantly lower among patients with CTD-PAH than IPAH (Table 1) and significantly lower in women than in men, in both groups (IPAH: 141g/L vs. 151 g/L, p<0.001; CTD-PAH: 131 g/L vs. 138 g/L, p=0.008). No differences in WHO-FC, renal function or PAH-targeted therapy were found between the groups. Patients with IPAH were more often treated with diuretics and anticoagulants compared to CTD-PAH. Characteristics for patients with CTD-PAH, with and without ILD, are shown in Table 2. Apart from worse results on the pulmonary function tests, and more pronounced desaturation after performing the 6MWT (lower median oxygen saturation 85% versus 90% p=0.039), the patients with ILD had similar characteristics to those without ILD.

*Risk assessment*

Patients with CTD-PAH more often had a low-risk profile (p=0.011) at baseline than patients with IPAH (Figure 1A); no difference in risk distribution between CTD-PAH patients with and without ILD was found (Figure 2A). At one-year follow-up, 40% of patients with IPAH had improved from the intermediate- or high-risk group to a lower risk group ($Z = -7.508$, $p$ <0.001), whereas 8% were stable, maintaining a low risk. No significant improvement was found among patients with CTD-PAH (Z= −1.576, p=0.115), (Figures 1B and C). Subgroup analyses by the presence or absence of ILD showed no difference among CTD-PAH patients with respect to risk stratification at follow-up (Figures 2B and C). The median number of available variables included in the risk assessment was 5 [IQR 5-6] at baseline and 2 [IQR 1-4] at one-year follow-up. Information regarding PAH-targeted treatment allocation by risk group is shown in Table 3.

*Transplantation-free survival*

One-year survival rates were 75, 82, and 83% in patients with CTD-PAH with ILD, CTD-PAH without ILD, and IPAH, respectively. In a Cox proportional regression analysis, age (HR 1.04; 95% CI 1.02-1.07; p=0.001), CTD-PAH with ILD (HR 1.98; 95% CI 1.12-3.53; p=0.020), and intermediate- versus high-risk group at baseline (HR 0.42; 95% CI 0.25-0.70; p=0.001) were independent predictors of survival (Table 4 and Figure 3A). No interaction effect between PAH type and risk group at baseline was found (p=0.177).

The mortality rates for low-, intermediate-, and high-risk patients in the whole cohort were 0, 18, and 34% (p<0.001), respectively. Corresponding percentages were 0, 26, and 67% (p=0.008) for CTD-PAH with ILD; 0, 19, and 39% (p=0.004) for CTD-PAH without ILD; and 0, 16, and 29% (p=0.001) for IPAH. The results of a separate age- and gender-adjusted Cox proportional regression analysis, of patients in intermediate- and high-risk, are shown in Figure 3B and C, respectively.

Risk assessment predicted one-year survival qualitatively, but the mortality rate of patients in the intermediate-risk group was much higher than the one suggested by the ESC/ERS PH-guidelines [16, 17] both for the CTD-PAH and the IPAH patients (Figure 4A, B and C).

## Discussion

In this retrospective longitudinal register study, we investigated the clinical utility of the ESC/ERS risk assessment tool, by use of the "SPAHR-equation", for mortality prediction in incident CTD-PAH patients with or without ILD as compared to IPAH. We found that, while the present risk assessment, applied at the time of diagnosis, qualitatively predicted the one-year survival, it underestimated the mortality rate of both CTD-PAH and IPAH patients with intermediate risk. Also, despite having better risk profile at baseline, the CTD-PAH patients without ILD had similar one-year survival to the patients with IPAH, while the survival of CTD-PAH patients with ILD was worse. Finally, clinical improvement, as reflected by reaching a lower risk, was inferior in CTD-PAH patients as compared to IPAH patients during the first year after diagnosis.

The utility of the SPAHR risk stratification model for mortality prediction in patients with CTD-PAH has not been established previously.

In a study including 513 patients with SSc-PAH [22], abbreviated baseline risk assessment based on the number of low-risk criteria, according to the French registry model [18], allowed only modest discrimination of future risk.

In the recently published post-hoc analysis of the modified intention to treat CTD-PAH patients included in the AMBITION-study [8], an abbreviated version of the SPAHR/COMPERA risk assessment [19, 20] based on three criteria (WHO-FC, NTproBNP and 6MWT), as well as, the low-risk non-invasive criteria model used by the French registry [18] were applied. The authors concluded that these abbreviated versions may be useful in predicting PAH-related outcomes in patients with CTD-PAH, but that further research including large patient cohorts for identifying the most optimal predictive tools is warranted.

Our results illustrate that risk assessment at baseline underestimates one-year mortality in both IPAH and CTD-PAH patients in intermediate risk and does so to a greater extent in the latter group. Conversely, independent of PAH type, no events were reported in patients in low risk during the first year after diagnosis. A presumed cause for the IPAH patients in intermediate risk having a higher mortality rate than the one predicted by the risk assessment tool may be the low percentage of patients receiving up-front PAH combination therapy; an explanation for this might be that a considerable proportion of patients was diagnosed prior to the AMBITION-trial [26], which advocates initial combination treatment. The atypical profile with a higher age and comorbidity burden of patients diagnosed with IPAH and CTD-PAH might be another reason for choosing single over combination therapy [27, 28]. Data regarding up-front combination therapy vary, with some registries reporting higher [28, 29] and other lower [30] percentages than SPAHR.

No significant difference in PAH-targeted treatment patterns between the IPAH and the CTD-PAH patients was noted. While the median age at diagnosis was similar in the CTD-PAH and IPAH patients, some differences in demographics, clinical characteristics, and outcomes between the groups were obvious; women were more frequent among patients with CTD-PAH, and exercise tolerance as well as hemodynamic data, were more favourable in this group; however, $D_{LCO}$ was lower. At the same time, the comorbidity burden was more pronounced among patients with IPAH. These findings confirm previously published data [5, 11, 31], thereby emphasizing the validity of our study cohort.

At baseline, as expected, patients with CTD-PAH and ILD had worse pulmonary function than those without ILD. Apart from this, baseline characteristics were similar between the groups, but survival rate was higher among patients with CTD-PAH without ILD. It is well-established that the presence of ILD in patients with CTD-PAH makes the prognosis distinctly deleterious [31] with a previously reported pooled 3-year overall survival rate of 35% in patients with ILD, as compared to 56% in those without [32]. At present, due to lack of clear-cut criteria, the discrimination of patients with CTD-PAH and limited ILD from those with moderate ILD and secondary pulmonary hypertension is difficult and mainly based on high-resolution computed tomography and spirometry data [33].

Including the diagnosis ILD or the results of pulmonary function test in the current model for risk assessment of patients with CTD-PAH might be a way to improve the risk estimation.

Notably, one year after baseline, only 21% of the CTD-PAH patients improved, transitioning to low or intermediate risk, while the corresponding percentage was 40% among the IPAH patients. Thus, treatment goals were not reached in a majority of patients with CTD-PAH. In light of this limited response to therapy, we need to consider how we can improve the treatment and the prognosis for the CTD-PAH population. For many years, the focus has been on systematic screening of SSc patients in order to achieve an early diagnosis of PAH [34]. While this is a commendable effort, additional focus on refined strategies for risk stratification and finding new therapies to improve the outcome of patients with CTD-PAH are needed. Our findings are in line with the recently published results by Chauvelot et al. showing that response to PAH specific therapy is poor in patients with SSc-PH and ILD but not hemodynamically different from that observed in SSc-PAH without ILD [35]. While these findings need to be confirmed in randomized controlled trials, they surely reflect the complexity of CTD, a multifaceted clinical entity leading to a combination of vascular and interstitial lung changes, as well as, diastolic dysfunction. Moreover, the presence of minor co-existing lung disease on thoracic computed tomography has recently been shown to affect survival in even IPAH patients [36]. Consequently, without an improved phenotyping prior to allocation of treatment, the poor response to targeted PAH-therapy is not unanticipated.

One of the strengths of this study is that it is the first study to investigate the utility of the ESC/ERS risk stratification tool, using the “SPAHR-equation”, for mortality prediction in a real-world CTD-PAH cohort. Another strength is that it addresses the impact of ILD on outcome in the context of risk stratification; finally, it includes a relatively large patient population with incident PAH, covering all Swedish PAH-centres.

**Limitations**

The study is prone to common standard limitations of a register-based descriptive study, such as lack of a standardized study protocol, selection bias with respect to treatment allocation, and handling of missing data. For a majority of the patients, not all parameters included in the "SPAHR-equation" were available, but at least functional class, one measure of physical activity level, and one measure of right ventricular function were reported for >80% of the study population at baseline and >50% at follow-up. Other limitations are related to inherent changes of treatment strategy during the study period, and lack of information on grading of ILD, which is not available in SPAHR.

**Conclusion**

In the first year after diagnosis, patients with CTD-PAH, in particular those with ILD, reached treatment goals less often than patients with IPAH. The "SPAHR-equation" underestimated the first year mortality rate in patients with an intermediate risk, but to a greater extent in patients with CTD-PAH than in those with IPAH.

While the present study highlights the usefulness of a comprehensive risk assessment in CTD-PAH patients, it also endorses the refining of risk stratification strategies, mainly of patients in intermediate risk, as well as the need of timely escalated therapy, along with that of developing new treatments.

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## Figure legends

**Figure 1**. Risk assessment presented by type of PAH (IPAH – idiopathic and hereditary PAH; CTD-PAH – connective tissue disease associated PAH). Panel A – baseline, Panel B – follow-up, and Panel C - change in risk group from baseline to follow-up

**Figure 2**. Risk assessment presented by presence of ILD (interstitial lung disease) in patients with CTD-PAH. Panel A – baseline, Panel B – follow-up, and Panel C - change in risk group from baseline to follow-up

**Figure 3.** Age and gender adjusted one-year transplantation-free survival, stratified by type of PAH (IPAH – idiopathic and hereditary PAH; CTD-PAH – connective tissue disease associated PAH; ILD – interstitial lung disease). Panel A – the whole study cohort, Panel B – patients in intermediate risk group, Panel C – patients in high risk group

**Figure 4.** Kaplan-Meier curves for time to event by risk category according to the SPAHR model at baseline. Panel A – idiopathic and hereditary PAH, Panel B – connective tissue disease associated PAH without interstitial lung disease, Panel C – connective tissue disease associated PAH with interstitial lung disease

**Table 1. Clinical, laboratoy, and hemodynamic characteristics of the study cohort at baseline**

| PAH TYPE | IPAH (n=305) | CTD-PAH (n=197) | Total (n=502) | *p-value* |
|---|---|---|---|---|
| **Demography and clinical data** | | | | |
| Age (years) | 68 (20) | 68 (11) | 68 (16) | 0.769 |
| Female gender, % | 57 | 78 | 65 | **<0.001** |
| BMI (kg/m$^2$) | 26 (6.5) | 24 (5.8) | 25 (6) | **<0.001** |
| WHO-FC (I/II/III/IV) | 1/15/74/10 | 1/19/67/13 | 1/17/71/11 | 0.307 |
| 6MWD (m) | 250 (211) | 288 (207) | 267 (210) | **<0.001** |
| SBP (mmHg) | 130 (32) | 131 (31) | 130 (31) | 0.906 |
| DBP (mmHg) | 75 (21) | 75 (15) | 75 (19) | 0.722 |
| eGFR (ml/min/1.73 m$^2$) | 64 (35) | 67 (34) | 65 (35) | 0.796 |
| Hb (g/L) | 147 (24) | 132 (23) | 141 (27) | **<0.001** |
| NTproBNP (ng/L) | 1792 (3354) | 1245 (3081) | 1573 (3077) | **0.004** |
| $D_{LCO}$, % pred, mean ±SD | 49 ±22 | 41 ±15 | 46 ±20 | **<0.001** |
| **Comorbidity** | | | | |
| Systemic hypertension, % | 44 | 35 | 40 | **0.035** |
| Diabetes mellitus, % | 25 | 10 | 19 | **<0.001** |
| Ischemic stroke, % | 5 | 5 | 5 | 0.843 |
| Ischemic heart disease, % | 14 | 16 | 15 | 0.712 |
| Atrial fibrillation, % | 14 | 11 | 13 | 0.435 |
| Interstitial lung disease, % | 0 | 32 | 13 | **<0.001** |
| Obesity, % | 25 | 11 | 19 | **<0.001** |
| Kidney dysfunction, % | 51 | 48 | 49 | 0.547 |
| **Hemodynamics** | | | | |
| MRAP (mmHg) | 8 (6) | 5 (7) | 7 (7) | **<0.001** |
| MPAP (mmHg) | 48 (13) | 38 (15) | 45 (16) | **<0.001** |
| PAWP (mmHg) | 9 (6) | 8 (6) | 8 (5) | **0.012** |
| CI (L/min/m2) | 2.2 (0.8) | 2.4 (1.0) | 2.3 (0.8) | **<0.001** |
| PVR (Wood units) | 10 (5) | 7 (6) | 9 (6) | **<0.001** |
| SaO2, % | 91 (8) | 93 (6) | 92 (7) | **0.001** |
| SvO2, % | 60 (13) | 64 (14) | 61 (11) | **<0.001** |
| Heart rate (bpm) | 76 (19) | 79 (22) | 77 (22) | **0.042** |
| **PAH-targeted therapy**[#] | | | | |
| Single, % | 65 | 69 | 67 | 0.383 |
| Dual, % | 21 | 19 | 20 | 0.733 |
| Triple, % | 1 | 1 | 1 | 0.710 |
| No treatment registered, % | 13 | 11 | 12 | 0.573 |
| **Supportive therapy** | | | | |
| Anticoagulants, % | 58 | 42 | 51 | **0.003** |
| Diuretics, % | 67 | 51 | 61 | **<0.001** |
| Supplemental oxygen, % | 32 | 25 | 29 | 0.169 |
| **Risk group** | | | | |
| Low/medium/high, % | 12/68/20 | 19/69/12 | 14/69/17 | **0.003** |
| **Transplantation-free survival** | | | | |
| one year, total (female/male), % | 83 (87/79) | 80 (81/74) | 82 (84/78) | 0.343 |

Data are presented as median (interquartile range), or %, unless otherwise indicated;
BMI: body mass index; WHO-FC: World Health Organization functional class; 6MWD: 6-min walking distance;
DLCO: diffusing capacity of the lung for carbon monoxide; SBP: systolic blood pressure; DBP: diastolic blood pressure;
eGFR: estimated glomerular filtration rate; Hb: haemoglobin; NT-proBNP: N-terminal pro-brain natriuretic peptide;
mRAP: mean right atrial pressure; mPAP: mean pulmonary arterial pressure;
PCWP: pulmonary capillary wedge pressure; CI: cardiac index; PVR: pulmonary vascular resistance;
SaO2: arterial oxygen saturation; SvO2: mixed venous oxygen saturation;
#: started within 3 months from diagnosis;
Bold indicates statistical significance at $p<0.05$.

**Table 2. Clinical, laboratory, and hemodynamic characteristics of CTD-PAH patients at baseline, by presence of interstitial lung disease**

| | with ILD (n=64) | without ILD (n=133) | *p-value* |
|---|---|---|---|
| **Demography and clinical data** | | | |
| Age (years) | 68 (9) | 67 (14) | 0.383 |
| Female gender, % | 72 | 81 | 0.145 |
| BMI (kg/m$^2$) | 24 (8) | 25 (5) | 0.188 |
| WHO-FC (I/II/III/IV) | 0/14/67/19 | 1/21/68/11 | 0.445 |
| 6MWD (m) | 296 (194) | 288 (210) | 0.875 |
| SBP (mmHg) | 132 (27) | 131 (32) | 1.000 |
| DBP (mmHg) | 75 (19) | 75 (13) | 1.000 |
| eGFR (ml/min/1.73 m$^2$) | 66 (36) | 67 (33) | 0.715 |
| Hb (g/L) | 134 (23) | 130 (25) | 0.370 |
| NTproBNP (ng/L) | 1210 (2843) | 1250 (3189) | 0.428 |
| $D_{LCO}$, % pred*, mean (±SD) | 36 (±13) | 45 (±15) | **0.001** |
| FEV1, % pred*, mean (±SD) | 66 (±27) | 89 (±19) | **0.002** |
| FVC, % pred*, mean (±SD) | 68 (±23) | 88 (±17) | **<0.001** |
| TLC, % pred*, mean (±SD) | 72 (±18) | 92 (±17) | **<0.001** |
| **Comorbidity** | | | |
| Systemic hypertension, % | 36 | 35 | 0.429 |
| Diabetes mellitus, % | 13 | 9 | 0.323 |
| Ischemic stroke, % | 6 | 5 | 0.336 |
| Ischemic heart disease, % | 13 | 17 | 0.236 |
| Atrial fibrillation, % | 9 | 12 | 0.433 |
| Obesity, % | 8 | 13 | 0.463 |
| Kidney dysfunction, % | 46 | 48 | 0.867 |
| **Hemodynamics** | | | |
| MRAP (mmHg) | 4 (6) | 6 (7) | 0.108 |
| MPAP (mmHg) | 36 (18) | 39 (13) | 0.131 |
| PAWP (mmHg) | 7 (5) | 8 (6) | 0.178 |
| CI (L/min/m2) | 2.6 (1.1) | 2.4 (0.9) | 0.074 |
| PVR (Wood units) | 6 (6) | 7 (6) | 0.153 |
| SaO2, % | 94 (6) | 93 (6) | 0.805 |
| SvO2, % | 65 (12) | 64 (15) | 0.309 |
| Heart rate (bpm) | 83 (22) | 78 (24) | 0.094 |
| **PAH-targeted therapy#** | | | |
| Single, % | 70 | 68 | 0.870 |
| Dual, % | 13 | 23 | 0.123 |
| Triple, % | 3 | 0 | 0.104 |
| No treatment registered, % | 14 | 9 | 0.326 |
| **Supportive therapy** | | | |
| Anticoagulants, % | 36 | 44 | 0.283 |
| Diuretics, % | 47 | 53 | 0.543 |
| Supplemental oxygen, % | 27 | 25 | 0.764 |
| **Risk group** | | | |
| Low/medium/high, % | 19/72/9 | 19/68/14 | 0.642 |
| **Transplantation-free survival** | | | |
| one year, total (female/male), % | 75 (76/72) | 82 (83/76) | 0.262 |

Data are presented as median (interquartile range), or %, unless otherwise indicated;
BMI: body mass index; WHO-FC: World Health Organization functional class; 6MWD: 6-min walking distance;
DLCO: diffusing capacity of the lung for carbon monoxide; SBP: systolic blood pressure; DBP: diastolic blood pressure;
eGFR: estimated glomerular filtration rate; Hb: haemoglobin; NT-proBNP: N-terminal pro-brain natriuretic peptide;
mRAP: mean right atrial pressure; mPAP: mean pulmonary arterial pressure;
PCWP: pulmonary capillary wedge pressure; CI: cardiac index; PVR: pulmonary vascular resistance;
SaO2: arterial oxygen saturation; SvO2: mixed venous oxygen saturation;
#: started within 3 months from diagnosis;
Bold indicates statistical significance at p<0.05.
*35% missing values among pulmonary functional tests

## Table 3. Treatment allocation by risk group at baseline and at follow-up (%)

| **Risk group** | Low | Intermediate | High |
|---|---|---|---|
| | IPAH/CTD-PAH | IPAH/CTD-PAH | IPAH/CTD-PAH |
| ***Baseline*** | 12/19 | 68/69 | 20/12 |
| Single therapy | 77/78 | 66/73 | 52/33 |
| Combination therapy | 9/5 | 20/15 | 32/67 |
| ***Follow-up*** | 43/28 | 52/67 | 5/5 |
| Single therapy | 41/56 | 38/38 | 20/14 |
| Combination therapy | 43/33 | 53/57 | 80/86 |

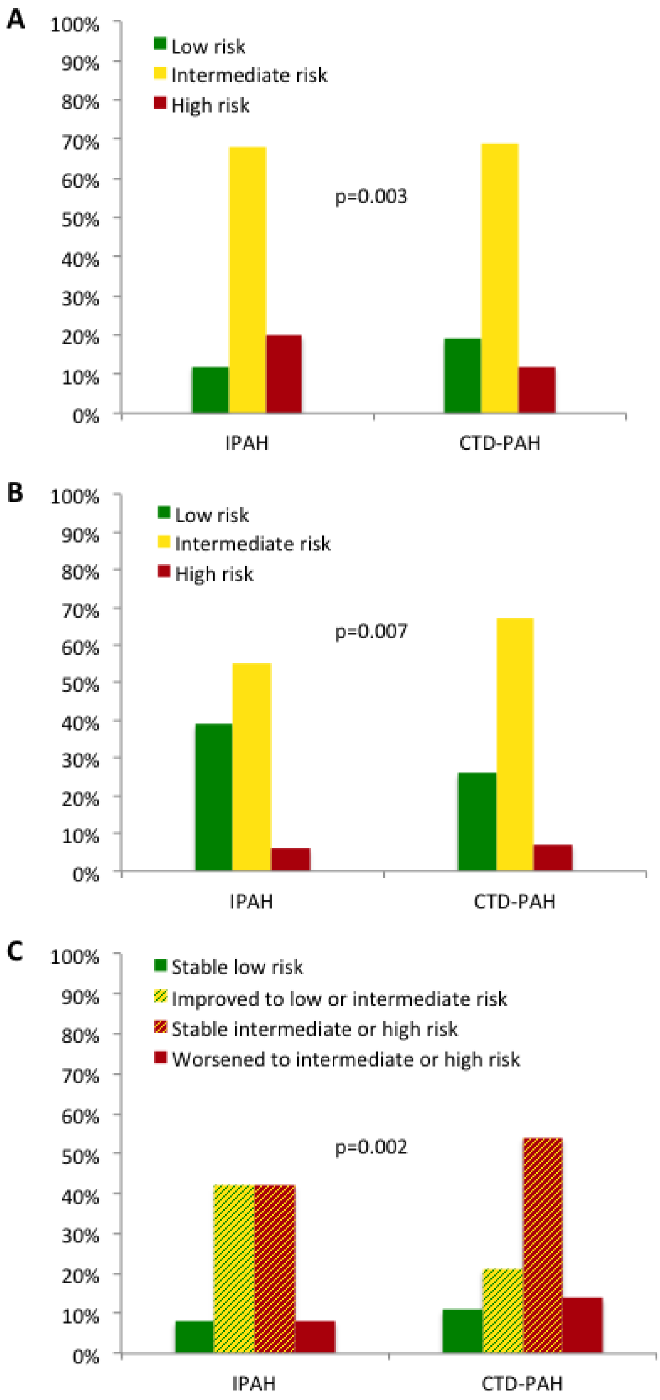
missing values accounting for up to 100% in the different categories represent patients without a recorded treatment
deceased patients were excluded from this analysis

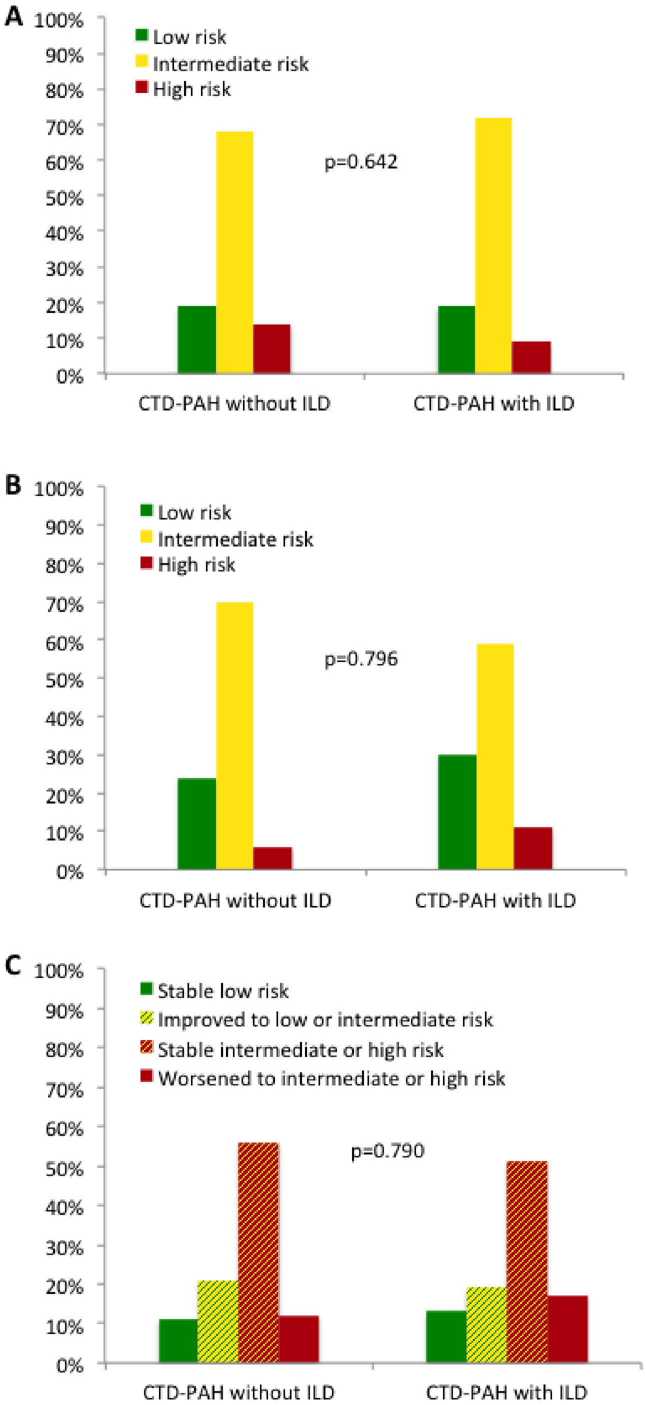
## Table 4. Univariate analysis and Cox proportional hazard regression evaluating the risk of endpoint (death or lung transplantation) of the whole study population

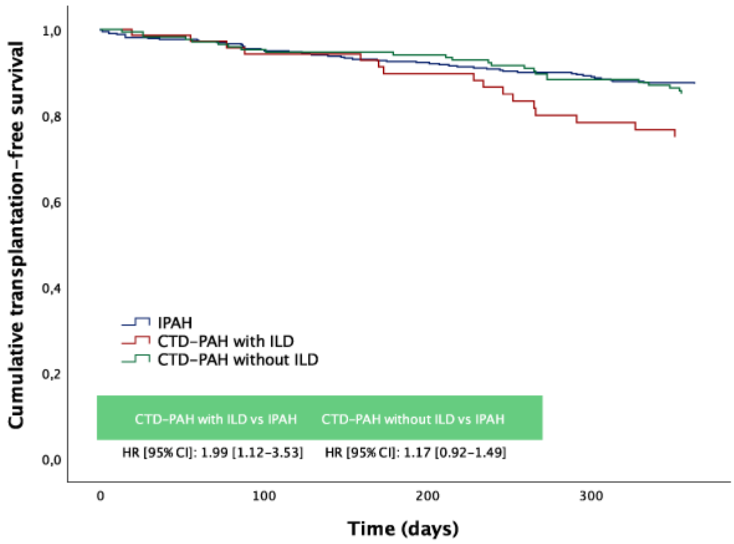
| | Univariate | Multivariate | |
|---|---|---|---|
| | P-value | HR [CI] | P-value |
| **Age** | 0.001 | 1.04 [1.02—1.07] | **0.001** |
| **Geder, female** | 0.077 | 0.77 [0.47—1.27] | 0.308 |
| Diabetes mellitus | 0.759 | | |
| Atrial fibrillation | 0.675 | | |
| Ischemic heart disease | 0.608 | | |
| Ischemic stroke | 0.546 | | |
| Systemic hypertension | 0.858 | | |
| **Risk group at baseline**[#] | <0.001 | 0.42 [0.25—0.70] | **0.001** |
| Obesity | 0.199 | | |
| Kidney dysfunction | 0.613 | | |
| **PAH-type**[§] | 0.145 | 1.98 [1.12—3.53] | **0.020** |

[#] intermediate vs. high risk

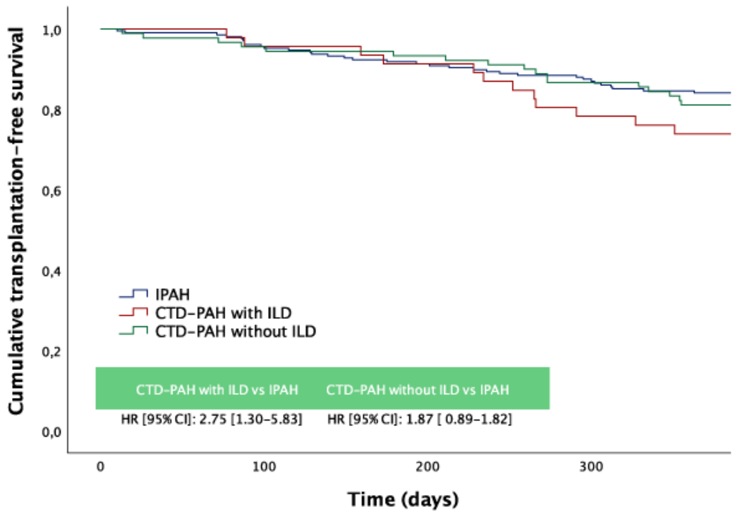
[§] CTD-PAH with ILD versus IPAH


A
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Low risk
Intermediate risk
High risk
p=0.003
IPAH
CTD-PAH
B
Low risk
Intermediate risk
High risk
p=0.007
IPAH
CTD-PAH
C
Stable low risk
Improved to low or intermediate risk
Stable intermediate or high risk
Worsened to intermediate or high risk
p=0.002
IPAH
CTD-PAH

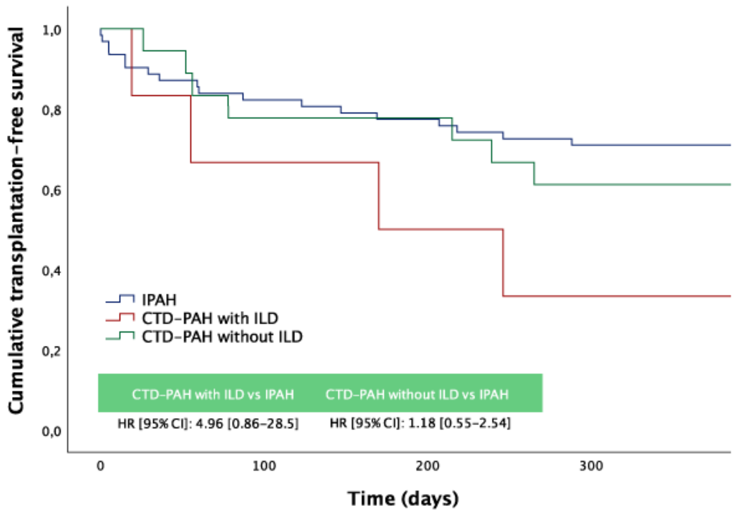

A
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Low risk
Intermediate risk
High risk
p=0.642
CTD-PAH without ILD
CTD-PAH with ILD
B
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Low risk
Intermediate risk
High risk
p=0.796
CTD-PAH without ILD
CTD-PAH with ILD
C
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Stable low risk
Improved to low or intermediate risk
Stable intermediate or high risk
Worsened to intermediate or high risk
p=0.790
CTD-PAH without ILD
CTD-PAH with ILD



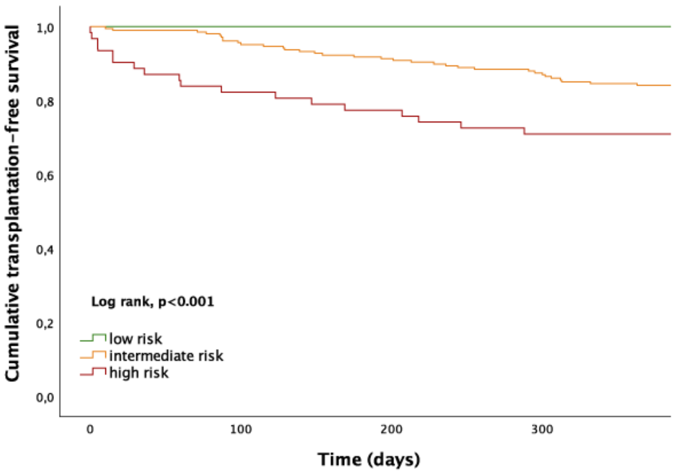
Cumulative transplantation-free survival
1,0
0,8
0,6
0,4
0,2
0,0
IPAH
CTD-PAH with ILD
CTD-PAH without ILD
CTD-PAH with ILD vs IPAH
CTD-PAH without ILD vs IPAH
HR [95% CI]: 1.99 [1.12-3.53]
HR [95% CI]: 1.17 [0.92-1.49]
0
100
200
300
Time (days)

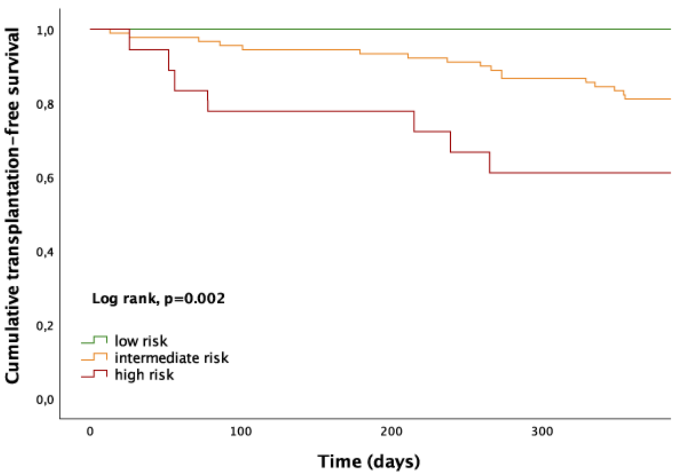



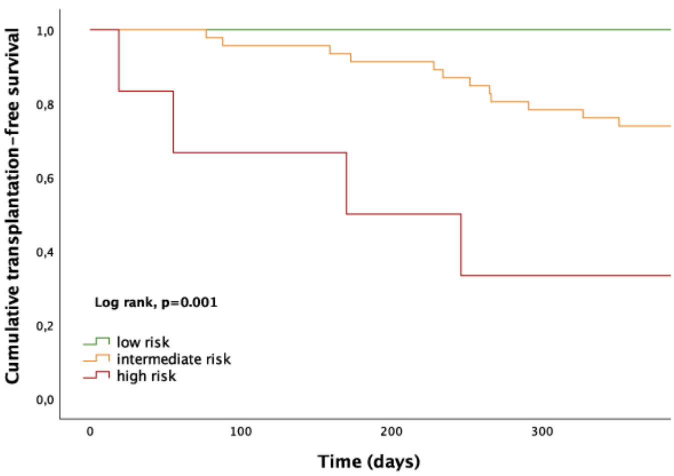
Cumulative transplantation-free survival
1,0
0,8
0,6
0,4
0,2
0,0
IPAH
CTD-PAH with ILD
CTD-PAH without ILD
CTD-PAH with ILD vs IPAH
CTD-PAH without ILD vs IPAH
HR [95% CI]: 2.75 [1.30-5.83]
HR [95% CI]: 1.87 [ 0.89-1.82]
0
100
200
300
Time (days)

Cumulative transplantation-free survival
1,0
0,8
0,6
0,4
0,2
0,0
IPAH
CTD-PAH with ILD
CTD-PAH without ILD
CTD-PAH with ILD vs IPAH
CTD-PAH without ILD vs IPAH
HR [95% CI]: 4.96 [0.86-28.5]
HR [95% CI]: 1.18 [0.55-2.54]
0
100
200
300
Time (days)


Cumulative transplantation-free survival
1,0
0,8
0,6
0,4
0,2
0,0
Log rank, p<0.001
low risk
intermediate risk
high risk
0
100
200
300
Time (days)


Cumulative transplantation-free survival
1,0
0,8
0,6
0,4
0,2
0,0
Log rank, p=0.002
low risk
intermediate risk
high risk
0
100
200
300
Time (days)


Cumulative transplantation-free survival
1,0
0,8
0,6
0,4
0,2
0,0
Log rank, p=0.001
low risk
intermediate risk
high risk
0
100
200
300
Time (days)