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Early View

Original article

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Please cite this article as: Kylhammar D, Hjalmarsson C, Hesselstrand R, *et al*. Predicting mortality during long-term follow-up in pulmonary arterial hypertension. *ERJ Open Res* 2021; in press (https://doi.org/10.1183/23120541.00837-2020).

PREDICTING MORTALITY DURING LONG-TERM FOLLOW-UP IN PULMONARY ARTERIAL HYPERTENSION

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Take home message: ESC/ERS guidelines' risk stratification table successfully predicts outcome during long-term follow-up in pulmonary arterial hypertension

Abstract

The European Society of Cardiology (ESC) and European Respiratory Society (ERS) guideline recommendation of comprehensive risk assessments, which classify patients with pulmonary arterial hypertension (PAH) as having low, intermediate or high mortality risk, has not been evaluated during long-term follow-up in a 'real-life' clinical setting. We therefore aimed to investigate the utility of risk assessment in a clinical setting for up to five years post diagnosis.

Three hundred and eighty-six patients with PAH from the Swedish PAH Registry were included. Risk group (low/intermediate/high) and proportion of low risk variables were investigated at 3-, 4- and 5-year follow-ups after time of diagnosis. In an exploratory analysis, survival rates of patients with low- or high intermediate risk scores were compared.

A low risk profile was in multivariate Cox proportional hazards regressions found to be a strong, independent predictor of longer transplant-free survival ($p<0.001$) at the 3-, 4- and 5-year follow-ups. Also, for the 3-, 4- and 5-year follow-ups, survival rates significantly differed ($p<0.001$) between the three risk groups. Patients with a greater proportion of low risk variables had better ($p<0.001$) survival rates. Patients with a high intermediate risk score had worse survival rates ($p<0.001$) than those with a low intermediate risk score. Results were similar when excluding patients with ≥3 risk factors for heart failure with preserved ejection fraction, atrial fibrillation and/or age >75 years at diagnosis.

Our findings suggest that the ESC/ERS guideline strategy for comprehensive risk assessments in PAH is valid also during long-term follow-up in a 'real-life' clinical setting.

Introduction

Pulmonary arterial hypertension (PAH) is a severe, progressive pulmonary vascular disease associated with significant morbidity and mortality [1-3]. The disease can be idiopathic, hereditary or associated to other conditions, most frequently connective tissue- or congenital heart diseases [4,5].

In order to optimize patient care, treatment and outcome, frequent monitoring is recommended with the consensus that comprehensive risk assessments should be performed at diagnosis and during follow-up. The European Society of Cardiology (ESC) and European Respiratory Society (ERS) guidelines from 2015 suggest that a specific 'risk table', classifying patients as low-, intermediate- or high risk, should be used to estimate mortality in patients with PAH [6]. This approach was later retrospectively validated at time of diagnosis and at an early follow-up, within a maximum of 1-2 years from diagnosis. Three abbreviated risk stratification models, based on the ESC/ERS 'risk table', were then applied to data from incident (*i.e.* newly diagnosed) patients with PAH included in the Swedish [7], French [8] and COMPERA [9] PAH registries.

The use of the 'risk table' is, nevertheless, also recommended for later follow-up of disease progression. Importantly, two recent studies performed *post hoc* analyses of the PATENT-1, its open-label extension PATENT-2 [10] and the GRIPHON [11] studies, respectively, and found that the abbreviated versions of the ESC/ERS 'risk table' discriminate patients with better or worse outcome, also in mostly prevalent and previously treated patients included in these randomized controlled trials.

The principal aim of this study was, however, to test the utility of the ESC/ERS risk stratification model for assessing mortality risk up to five years, post diagnosis in a 'real-life' population of patients from the Swedish PAH registry (SPAHR).

Methods

SPAHR and the study population

The study was based on data from SPAHR, which was launched in 2008 and includes consecutive data from incident cases of PAH diagnosed thereafter at the PAH centres in Gothenburg, Linköping, Lund, Stockholm, Umeå/Sundsvall, Uppsala and Örebro. Data from retrospectively registered cases diagnosed 2000-2007 are also included. Data registration is manually and voluntarily performed at each centre. SPAHR includes information on demographics, comorbidities (hypertension, diabetes mellitus, atrial fibrillation, previous stroke, ischaemic heart disease and thyroid disease at time of diagnosis), treatments, WHO functional class (FC), 6-minute walk 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 Inspection. Patients are locally informed about SPAHR participation and have the right to decline. The study complies with the Declaration of Helsinki and was approved by the local ethics committee in Lund (Dnr. 2010-114, Dnr. 2017-531).

All cases classified as PAH group I according to the Nice classification [4,5], who were not acute vaso-responders, and diagnosed from 2002 to 2015 were included, if they had survived ≥2.5 years from diagnosis. The exclusion of acute vaso-responders was motivated by their different treatment and prognosis. The diagnosis of PAH was set according to guidelines at that time [6,12,13]. Patients were convened as idiopathic/familial- (IPAH/FPAH), connective tissue disease-associated (APAH-CTD), congenital heart disease-associated (APAH-CHD), or other forms of associated PAH (APAH-Others), including drugs- and toxins-induced-, HIV-associated-, and portal hypertension-associated PAH. Registered follow-ups performed after

30-42, 43-54, and 55-66 months from diagnosis were included, representing 3-, 4-, and 5-year follow-ups, respectively. If multiple follow-ups were registered within any of these timeframes, the follow-up with most variables for risk assessment was included. If the number of variables were equal, the earliest follow-up was chosen. A patient could be included at one, two or three follow-ups.

Creatinine levels were used to estimate glomerular filtration rate (eGFR) according to the Cockcroft–Gault formula [14]. Kidney dysfunction was defined as eGFR <60 ml/min/m^2. Body mass index (BMI) was calculated as weight/$(length)^2$.

Comprehensive risk assessments

Patients were classified as low-, intermediate- or high risk according to the previously described 'SPAHR equation', an adjustment of the ESC/ERS guidelines' risk stratification model to fit a retrospective registry-based data set, and by which the risk group for a specific patient is determined by the use of cut-off values for FC, 6MWD, N-terminal pro-hormone of brain natriuretic peptide, right atrial area, mean right atrial pressure, pericardial effusion, cardiac index and/or mixed venous oxygen saturation, as defined in the 'risk table' of the 2015 ESC/ERS guidelines [6] (table 1). Patients in the intermediate risk group were in an exploratory analysis further divided into a low- (risk score 1.5-1.99) and a high (risk score 2.0-2.4) intermediate risk group. Patients were also divided into four groups based on the proportion of low risk variables (0-24, 25-49, 50-74 or 75-100%, respectively), as defined by the ESC/ERS 'risk table' [6]. Risk stratification was performed at diagnosis and during follow-up. SPAHR does not include data on clinical signs of right heart failure, progression of symptoms or syncope, and all variables in the ESC/ERS 'risk table', could therefore not be used for risk assessments.

Statistics

Transplantation-free survival in relation to risk assessments was analysed using Kaplan–Meier estimates and Cox proportional hazards regressions. In multivariate models, a backward stepwise approach was used and only complete cases were analysed. Risk profile (low or intermediate/high risk), age, sex, BMI, eGFR and comorbidities were used as covariates. BMI, eGFR, and comorbidities were included in the multivariate analyses if the p-value was <0.15 in univariate analyses. An event was defined as death or lung transplantation. Patients were censored May 21 2018. Results are presented as the hazard ratio with 95% confidence intervals. Survival analyses were performed based on available 3-, 4- and 5-year follow-up data and survival time was calculated from the respective follow-up. Analyses were performed on the entire study cohort, but also after excluding patients who, at diagnosis, fulfilled one of the three following criteria: 1. ≥3 risk factors for heart failure with preserved ejection fraction (HFpEF; i.e. BMI ≥30 kg/m2, diabetes mellitus, hypertension, ischaemic heart disease), 2. atrial fibrillation, or 3. age >75 years. The strategy was adopted from the inclusion and exclusion criteria of the TRITON study (NCT02558231). For these latter analyses, BMI, eGFR, and comorbidities were not included as covariates in the COX proportional hazards regressions. Descriptive data are presented as median (interquartile range) for continuous and absolute or per cent for categorical variables. A p-value<0.05 was considered statistically significant. Analyses were performed in IBM SPSS Statistics v.25.

Results

Study population

Characteristics at diagnosis and at follow-ups, 3-, 4-, and 5 years post diagnosis, are shown in tables 2 and 3. The most common PAH subset was IPAH/FPAH (49%), followed by APAH-CTD (30%) and APAH-CHD (13%). Median age at diagnosis was 60 (43-70) years and 68% of patients were female. Thirteen per cent received upfront combination therapy, whereas 54-58% received sequential combination therapy during follow-up. Median follow-up time was 33 (14-64) months for the 3-, 33 (13-59) for the 4-, and 35 (19-54) for the 5-year follow-up groups. There were 99 deaths or lung transplantations in the 3-, 71 in the 4-, and 44 in the 5-year follow-up groups.

Characteristics of the population after excluding patients who presented at diagnosis with ≥3 risk factors for HFpEF, atrial fibrillation and/or age >75 years are shown in table 2 and in online supplementary table S1. Characteristics of the excluded patients are shown in online supplementary table S2. Fifty-three patients could not be classified due to incomplete data with regards to comorbidities or BMI.

Risk group distributions at baseline and during follow-up

There were seven (6-7), five (3-5), four (3-5) and four (3-5) variables available for risk assessments at diagnosis, the 3-, 4- and 5-year follow-ups, respectively. The frequency by which each variable was used for risk assessment is depicted in online supplementary table S3.

In this population of patients who survived for at least 2.5 years from diagnosis, 31% were at diagnosis classified as low risk, 62% as intermediate risk and 7% as high risk, respectively (table 3). At the 3-, 4- and 5-year follow-ups, the corresponding numbers were 39, 54 and 8%; 48, 45 and 8%; and 47, 49 and 4%, respectively (table 3). Risk group distributions per PAH subset are shown in online supplementary table S4.

After exclusion of patients who presented at diagnosis with ≥3 risk factors for HFpEF, atrial fibrillation and/or age >75 years, 38% were at diagnosis classified as low risk, 55% as intermediate risk and 7% as high risk. Corresponding numbers at the 3-, 4- and 5-year follow-ups were 47, 47 and 6%; 58, 37 and 5%; and 57, 38 and 5%, respectively (online supplementary table S1). Risk group distributions per PAH subset are shown in online supplementary table S5.

Risk group distributions for the excluded patients are shown in online supplementary table S2.

Transplantation-free survival in relation to risk assessments

In multivariate Cox proportional hazards regressions, a low risk profile at the 3-, 4-, or 5-year follow-ups was an independent predictor of longer transplant-free survival (table 4). Results from the univariate analyses are found in online supplementary table S6. Survival rates differed significantly ($p<0.001$) for patients in the low-, intermediate-, and high risk groups at the 3-, 4-, and 5-year follow-ups, respectively (figure 1). Survival rates also differed significantly ($p<0.001$) based on the proportion of low risk variables at the 3-, 4-, and 5-year follow-ups, respectively (figure 2).

Patients with a high intermediate risk score had significantly worse survival rates ($p<0.001$) than those with a low intermediate risk score at the 3-, 4- and 5-year follow-ups, respectively.

Similar results were found after excluding patients who presented at diagnosis with ≥3 risk factors for HFpEF, atrial fibrillation, and/or age >75 years, see table 4 and online supplementary figures S1 and S2.

Discussion

The main findings of the present study emphasize that a low risk profile based on the ESC/ERS guidelines' 'risk table' presents as a strong, independent predictor of longer transplant-free survival during long-term follow-up of patients with PAH in a 'real-life' clinical setting. In addition, the more low risk variables a patient presented with during follow-up, the better was the prognosis. In previous studies from the Swedish [7], French [8] and international COMPERA [9] PAH registries, three abbreviated versions of the ESC/ERS 'risk table' predicted outcome when applied to findings at the diagnostic check-up and at an early follow-up performed within a maximum of 1-2 years from diagnosis. However, the median time from diagnosis to follow-up was only approximately three to four months in the Swedish [7] and French [8] studies. In the present study, using 'real-life' clinical data, we found that the risk assessment strategy appears to be applicable also during follow-ups for up to five years post diagnosis. Our findings hence suggest that the ESC/ERS 'risk table' indeed appear to be a valuable tool for the long-term follow-up of patients with PAH. Our data support and add to those of two recent studies, which found that abbreviated versions of the ESC/ERS 'risk table' were, in *post hoc* analyses, successful in discriminating patients with better or worse outcome in the mixed incident and prevalent, treatment-naïve, and previously treated populations of the randomized controlled trials PATENT-1, its open-label extension PATENT-2 [10] and GRIPHON [11]. The present findings are of clinical importance as ESC/ERS guidelines recommend that the risk stratification model should be used frequently and repeatedly at consecutive follow-ups during the course of disease and that a low risk profile should be considered a treatment goal, an approach based on 'expert opinion' [6].

As compared to previous studies from the Swedish [7] and COMPERA [9] PAH registries, which used the 'SPAHR equation' for risk group allocation at diagnosis and early follow-up,

there was in the present study a greater proportion of patients in the low risk, and a smaller proportion of patients in the high risk group, both at baseline and during follow-up. This is likely related to selection bias, as the present study set to investigate the utility of risk assessments during long-term follow-up and included only patients who survived the first years of disease. Nevertheless, those patients who were, based on the risk stratification model, classified as having a high mortality risk at the 3-, 4- or 5-year follow-ups indeed had high mortality rates of approximately 50-70% within a year. This suggests that escalation of medical treatment and/or listing for lung transplantation, as well as close clinical monitoring, is to be recommended for patients presenting with a high risk profile also later in the disease.

Interestingly, in an exploratory analysis we found that patients with a high intermediate risk score had significantly worse survival rates than those with a low intermediate risk score. This indicates that the large intermediate risk group should possibly be re-defined to take into account the probable need for more aggressive treatment of subjects with a higher intermediate risk score, although further investigation of this in future studies is still needed. Beside the present approach for subgrouping the intermediate risk group by use of the 'SPAHR equation', one may for future studies for instance adjust the cut-offs for the intermediate- and high risk groups so that high-intermediate risk patients are classified as high risk or create new cut-offs for classification of low-intermediate and high-intermediate risk patients, respectively. The good prognosis of patients in the low risk group underlines that a low risk profile indeed is a rational treatment-goal.

Recent registry data show that there has been a shift in demographics among PAH patients, with a higher proportion of older, more frequently male patients with a greater comorbidity burden [1,15]. Therefore, we chose to perform separate sensitivity analyses after excluding patients who presented at diagnosis with multiple risk factors for HFpEF, atrial fibrillation and/or age >75 years, in addition to our main examinations of the full study cohort. At

diagnosis, NT-proBNP levels were lower and 6MWD was longer after exclusion of patients who presented at diagnosis with multiple risk factors for HFpEF, atrial fibrillation, and/or age >75. This may reflect the lower age and a smaller burden or cardiovascular comorbidity in this subgroup even though there were no differences in invasively measured haemodynamic variables at rest. Importantly, a low risk profile and the proportion of low risk variables were strong, independent predictors of transplant-free survival also in this group of patients with a diagnosis of PAH, representing patients similar to those previously included in randomized controlled trials.

The group of PAH patients with multiple risk factors for HFpEF, atrial fibrillation and/or age >75 years was rather small and was not further analysed with respect to risk assessments or outcome. Patients with such "atypical", but clinically relevant, characteristics have normally not been included in randomized controlled trials, but registry data suggest that they respond less well to PAH-targeted treatments [15-17]. It has been proposed that these patients may represent individuals with misdiagnosed HFpEF with excessive vasoconstriction and/or remodelling or alternatively a new "phenotype" of PAH. We acknowledge the diagnostic difficulties that clinicians encounter when confronted with such patients.

Limitations

This study encompasses general standard limitations of a multi-centre, registry-based observational study, such as lack of a standardized study protocol, missing data and the possibility of selection bias with respect to follow-ups. The patients included in the study were diagnosed during a time-span of approximately 14 years, a period when diagnostic criteria, available treatments, treatment strategies and guidelines have varied. As SPAHR does not include data on clinical signs of right heart failure, progression of symptoms or syncope,

all variables in the ESC/ERS 'risk table', could not be used for risk assessments in the present study. The method for risk assessment was additionally adjusted to fit a retrospective registry-based data set. There were fewer variables available for risk assessment during follow-up than at diagnosis and we do not know whether this affected the risk group assessment. The study population is, in a wider context, rather small, but in light of PAH being a rare disease, larger study groups are infrequent. There were no specific analyses for different PAH subsets, although separate analyses were performed for patients with or without multiple risk factors for HFpEF, atrial fibrillation and/or age >75 years at diagnosis. Application of comprehensive risk stratification models to future prospective studies and studies of various PAH subsets are thus warranted, including studies of PAH patients not typically included in clinical trials.

Conclusions

The results of the present study suggest that the ESC/ERS guidelines' 'risk table' for patients with PAH is valid also during long-term follow-up in a 'real-life' setting. Our findings endorse the ESC/ERS guidelines 'expert opinion' of using the 'risk table' for repeated comprehensive risk evaluations and goal-oriented therapy in order to improve outcome in PAH.

We furthermore encourage future international collaborations that in addition aim to investigate the characteristics, treatment response, risk factors and outcome for the subset of patients with multiple comorbidities and/or high age, as well as for various PAH subsets. Future studies for better characterization of the intermediate risk group are also wanted.

Acknowledgements

We acknowledge the work of the SPAHR registrars at the Swedish PAH centres and Uppsala Clinical Research Centre for developing and administering the SPAHR platform. We acknowledge the SPAHR steering committee and colleagues involved in the initiation of SPAHR and the Swedish Association for Pulmonary Hypertension (SveFPH).

Funding

During the initiation of SPAHR, Actelion Pharmaceuticals Sweden AB, Bayer Health Care, Eli Lilly Sweden, Glaxo-SmithKline, NordInfu Care and Pfizer gave financial support. Since 2011, SPAHR has qualified as a national quality register and the Swedish Association of Local Authorities and Regions give financial support. Financial supporters had no role in data collection, analysis or interpretation and no right in disapproving the manuscript.

Conflicts of interest

DK reports unrestricted research grants from Actelion Pharmaceuticals Sweden AB, Pfizer and Bayer HealthCare, and lecture fees from Actelion Pharmaceuticals Sweden AB and GlaxoSmith-Kline.

CH reports unrestricted research grants from Actelion Pharmaceuticals Sweden AB, Janssen, and MSD. CH is, and has been, primary or co-investigator in clinical PAH trials for Actelion Pharmaceuticals Sweden AB, Janssen, and United Therapeutics, and has been involved in research advisory boards for Actelion Pharmaceuticals Sweden AB and Janssen.

MN has been primary or co-investigator in clinical trials or studies sponsored by United Therapeutics, and received lecture- and consultation fees from Actelion Pharmaceuticals Sweden AB, Pfizer, Bayer HealthCare, NordicInfu Care and GlaxoSmith-Kline.

RH, KJ, MK and BK report no conflicts of interest.

SS reports unrestricted research grants from Actelion Pharmaceuticals Sweden AB and Pfizer, and lecture fees from Actelion Pharmaceuticals AB.

GR reports unrestricted research grants from Actelion Pharmaceuticals Sweden AB and Glaxo-SmithKline, and personal lecture fees from Actelion Pharmaceuticals Sweden AB, Bayer Health Care, Glaxo-SmithKline, Janssen, NordicInfu Care and Sandoz/Novartis. GR is, and has been, primary or co-investigator in clinical PAH trials for Glaxo-SmithKline, Actelion Pharmaceuticals Sweden AB, Pfizer, Bayer Health Care and United Therapeutics, and has been involved in research advisory boards for Acceleron, Actelion Pharmaceuticals Sweden AB, Arena, Bayer Health, Care, Eli-Lilly, Glaxo-SmithKline, Janssen, and Sanofi-Aventis.

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Tables and their legends

Table 1. Included variables from the 'risk table' in the 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension and their cut-off values

Determinants of prognosis	Low risk	Intermediate risk	High risk
WHO functional class	I, II	III	IV
6MWD	>440 m	165-440 m	<165 m
NT-proBNP levels	<300 ng/L	300-1400 ng/L	>1400 ng/L
Imaging (echocardiography)	RA area <18 cm^2 No pericardial effusion	RA area 18-26 cm^2	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 L/min/m^2 S_vO_2 >65%	RAP 8-14 mmHg CI 2.0-2.4 L/min/m^2 S_vO_2 60-65%	RAP >14 mmHg CI <2.0 L/min/m^2 S_vO_2 <60%

Adopted from the 'risk table' in the 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension [6].

6MWD, 6-minute walking distance; CI, cardiac index; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; RA, right atrium; RAP, right atrial pressure; S_vO_2, mixed venous oxygen saturation; WHO, World Health Organization.

Table 2. Characteristics at time of diagnosis for the full study population and after exclusion of patients who presented at diagnosis with multiple risk factors for HFpEF, atrial fibrillation and/or age >75 years.

	Full study population (n=386)	**Study population after exclusion of patients with multiple risk factors for HFpEF, atrial fibrillation and/or age >75 years at diagnosis (n=252)**
Age	60 (43-70)	53 (37-66)
WHO functional class		
I, *%*	2	2
II, *%*	23	26
III, *%*	68	64
IV, *%*	7	8
6MWD, *m*	330 (228-445)	373 (251-470)
NT-proBNP, *pg/mL*	958 (299-2424)	803 (230-2087)
MPAP, *mmHg*	47 (38-56)	47 (38-57)
MRAP, *mmHg*	6 (4-10)	6 (3-8)
PAWP, *mmHg*	8 (6-11)	7 (6-10)
CO, *L/min*	4.5 (3.6-5.3)	4.5 (3.7-5.3)
CI, $L/min/m^2$	2.5 (2.0-3.0)	2.5 (2.0-3.1)

PVR, *WU*	8.6 (5.8-12.0)	8.7 (5.7-12.2)
SvO_2, *%-units*	65 (58-70)	66 (60-71)
SaO_2, *%-units*	93 (89-95)	93 (89-96)
MAP, *mmHg*	95 (85-105)	95 (85-105)

6MWD, 6-minute walk distance; CI, cardiac index; CO, cardiac output; MAP, mean systemic arterial pressure; MPAP, mean pulmonary arterial pressure; MRAP, mean right atrial pressure; NT-proBNP, N-terminal pro-hormone of brain natriuretic peptide; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; S_aO_2, arterial oxygen saturation; S_vO_2, mixed venous oxygen saturation; WHO, World Health Organization

Table 3. Additional characteristics at diagnosis and during follow-up for the full study population

	Diagnosis (n=386)	**3-year follow-up (n=251)**	**4-year follow-up (n=193)**	**5-year follow-up (n=139)**
Age, *years*	60 (43-70)	60 (43-72)	60 (42-72)	58 (40-71)
Female gender, *%*	68	69	69	71
PAH subsets				
IPAH/FPAH, *%*	49	52	51	49
APAH-CTD, *%*	30	26	23	22
APAH-CHD, *%*	13	13	17	19
APAH-Others, *%*	9	9	9	10
Co-morbidities				
Hypertension, *%*	31	31	25	21
Diabetes mellitus, *%*	13	13	10	8
Atrial fibrillation, *%*	9	8	8	8
Previous stroke, *%*	4	4	2	4
Ischaemic heart disease, *%*	10	11	9	7

Thyroid disease, %	12	14	12	14
Obesity (BMI > 30 kg/m^2)	19	21	15	14
Kidney dysfunction (eGFR < 60 ml/kg/m^2)	27	34	26	21
PAH-targeted treatment				
ERA, %	50	20	23	22
PDE5 inhibitor, %	20	13	15	12
Prostacyclin, %	3	1	1	1
sGC stimulator, %	0	0	0	0
Study drug, %	3	1	0	0
Dual therapy, %	12	48	43	42
Triple therapy, %	1	10	10	14
Quadruple therapy, %	0	0	1	0
No treatment registered, %	12	7	8	7
Supportive therapy				
Anticoagulants, %	58	61	64	62

Diuretics, *%*	56	65	59	57
Supplemental oxygen, *%*	17	26	22	18
Risk group				
Low risk, *%*	31	39	48	47
Intermediate risk, *%*	62	54	45	49
High risk, *%*	7	8	8	4

APAH, associated pulmonary arterial hypertension; CHD, congenital heart disease; CTD, connective tissue disease; ERA, endothelin receptor antagonist; FPAH, familial pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; PAH, pulmonary arterial hypertension; PDE5, phosphodiesterase 5; sGC, soluble guanylate cyclase.

Table 4. Independent predictors of transplant-free survival during follow-up for the full study population (A) and the study population after exclusion of patients with multiple risk factors for HFpEF, atrial fibrillation and/or age >75 years at diagnosis (B)

A.			
	3-year follow-up (n=158*)	**4-year follow-up (n=156*)**	**5-year follow-up (n=121*)**
Low risk	0.27 (0.13-0.58)	0.32 (0.16-0.65)	0.33 (0.14-0.80)
Age	NS	1.03 (1.01-1.05)	1.03 (1.01-1.05)
Female sex	0.455 (0.26-0.79)	NS	NS
eGFR	0.98 (0.96-0.99)	NS	NS
B.			
	3-year follow-up (n=167*)	**4-year follow-up (n=132*)**	**5-year follow-up (n=99*)**
Low risk	0.24 (0.12-0.48)	0.37 (0.18-0.75)	0.37 (0.15-0.90)
Age	1.03 (1.01-1.04)	1.03 (1.01-1.05)	1.04 (1.01-1.07)
Female sex	0.51 (0.29-0.91)	NS	NS

*****Only patients with full coverage of the variables are included in the multivariate analyses.

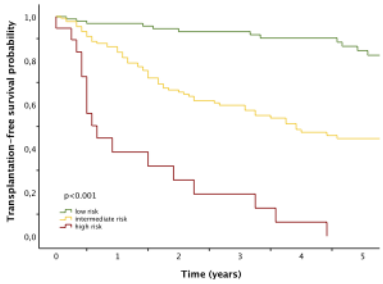
Data are presented as hazard ratio with 95 % confidence intervals in parentheses. During follow-up in the full study cohort there were 56 events in the 3-year follow-up group, 51 in the 4-year follow-up group and 36 in the 5-year follow-up group. During follow-up in the cohort of patients where those who presented with multiple risk factors for HFpEF, atrial fibrillation and/or age >75 years at diagnosis had been excluded, there were 53 events in the 3-year follow-up group, 36 in the 4-year follow-up group and 25 in the 5-year follow-up group.

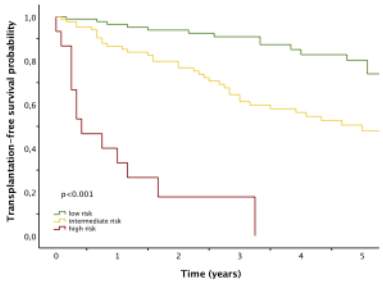
HFpEF, heart failure with preserved ejection fraction; NS, not significant.

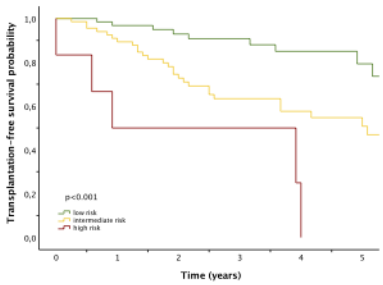
Figure legends

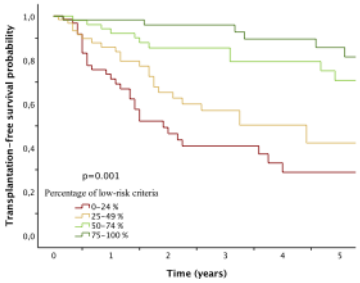
Figure 1. Transplant-free survival rates according to risk group at the A. 3-, B. 4- and C. 5-year follow-up, respectively, for the full study population.

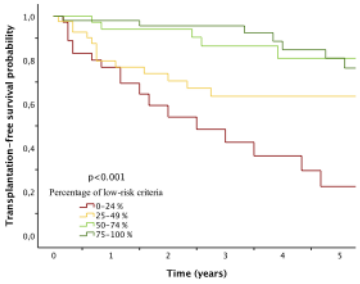
Figure 2. Transplant-free survival rates according to the proportion of low risk variables at the A. 3-, B. 4- and C. 5-year follow-up, respectively, for the full study population.

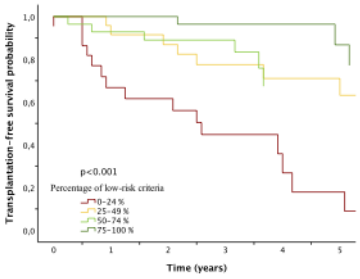

Transplantation-free survival probability
1,0
0,8
0,6
0,4
0,2
0,0
p<0.001
low risk
intermediate risk
high risk
0
1
2
3
4
5
Time (years)


Transplantation-free survival probability
1,0
0,8
0,6
0,4
0,2
0,0
p<0.001
low risk
intermediate risk
high risk
0
1
2
3
4
5
Time (years)


Transplantation-free survival probability
1,0
0,8
0,6
0,4
0,2
0,0
p<0.001
low risk
intermediate risk
high risk
0
1
2
3
4
5
Time (years)


Transplantation-free survival probability
1,0
0,8
0,6
0,4
0,2
0,0
p=0.001
Percentage of low-risk criteria
0–24 %
25–49 %
50–74 %
75–100 %
0
1
2
3
4
5
Time (years)


Transplantation-free survival probability
1,0
0,8
0,6
0,4
0,2
0,0
p<0.001
Percentage of low-risk criteria
0–24 %
25–49 %
50–74 %
75–100 %
0
1
2
3
4
5
Time (years)


Transplantation-free survival probability
1,0
0,8
0,6
0,4
0,2
0,0
p<0.001
Percentage of low-risk criteria
0–24 %
25–49 %
50–74 %
75–100 %
0
1
2
3
4
5
Time (years)

Supplementary material

Table S1. Additional characteristics at diagnosis and during follow-up for the study population after exclusion of patients who presented at diagnosis with multiple risk factors for HFpEF, atrial fibrillation, and/or age >75 years

	Diagnosis (n=252)	**3-year follow-up (n=167)**	**4-year follow-up (n=132)**	**5-year follow-up (n=99)**
Age, *years*	53 (37-66)	54 (38-67)	51 (37-68)	50 (36-67)
Female gender, *%*	73	72	74	73
PAH subsets				
IPAH/FPAH, *%*	46	50	49	50
APAH-CTD, *%*	33	30	26	26
APAH-CHD, *%*	13	13	17	17
APAH-Others, *%*	8	8	8	7

Co-morbidities				
Hypertension, *%*	24	22	17	13
Diabetes mellitus, *%*	8	7	6	3
Atrial fibrillation, *%*	0	0	0	0
Previous stroke, *%*	4	4	2	3
Ischaemic heart disease, *%*	7	7	6	5
Thyroid disease, *%*	13	14	13	15
Obesity (BMI > 30 kg/m^2)	15	16	8	12
Kidney dysfunction (eGFR < 60 ml/kg/m^2)	20	24	19	17
PAH-targeted treatment				
ERA, *%*	50	19	23	19

PDE5 inhibitor, %	20	13	14	12
Prostacyclin, %	2	1	2	1
sGC stimulator, %	0	0	0	0
Study drug, %	3	1	0	0
Dual therapy, %	12	44	37	42
Triple therapy, %	2	13	13	16
Quadruple therapy, %	0	0	1	0
No treatment registered, %	11	10	11	9
Supportive therapy				
Anticoagulants, %	53	61	63	63
Diuretics, %	46	56	49	50
Supplemental oxygen, %	13	17	17	14

Follow-up time, *months*	NA	37 (18-68)	40 (13-61)	38 (17-56)
Death or lung transplantation	NA	53	36	25
Risk group				
Low risk, *%*	38	47	58	57
Intermediate risk, *%*	55	47	37	38
High risk, *%*	7	6	5	5

APAH, associated pulmonary arterial hypertension; CHD, congenital heart disease; CTD, connective tissue disease; ERA, endothelin receptor antagonist; FPAH, familial pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; PAH, pulmonary arterial hypertension; PDE5, phosphodiesterase 5; sGC, soluble guanylate cyclase.

Table S2. Characteristics at diagnosis and during follow-up for patients who presented with multiple risk factors for HFpEF, atrial fibrillation, and/or age >75 years at diagnosis

	Diagnosis (n=81)	**3-year follow-up (n=55)**	**4-year follow-up (n=33)**	**5-year follow-up (n=20)**
Age, *years*	73 (67-78)	76 (66-80)	74 (67-81)	73 (65-78)
Female gender, *%*	53	58	58	60
PAH subsets				
IPAH/FPAH, *%*	61	66	64	65
APAH-CTD, *%*	26	20	18	10
APAH-CHD, *%*	11	13	15	20
APAH-Others, *%*	2	2	3	5
Co-morbidities				

Hypertension, *%*	69	71	76	75
Diabetes mellitus, *%*	36	40	33	40
Atrial fibrillation, *%*	43	35	46	55
Previous stroke, *%*	6	7	3	10
Ischaemic heart disease, *%*	27	29	27	25
Thyroid disease, *%*	16	18	18	20
Obesity (BMI > 30 kg/m^2)	30	33	39	46
Kidney dysfunction (eGFR < 60 ml/kg/m^2)	46	68	50	50
PAH-targeted treatment				
ERA, *%*	51	16	18	15
PDE5 inhibitor, *%*	25	18	24	20

Prostacyclin, %	0	0	0	5
sGC stimulator, %	0	0	0	0
Study drug, %	4	0	0	0
Dual therapy, %	15	56	55	45
Triple therapy, %	0	6	0	10
Quadruple therapy, %	0	0	0	0
No treatment registered, %	6	4	3	5
Supportive therapy				
Anticoagulants, %	73	73	79	75
Diuretics, %	86	96	97	95
Supplemental oxygen, %	26	44	36	30
WHO functional class				

I, *%*	0	NA	NA	NA
II, *%*	11	NA	NA	NA
III, *%*	79	NA	NA	NA
IV, *%*	9	NA	NA	NA
6MWD, *m*	250 (180-330)	NA	NA	NA
NT-proBNP, *pg/mL*	1556 (784-3826)	NA	NA	NA
MPAP, *mmHg*	43 (35-50)	NA	NA	NA
MRAP, *mmHg*	8 (5-12)	NA	NA	NA
PAWP, *mmHg*	10 (7-13)	NA	NA	NA
CO, *L/min*	4.4 (3.6-5.4)	NA	NA	NA
CI, *L/min/m^2*	2.4 (1.9-2.8)	NA	NA	NA
PVR, *WU*	7.7 (5.3-10.2)	NA	NA	NA

SvO_2, *%-units*	62 (55-67)	NA	NA	NA
SaO_2, *%-units*	92 (88-94)	NA	NA	NA
MAP, *mmHg*	95 (84-104)	NA	NA	NA
Risk group				
Low risk, *%*	10	18	18	5
Intermediate risk, *%*	85	67	70	90
High risk, *%*	5	15	12	5

APAH, associated pulmonary arterial hypertension; CHD, congenital heart disease; CTD, connective tissue disease; ERA, endothelin receptor antagonist; FPAH, familial pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; NA, not applicable; PAH, pulmonary arterial hypertension; PDE5, phosphodiesterase 5; sGC, soluble guanylate cyclase.

Table S3. Frequency by which each variable from the 'risk table' was used for risk assessment at diagnosis, the 3-, 4-, and 5-year follow-ups, respectively

	Diagnosis	3-year follow-up	4-year follow-up	5-year follow-up
FC	99 %	95 %	97 %	97 %
6MWD	78 %	77 %	77 %	78 %
NT-proBNP	77 %	91 %	91 %	91 %
RA area	24 %	40 %	48 %	39 %
Pericardial effusion	77 %	54 %	59 %	50 %
RAP	97 %	31 %	19 %	29 %
CI	94 %	31 %	18 %	27 %
S_vO_2	76 %	28 %	17 %	27 %

6MWD, 6-minute walk distance; CI, cardiac index; FC, functional class; NT-proBNP, N-terminal pro-hormone of brain natriuretic peptide; RA, right atrial; RAP, mean right atrial pressure; S_vO_2, mixed venous oxygen saturation.

Table S4. Risk group distributions per PAH subset at diagnosis and during follow-up for the full study population

	Diagnosis			**3-year follow-up**			**4-year follow-up**			**5-year follow-up**		
	Low, %	Intermediate, %	High, %	Low, %	Intermediate, %	High, %	Low, %	Intermediate, %	High, %	Low, %	Intermediate, %	High, %
IPAH/FPAH	21	68	11	40	53	8	50	37	13	46	50	4
APAH-CTD	34	63	4	28	62	11	41	57	2	39	52	10
APAH-CHD	55	43	2	49	46	6	47	53	0	62	39	0
APAH-Others	41	56	3	50	50	0	56	39	6	43	57	0

APAH, associated pulmonary arterial hypertension; CHD, congenital heart disease; CTD, connective tissue disease; FPAH, familial pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension. At diagnosis, there were 186 patients with IPAH/FPAH, 115 with APAH-CTD, 51 with APAH-CHD and 34 with APAH-Others. At the 3-year follow-up, there were 131 patients with IPAH/FPAH, 65 with APAH-CTD, 33 with APAH-CHD and 22 with APAH-Others. At the 4-year follow-up, there were 99 patients with IPAH/FPAH, 44 with

APAH-CTD, 32 with APAH-CHD and 18 with APAH-Others. At the 5-year follow-up, there were 68 patients with IPAH/FPAH, 31 with APAH-CTD, 26 with APAH-CHD and 14 with APAH-Others.

Table S5. Risk group distributions per PAH subset at diagnosis and during follow-up for the study population after exclusion of patients who presented at diagnosis with multiple risk factors for HFpEF, atrial fibrillation, and/or age >75 years

	Diagnosis			**3-year follow-up**			**4-year follow-up**			**5-year follow-up**		
	Low, %	**Intermediate, %**	**High, %**	**Low, %**	**Intermediate, %**	**High, %**	**Low, %**	**Intermediate, %**	**High, %**	**Low, %**	**Intermediate, %**	**High, %**
IPAH/FPAH	27	62	11	55	39	6	66	27	8	57	39	4
APAH-CTD	41	56	4	26	64	10	47	50	3	46	42	12
APAH-CHD	63	34	3	57	43	0	52	48	0	71	29	0
APAH-Others	48	48	5	54	46	0	64	36	0	57	43	0

APAH, associated pulmonary arterial hypertension; CHD, congenital heart disease; CTD, connective tissue disease; FPAH, familial pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension. At diagnosis, there were 115 patients with IPAH/FPAH, 84 with APAH-CTD, 32 with APAH-CHD and 21 with APAH-Others. At the 3-year follow-up, there were 83 patients with IPAH/FPAH, 50 with APAH-CTD, 21 with APAH-CHD and 13 with APAH-Others. At the 4-year follow-up, there were 64 patients with IPAH/FPAH, 34 with APAH-CTD, 23

with APAH-CHD and 11 with APAH-Others. At the 5-year follow-up, there were 49 patients with IPAH/FPAH, 26 with APAH-CTD, 17 with APAH-CHD and 7 with APAH-Others.

Table S6. Results from univariate Cox proportional hazards models at the 3-year-, 4-year- and 5-year follow-ups

	3-year follow-up	4-year follow-up	5-year follow-up
BMI	**p=0.079**	p>0.15	p>0.15
eGFR	**p<0.001**	**p=0.017**	p>0.15
Hypertension	**p=0.128**	**p=0.128**	**p=0.128**
Diabetes mellitus	p>0.15	p>0.15	p>0.15
Atrial fibrillation	p>0.15	p>0.15	p>0.15
Previous stroke	p>0.15	p>0.15	p>0.15
Ischaemic heart disease	**p=0.005**	**p=0.005**	**p=0.005**
Thyroid disease	p>0.15	p>0.15	p>0.15

BMI, body mass index; eGFR, estimated glomerular filtration rate.

Figure S1. Transplant-free survival rates according to risk group at the A. 3-year-, B. 4-year- and C. 5-year follow-up, respectively, for the study population after exclusion of patients who presented at diagnosis with multiple risk factors for HFpEF, atrial fibrillation and/or age >75 years

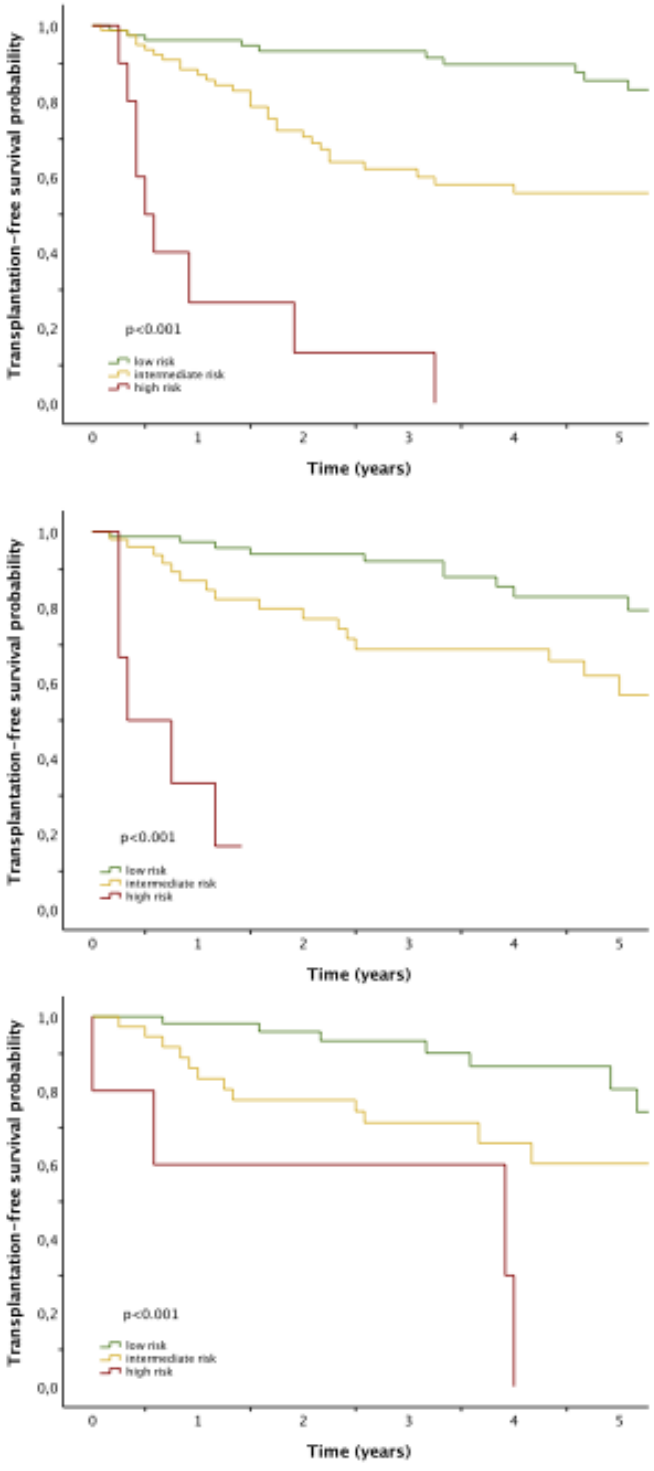
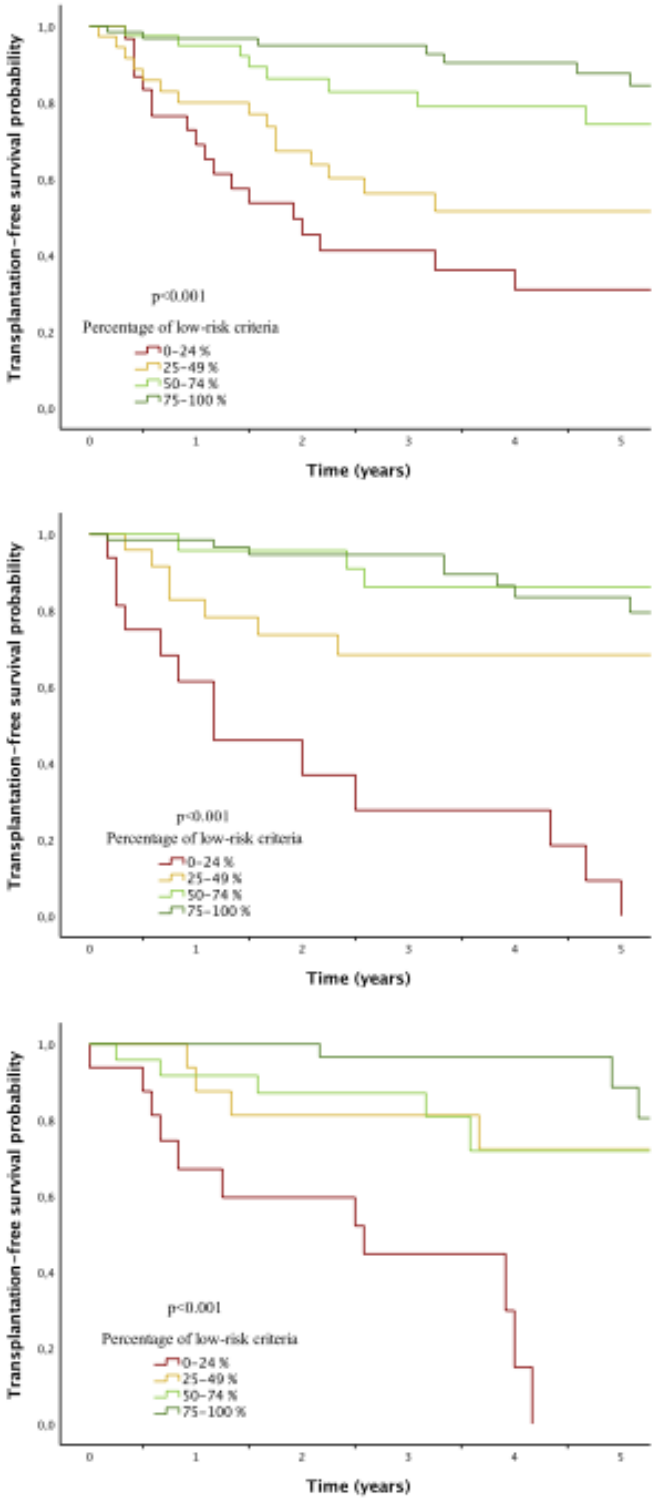


Figure S2. Transplant-free survival rates according to the proportion of low risk variables at the A. 3-year-, B. 4-year- and C. 5-year follow-up, respectively, for the study population after exclusion of patients who presented at diagnosis with multiple risk factors for HFpEF, atrial fibrillation and/or age >75 years



Appendix

The Swedish Association for pulmonary hypertension (*in Swedish*, Svensk förening för pulmonell hypertension, SveFPH) was initiated in 2007 to survey PAH and CTEPH patients in Sweden, and to support education, research and clinical development in the area of pulmonary hypertension. The SveFPH steering committee initiated the Swedish Pulmonary Arterial Hypertension Registry (SPAHR) in 2008. SPAHR has since then evolved as a national quality registry, where the Swedish Association of Local Authorities and Regions (*in Swedish*, Sveriges kommuner och regioner, SKR) has the economic responsibility. The SPAHR steering committee meets regularly for data validation, quality control, and continuous registry management and update.