Impact of age and comorbidity on risk stratification in idiopathic pulmonary arterial hypertension

Clara Hjalmarsson[1,2], Göran Rådegran[3,4], David Kylhammar[5], Bengt Rundqvist[1,2], Jonas Multing[1,2], Magnus D. Nisell[6] and Barbro Kjellström[6] on behalf of SveFPH and SPAHR

Affiliations: [1]Dept of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden. [2]Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden. [3]Dept of Cardiology, Skåne University Hospital, Lund, Sweden. [4]Dept of Clinical Sciences, Lund University, Lund, Sweden. [5]Dept of Medicine and Health Sciences, Clinical Physiology, Linköping University, Linköping, Sweden. [6]Cardiology Unit, Dept of Medicine, Karolinska Institute, Stockholm, Sweden.

Correspondence: Clara Hjalmarsson, Dept of Cardiology, Blå Stråket 3, 1st Floor, Sahlgrenska University Hospital, SE-405 30 Gothenburg, Sweden. E-mail: clara.hjalmarsson@vgregion.se

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ABSTRACT Recent reports from worldwide pulmonary hypertension registries show a new demographic picture for patients with idiopathic pulmonary arterial hypertension (IPAH), with an increasing prevalence among the elderly.

We aimed to investigate the effects of age and comorbidity on risk stratification and outcome of patients with incident IPAH.

The study population (n=264) was categorised into four age groups: 18–45, 46–64, 65–74 and ⩾75 years. Individual risk profiles were determined according to a risk assessment instrument, based on the European Society of Cardiology and the European Respiratory Society guidelines. The change in risk group from baseline to follow-up (median 5 months) and survival were compared across age groups. In the two youngest age groups, a significant number of patients improved (18–45 years, Z= −4.613, p<0.001; 46–64 years, Z= −2.125, p=0.034), but no significant improvement was found in the older patient groups. 5-year survival was highest in patients aged 18–45 years (88%), while the survival rates were 63%, 56% and 36% for patients in the groups 46–64, 65–74 and ⩾75 years, respectively (p<0.001). Ischaemic heart disease and kidney dysfunction independently predicted survival.

These findings highlight the importance of age and specific comorbidities as prognostic markers of outcome in addition to established risk assessment algorithms.

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Introduction

Pulmonary arterial hypertension (PAH) is a deleterious, incurable disease that affects the small pulmonary arteries, with vasoconstriction and vascular proliferation leading to severe remodelling and an increased pulmonary vascular resistance. The increased right ventricular afterload results in right ventricular failure and ultimately death [1, 2].

The National Institutes of Health in the United States initiated the first large registry enrolling patients with idiopathic PAH (IPAH) 40 years ago [3]. This registry included 194 patients, with a mean age of 36 years, of whom 68% were women. Without effective treatments, the median survival time was estimated to be 2.8 years [1]. The first consensus guidelines for the diagnosis and treatment of IPAH were published in 1993 [4]. Now, new treatments are available that target the disease-related vasoactive pathways and influence symptoms, quality of life and survival [5, 6]. However, contemporary reports from worldwide pulmonary hypertension (PH) research registries show a new demographic picture for the IPAH population [7–9]. Prevalence among the elderly is increasing, with a mean age of 50–65 years reported at diagnosis [10–13]. The reason for this shift is not clear. Late-onset IPAH among older patients may include some degree of left ventricular diastolic dysfunction leading to a particular phenotype of "mixed" pre- and postcapillary PH [13]. These patients may share features of both IPAH and PH secondary to diastolic heart failure, as shown by Opitz *et al.* [14]. Improved evaluation of older patients with dyspnoea might also contribute to this demographic shift [15]. Interestingly, and in contrast to what is seen at many PAH clinics, most randomised controlled drug trials exclude elderly patients with multiple comorbidities [16, 17]. Similarly, apart from the REVEAL score [18], which includes age >60 years and kidney dysfunction, the actual risk assessment instruments do not take into account age or comorbidity as prognostic markers. More data are required to support the use of risk equations and risk scores to assess subsequent risk [19].

Kylhammar *et al.* [20] recently validated the feasibility of the new European Society of Cardiology and the European Respiratory Society guidelines' instrument for risk assessment [5, 21] in a cohort of 530 patients with associated or familial/idiopathic PAH reported in the Swedish Pulmonary Arterial Hypertension Register (SPAHR). The findings showed that the recommended comprehensive risk assessment successfully discriminated patients' outcomes.

The aim of the present study was to further investigate the predictive value of the risk assessment instrument in the set-up of different age categories and associated comorbidities in a population with incident IPAH.

Methods

This study was based on data recorded in SPAHR [22]. All seven Swedish PAH centres report to SPAHR, enabling high national coverage [23]. SPAHR was initiated in 2008, after being approved by the National Board of Health and Welfare and the Swedish Data Protection Authority. All patients are informed about their participation and have the right to decline. Source data are regularly subjected to random monitoring onsite. The present study complies with the Declaration of Helsinki and was approved by the local ethics committee in Gothenburg, Sweden (Dnr. 2015/1002).

Study population

Patients with incident, adult IPAH registered in SPAHR between January 1, 2008 and June 29, 2016 were considered for the analyses. The day of diagnosis, confirmed by right heart catheterisation (RHC), was used as baseline. Follow-up was defined as the first registered visit at the PAH clinic occurring within 3–15 months after diagnosis.

The study population was categorised into four age groups: 18–45, 46–64, 65–74 and ⩾75 years. The presence of seven common comorbidities was assessed: arterial hypertension, diabetes mellitus, ischaemic stroke, ischaemic heart disease, atrial fibrillation, obesity and kidney dysfunction.

Variables

The diagnosis of IPAH was determined by RHC, according to the 2009 [24] or 2015 [5, 21] guidelines criteria. The variables of interest extracted from SPAHR at baseline and follow-up comprised demographics, comorbidities, medical treatment, World Health Organization functional class (FC), data from RHC, 6-min walk distance (6MWD), blood biochemistry and echocardiography. Pulmonary capillary wedge pressure (PCWP) measurements by RHC, echocardiography and/or cardiac magnetic resonance imaging were performed to exclude PH due to left heart disease. Pulmonary function testing, including diffusing capacity of the lung for carbon monoxide (*D*LCO, % of predicted value) and high-resolution computed tomography were performed to exclude PH due to lung disease. Chronic thromboembolic PH was excluded by pulmonary scintigraphy and/or pulmonary angiography. Creatinine levels were used to

estimate glomerular filtration rate (eGFR) according to the Cockroft–Gault formula [25]. Kidney dysfunction was defined as an eGFR <60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ at baseline. Obesity was defined as a body mass index >30 $kg \cdot m^{-2}$ at baseline.

Risk assessment

Risk assessment was based on the following specific variables according to the risk assessment instrument from the 2015 guidelines [5, 21]: FC, 6MWD, N-terminal pro-brain natriuretic peptide (NT-proBNP), right atrial area, mean right atrial pressure, pericardial effusion, cardiac index (CI) and mixed venous oxygen saturation (S_{vO_2}). Each variable was graded from 1 to 3 where 1=low risk, 2=intermediate risk and 3=high risk. 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 to the nearest integer, which was then used to define the patient's risk group. Details regarding this method for risk assessment have been previously published elsewhere [20].

Statistical methods

Fisher's exact test or Chi-squared test was used to compare categorical variables. For continuous data, between-group differences were compared using one-way ANOVA, with *post hoc* Bonferroni testing. All analyses were stratified by age group. Survival was analysed using Kaplan–Meier estimates and Cox proportional hazard regression, for which sex, comorbidity and change in risk category from baseline to follow-up were used as covariates. The results are presented as the hazard ratio (HR) with 95% confidence intervals. Change in risk group from baseline to follow-up in relation to age was compared using the Wilcoxon signed-rank test. The Z-score (also known as the standard score) was produced by using the deviation from the mean, in terms of standard deviation units, and was used for samples with >20 observations in order to obtain a standardised, normal distribution. Absolute values >1.96 were considered significant. p-values <0.05 were regarded as statistically significant (two-sided test). All statistical analyses were performed using SPSS Statistical Software Package, version 22.0 (SPSS Inc., Chicago, IL, USA).

Results

This analysis included 264 patients with IPAH. PAH-targeted therapy was initiated at baseline (<3 months from diagnosis) in 236 patients (88%), of which 23 (10%) fulfilled the criteria as responders to an acute vaso-reactivity test [5, 21] and were treated with a high dose of calcium-channel blocker. For the remaining 31 patients, treatment was recorded in SPAHR >3 months after diagnosis. Follow-up visits were available for 220 patients; of these, 87 patients had RHC. The median time from baseline to first follow-up was 5 months (interquartile range (IQR) 4–6 months).

Baseline characteristics by age group

Women were predominant in the two youngest age groups, and accounted for ~50% or less of the patients in the oldest groups (table 1). The youngest patients, 18–45 years, were more often diagnosed with FC II and had the lowest body mass index, NT-proBNP level and systolic blood pressure, as well as the longest 6MWD and the highest CI, arterial saturation (S_{aO_2}) and S_{vO_2}, compared to the other age groups. This group also had the highest eGFR and mean pulmonary arterial pressure (mPAP). In contrast, patients ⩾75 years had the lowest mPAP, the shortest 6MWD and the highest NT-proBNP level.

The D_{LCO} significantly declined with age. Patients in the age group 18–45 years were more often treated with combination PAH-targeted therapy at baseline and less often used diuretics or oxygen treatment compared to the older age groups. Treatment was similar among the two oldest age groups.

Risk assessment

A median of seven variables (IQR 6–7) per patient were available for assessment at baseline and five (IQR 3–6) at follow-up. FC, 6MWT and at least one measure of right ventricular function (NT-proBNP, echocardiography and/or RHC) were available for 82% of patients at baseline and 84% of patients at follow-up. At baseline, 29% of patients 18–45 years of age were in the low-risk group, compared to 22%, 9% and 6% of the patients in the age groups 46–64 years, 65–74 years and ⩾75 years, respectively (table 1). In the two youngest age groups, a significant number of patients improved, moving from the intermediate or high-risk group at baseline to the low-risk group at follow-up (18–45 years $Z = -4.613$, $p<0.001$; 46–64 years $Z = -2.125$, $p=0.034$). There was no significant difference in risk group distribution between baseline and follow-up in the two oldest age groups (65–74 years $Z = -0.707$, $p=0.480$; ⩾75 years $Z = -0.832$, $p=0.405$) (figure 1).

TABLE 1 Baseline characteristics of the study population by age

Age group years	18–45	46–64	65–74	⩾75	Total	p-value
Subjects n	48	59	90	67	264	
Demography and clinical data						
Age years	36 (14)	59 (11)	70 (5)	78 (4)	68 (22)	**<0.001**
Female	65	70	52	43	56	**0.013**
Smoking						**<0.001**
Active	10	11	1	0	5	
Previous	27	60	71	60	58	
BMI kg·m^{-2}	25±4.9	29±7.3	28±5.1	26±4.1	27±5.5	**0.003**
WHO-FC						**<0.001**
I	0	0	0	0	0	
II	30	24	9	10	17	
III	48	66	85	82	73	
IV	22	10	6	8	10	
6MWD m	405±145	311±148	248±109	221±115	282±140	**<0.001**
D_{LCO} % pred	66±21	57±22	44±18	45±18	50±22	**<0.001**
SBP mmHg	123±16	131±25	136±24	136±23	133±23	**0.012**
DBP mmHg	74±17	76±13	73±14	73±14	74±14	0.660
eGFR mL·min^{-1}·1.73 m^{-2}	97±38	75±30	55±18	43±16	64±32	**<0.001**
Hb g·L^{-1}	150±17	146±18	147±19	144±19	146±18	0.520
NT-proBNP ng·L^{-1}	1090 (1862)	1229 (1954)	1761 (2573)	2100 (4490)	1715 (2903)	**<0.001**
Comorbidity						
Systemic hypertension	11	57	61	66	51	**<0.001**
Diabetes mellitus	11	23	42	30	29	**0.002**
Ischaemic stroke	0	4	9	13	7	0.063
Ischaemic heart disease	0	17	23	26	18	**0.003**
Atrial fibrillation	2	10	21	29	17	**0.002**
Obesity	13	30	24	14	21	0.070
Kidney dysfunction	9	30	63	85	51	**<0.001**
Number of comorbidities						
None	65	21	4	0	19	**<0.001**
1–3	35	72	76	76	67	**0.006**
4–7	0	7	20	24	14	**0.003**
Haemodynamics						
mRAP mmHg	8±6	8±6	8±5	8±4	8±5	0.735
mPAP mmHg	56±11	48±10	47±9	46±9	49±10	**<0.001**
PCWP mmHg	8±3	9±6	9±4	9±3	9±4	0.337
CI L·min^{-1}·m^{-2}	2.4±0.8	2.3±0.7	2.3±0.6	2.0±0.5	2.3±0.6	**0.005**
PVR Wood units	11.9±5.6	9.8±4.3	9.4±3.7	10.8±4.8	10.3±4.6	**0.010**
S_{aO_2} %	94±3	92±6	88±7	87±8	90±7	**<0.001**
S_{vO_2} %	65±11	61±9	58±8	56±10	59±10	**<0.001**
PAH-targeted therapy[#]						
Single	63	69	72	78	71	0.210
Dual	27	19	14	9	16	**0.019**
Triple	6	0	0	0	1	**0.003**
No treatment registered	4	12	14	13	12	0.324
Supportive therapy						
Anticoagulants	67	58	63	61	62	0.432
Diuretics	38	70	78	75	68	**<0.001**
Supplemental oxygen	6	20	46	46	33	**0.002**
Risk group						**0.002**
Low	29	22	9	6	15	
Medium	52	64	81	78	71	
High	19	14	10	16	14	

Data are presented as median (interquartile range), % or mean±SD, unless otherwise indicated. BMI: body mass index; WHO-FC: World Health Organization functional class; 6MWD: 6-min walking distance; D_{LCO}: 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; S_{aO_2}: arterial oxygen saturation; S_{vO_2}: mixed venous oxygen saturation; PAH: pulmonary arterial hypertension. [#]: started within 3 months from diagnosis. Bold indicates statistical significance at p<0.05.

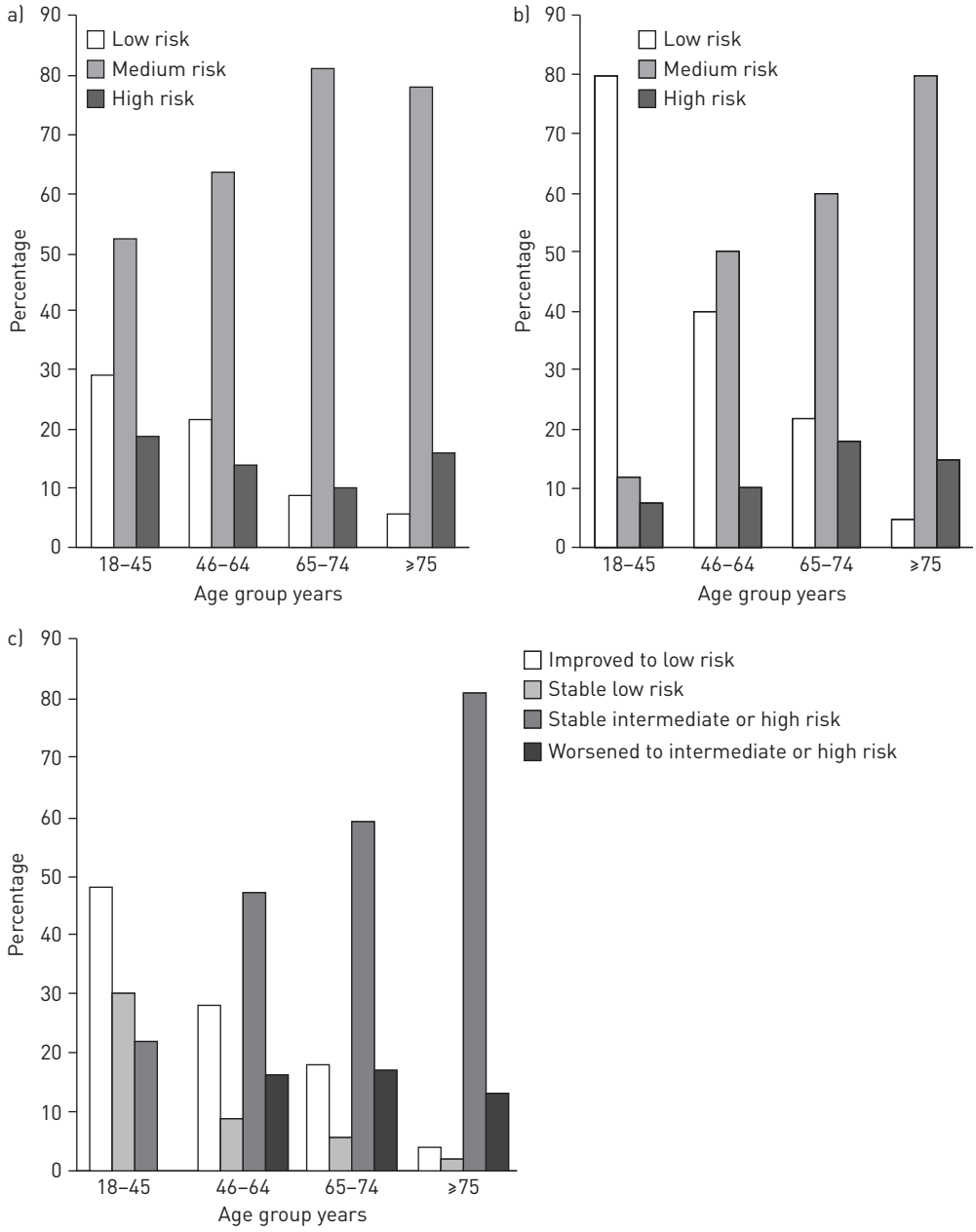

FIGURE 1 Risk assessment presented by age at a) baseline and b) follow-up, and c) change in risk group from baseline to follow-up.

Comorbidity

The comorbidity profile by age group is shown in table 1. Comorbidity was more frequent in the two oldest age groups, in which 20% had at least four comorbidities. In a Cox proportional regression analysis, adjusted for sex and change in risk group from baseline to follow-up, ischaemic heart disease and kidney dysfunction were the only comorbidities that independently affected survival (table 2).

Survival

Up to study-end (median 73 months, IQR 37–133 months), 114 deaths and 11 lung transplants were recorded. Of these, 106 deaths and 10 lung transplants occurred within 5 years from baseline and 52% of those who died or underwent transplant were women (p=0.217). The transplant-free 1-, 3- and 5-year survival rates for the whole study population were 87%, 67% and 58%, respectively. Patients 18–45 years had the highest transplant-free 5-year survival rate of 88%, compared with 63%, 56% and 36% for patients in the groups 46–64, 65–74 and ⩾75 years, respectively (p<0.001). In an analysis adjusted for age

TABLE 2 Cox proportional regression analysis adjusted for comorbidity, showing the relationship between mortality and explanatory variables

Explanatory variable	HR (95% CI)	p-value
Sex	0.82 (0.48–1.41)	0.473
Worsening of risk group from baseline	1.75 (1.14–2.69)	**0.011**
Hypertension	0.89 (0.51–1.56)	0.685
Diabetes mellitus type 2	1.01 (0.56–1.82)	0.973
Atrial fibrillation	1.00 (0.48–2.10)	1.000
Ischaemic heart disease	2.14 (1.21–3.78)	**0.009**
Stroke	2.00 (0.85–4.74)	0.114
Obesity	1.44 (0.78–2.66)	0.245
Kidney dysfunction	1.85 (1.09–3.14)	**0.022**

Worsening of risk group from baseline, ischaemic heart disease and kidney dysfunction were independent predictors of survival. Bold indicates statistical significance at p<0.05. HR: hazard ratio.

categories, survival was independently predicted by change in risk category from baseline to first follow-up visit (figure 2).

Discussion

The main findings of the present study illustrate that improvement in risk category at follow-up is a strong predictor of survival across all age groups. Young patients of 18–45 years had a high and significantly better 5-year survival rate than patients in the older age groups. In contrast, elderly patients were less often initially treated with combination PAH-targeted therapy and had a poorer outcome. They also exhibited a worse treatment response, which might be attributable to a different PAH phenotype, delayed diagnosis, less intense treatment or associated comorbidity. Ischaemic heart disease and kidney dysfunction were independently associated with poor prognosis.

Few studies have assessed the characteristics of patients with IPAH based on their age [10, 26] or the effect of age on treatment response [10, 27]. The COMPERA study used a cut-off age of 65 years [10]. The results were similar to the present study: younger patients were more often female and, despite a worse hemodynamic profile at baseline, had a lower FC, better NT-proBNP level and longer 6MWD. Another interesting observation was that mPAP at diagnosis declined with age, confirming the findings by Hoeper *et al.* [10]. A possible explanation for this would be that elderly people have worse adaptive mechanisms for increased right ventricle pressure load, and probably develop right ventricle failure at lower pulmonary

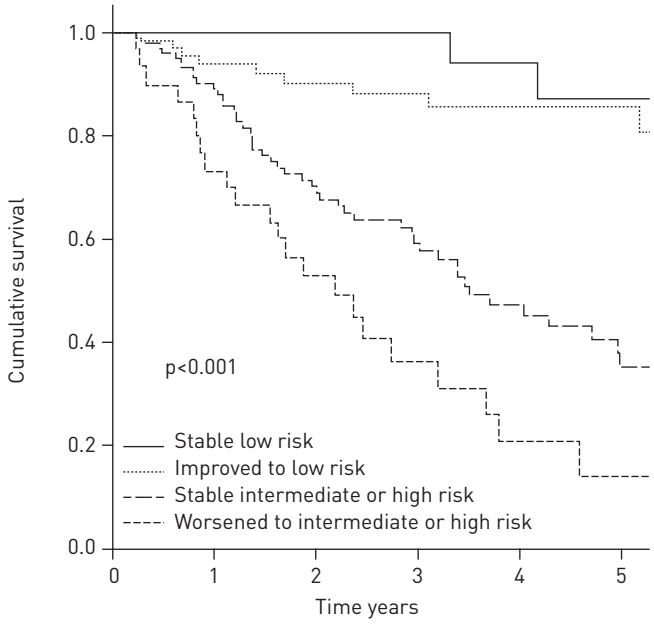

FIGURE 2 Cumulative survival of the study population adjusted for age and stratified by risk category.

arterial pressures. This, in combination with comorbidity and frailty, may influence the patients to seek medical attention before the mPAP reaches higher levels.

Recently, an abbreviated version of the risk assessment strategy proposed by the current European PH guidelines was proven to accurately predict transplant-free survival in the French PAH registry population [28] and the COMPERA [29]. Additionally, work by Kylhammar *et al.* [20] showed that change in risk profile from baseline to follow-up is an even stronger predictor of survival in comparison to risk at baseline.

In the present study, patients aged 18–45 years had better outcomes than those in the intermediate age group (46–64 years), with a 5-year survival rate of almost 90%. In a report from the PH registry of the United Kingdom and Ireland [26], the median age was 50 years and the estimated 5-year survival rate for patients <50 years was lower than in the present study; similarly, a study by D'Alonzo *et al.* [1] estimated a median survival time of 2.8 years. The discrepancy between the results of these studies and our study may be due to a different inclusion period (2000–2009 and 1985–1988, respectively, *versus* 2008–2016), with less-developed treatment strategies.

In 2016, data from six large randomised controlled trials including patients with IPAH and associated PAH were presented in a meta-analysis [27]. The results indicated that older patients were more often classified into New York Heart Association FC III–IV and had shorter 6MWD, but had better hemodynamic status at baseline than younger patients. These results, as well as those from the COMPERA study [10], are in accordance with our findings, suggesting that our patient population is highly representative of the IPAH population, according to the present definition.

The improvement in risk score from baseline to follow-up was greater for the younger than the older patients. Given that age and comorbidity are usually correlated, it is difficult to assess the exact contribution of each of these factors to outcome. However, while the number of associated comorbidities did not affect survival (data not shown), the type of comorbidity did: ischaemic heart disease and kidney dysfunction were strongly associated with poor prognosis. Among patients ⩾75 years, ischaemic heart disease and kidney dysfunction were, as expected, more frequent; apart from this, the demographic and comorbidity profiles in this group were very similar to those of the 65–74 years group. Thus, the clinical improvement, estimated as change in risk category from baseline to follow-up, was smaller and survival worse in the oldest group. To some extent, this might reflect the natural effect of age, as well as the deleterious effect of specific comorbidities on outcome, but it could also be due to delayed diagnosis, or to a different "PAH phenotype" with worse treatment response. It is very important to take into account the difference in treatment strategies, because older patients were less often treated with initial combination PAH-targeted therapy at baseline, probably due to biased allocation of treatment or to worse tolerability among older patients.

While it is well known that comorbid conditions can affect the course of many underlying disease states, data relating comorbidity to outcome in IPAH patients are scarce [10, 12, 30]. Trip *et al.* [31] reported that a severely reduced D_{LCO} in IPAH is associated with advanced age and greater tobacco exposure and it relates to worse exercise performance and decreased survival. A study from the REVEAL registry found that of seven common comorbidities, only diabetes and obstructive pulmonary disease were associated with an increased risk for death [12]. However, other diseases common among the elderly, *e.g.* atrial fibrillation, ischaemic heart disease, stroke and reduced kidney function, were not included in this analysis. This might be explained by the mean age being <50 years in the REVEAL registry study [7].

Serum creatinine has previously been associated with a worse hemodynamic profile and has been suggested as an independent predictor of mortality in PAH patients [32]. However, serum creatinine is a rough measure of kidney function, and can be influenced by other biological factors. Moreover, few studies have investigated the impact of renal function on outcome in IPAH patients [33, 34], and those studies included heterogeneous populations, with PH of mixed aetiologies. In the present work, ischaemic heart disease and kidney dysfunction (eGFR <60 $mL^{-1}{\cdot}min^{-1}{\cdot}1.73\ m^{-2}$) were the only independent predictors of survival among the investigated comorbidities, suggesting that these two important comorbidities should be taken into account when making prognostic evaluations.

Strengths and limitations

One of the strengths of the present study is that it includes only patients with incident IPAH from 2008 forwards, thus giving an insight into an aetiologically homogenous group at a time with modern treatment strategies. All PAH centres in Sweden participate in SPAHR, allowing for a national coverage of 89% (for 2015). Registry data reflect patients seen in clinical practice and offer a real-life perspective as compared to data collected in randomised clinical trials. Categorising the study population in four age groups allows a more accurate description of comorbidity profile and outcome than in previous investigations.

The limitations of the present work are those typically associated with observational registry studies, *e.g.* selection bias, lack of standardisation of registered variables and missing follow-up data. Another limitation is the relatively small size of the study population; however, in light of IPAH being an unusual disease, it is difficult to achieve large national study groups.

Conclusion

Improvement in risk category at follow-up was a strong predictor of survival across the age groups. The survival rate among young IPAH patients in the present study was considerably higher than previously shown, likely reflecting the improvement in modern treatment strategies. Elderly patients were more often treated with single rather than combination PAH-targeted therapy at baseline and had a poorer outcome. Ischaemic heart disease and kidney dysfunction independently predicted worse survival. The present study highlights the importance of age and specific comorbidity as prognostic markers of outcome, suggesting the usefulness of adding these parameters to previously established risk assessment algorithms.

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