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IMPACT OF AGE AND COMORBIDITY ON RISK STRATIFICATION IN IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION

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Take-home message: Change in risk category at follow-up and specific comorbidity predict survival in IPAH across age groups.

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Abstract and keywords

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

Aim. To investigate the effect of age and comorbidity on risk stratification and outcome of patients with incident IPAH.

Methods and results. The study population (n=264) was categorized in four age groups; 18-45, 46-64, 65-74, and ≥ 75 years. Individual risk profile was determined according to a risk assessment instrument, based on the ESC/ERS guidelines. 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; $Z = -4.613$, $p < 0.001$ and 46-64 years; $Z = -2.125$, $p = 0.034$), but no significant improvement was found in the older patients. Five-year survival was highest in patients 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 ($p<0.001$). Ischemic heart disease and kidney dysfunction independently predicted survival.

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

Keywords: PAH, age, comorbidity, survival, risk, prognosis

Introduction

Pulmonary arterial hypertension (PAH) is a deleterious, incurable disease affecting the small pulmonary arteries by 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 first large registry enrolling patients with idiopathic PAH (IPAH) was initiated forty years ago by the National Institutes of Health in the United States [3]. This registry included 194 patients, with a mean age of 36 years, of which 68% were women. Without effective treatments, the median survival time was estimated to 2.8 years [1]. The first consensus guidelines for diagnosis and treatment of IPAH were published in 1993 [4]. Nowadays, new treatments − targeting the disease related vasoactive pathways and influencing symptoms, quality of life, and survival − have become available [5, 6]. However, contemporary reports from worldwide pulmonary hypertension research registries show a new demographic picture of the IPAH population [7-9]. The prevalence among the elderly is increasing, with a mean age of 50 to 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 post-capillary pulmonary hypertension [13]. These patients may share features of both IPAH and pulmonary hypertension secondary to diastolic heart failure, as shown by Opitz *et al* [14]. Improved evaluation of older patients with dyspnea might also contribute [15]. Interestingly, and in contrast to patients seen at many PAH-clinics, most randomized 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 and/or

comorbidity as prognostic markers. Furthermore, more data are required to support the use of the risk equations and risk scores to assess subsequent risk [19].

In a recent publication by Kylhammar *et al* [20], feasibility of the new ESC/ERS guidelines' instrument for risk assessment [5, 21] was validated in a cohort of 530 patients with associated or familial/idiopathic PAH reported in the Swedish Pulmonary Arterial Hypertension Register (SPAHR). Our findings showed that the recommended comprehensive risk assessment successfully discriminate patients' outcome.

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 an incident IPAH population.

Methods

This study was based on data recorded in SPAHR [22]. All seven Swedish PAH centers report to SPAHR enabling a 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 is approved by the local ethics committee in Gothenburg, Sweden (Dnr. 2015/1002).

Study population

Incident, adult IPAH patients registered in SPAHR between January 1, 2008 and June 29, 2016 were considered for the analyses. Day of diagnosis, confirmed by right heart catheterization (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 categorized 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, ischemic heart disease, atrial fibrillation, obesity, and kidney dysfunction.

Variables

The diagnosis of IPAH was set by RHC, according to the 2009 [24] or 2015 [5, 21] guidelines criteria. Variables of interest, at baseline and follow-up, were extracted from SPAHR: demographics, comorbidities, medical treatment, World Health Organization functional class (FC), data from RHC, six minute walk distance (6MWD), blood biochemistry, and echocardiography. PAWP measurements by RHC, echocardiography, and/or cardiac magnetic resonance imaging were performed to exclude PH due to left heart disease. Pulmonary function

testing, including lung diffusing capacity of carbon monoxide (DLCO, % of predicted value) and high-resolution computer tomography were performed to exclude PH due to lung diseases. Chronic thromboembolic PH was excluded by pulmonary scintigraphy and/or pulmonary angiography. Creatinine levels were used to estimate glomerular filtration rate (eGFR) according to Kockroft-Gault formula [25]. Kidney dysfunction was defined as an eGFR < 60 ml/min x 1.73m^2 at baseline. Obesity was defined as a BMI >30 kg/m^2 at baseline.

Risk assessment

Risk assessment was based on specific variables, according to the risk assessment instrument from the 2015 guidelines [5, 21]: FC, 6MWD, NT-proBNP, 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 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 χ^2 -test were 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 groups. Survival was analysed by use of Kaplan-Meier estimates and Cox proportional hazard regression, where gender, 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 (CI). Change in risk group from baseline to follow-up in relation to age was compared by the Wilcoxon signed-rank test. Z-score (also known as standard score) is produced by using the deviation from the mean, in terms of standard deviation units, and is used for samples larges than 20 observations in order to obtain a

standardized, normal distribution. Absolute values above 1.96 are considered significant. P-values <0.05 were regarded as statistically significant (2-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. At baseline (within three months from diagnosis), PAH-targeted therapy was initiated 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 later than three months after diagnosis. Follow-up visits were available for 220 patients, of these 87 patients were subjected to RHC. The median time from baseline to first follow-up was 5 (interquartile range 4-6) months.

Baseline characteristics by age group

In the two youngest age groups women were predominant, while in the oldest groups, women accounted for around 50% of the patients or less (Table 1). The youngest patients, 18-45 years, were more often diagnosed in FC II and had the lowest BMI, NT-proBNP, and systolic blood pressure, as well as the longest 6MWD, and the highest CI, arterial saturation (SaO_2), and SvO_2, compared to the other age groups. This group also had the highest eGFR and MPAP. In contrast, patients ≥75 years had the lowest MPAP, the shortest 6MWD and the highest NT-proBNP.

The lung diffusing capacity for carbon monoxide was significantly declining with the 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 amongst the two oldest age groups.

Risk assessment

At baseline a median of 7 [Q1-Q3; 6-7] variables per patient were available for assessment and at follow-up 5 [Q1-Q3; 3-6] variables. FC, 6MWT, and at least one measure of right ventricular function (NT-proBNP, echocardiography and/or right heart catheterization) were available for 82% of patients at baseline and 84% of patients at follow-up. At baseline, 29% of the 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 intermediate or high risk group at baseline to low risk group at follow-up (18-45 years; $Z = -4.613$, $p < 0.001$ and 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 ($Z = -0.707$, $p = 0.480$); and 75 years ($Z = -0.832$, $p = 0.405$), (Figure 1).

Comorbidity

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

Survival

Until study-end (median 73, interquartile range 37-133 months), 114 deaths and 11 lung transplants were recorded. Of these, 106 deaths and 10 lung transplants occurred within five years from baseline and 52% of those who died or underwent transplant were women ($p = 0.217$). The transplant-free 1, 3 and 5 years survival rates for the whole study population were 87, 67 and 58% respectively. Patients 18-45 years had the highest transplant-free five-year survival rate (88%), while the survival rates were 63, 56, and 36% for patients in the groups 46-64, 65-74 and ≥75 years, respectively ($p < 0.001$). In an analysis adjusted for age 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, 18-45 years, have a high and significantly better 5-year survival rate than patients in the older age groups. In contrast, elderly patients are less often initially treated with combination PAH-targeted therapy and have a poorer outcome. They also exhibit a worse treatment response, which might be due to a different PAH-phenotype, to delayed diagnosis, to less intense treatment, or to associated comorbidity. Ischemic heart disease and kidney dysfunction are independently associated with poor prognosis.

Few studies have assessed characteristics of patients with IPAH based on their age [10, 26] or the effect of age on treatment response [10, 27]. In the COMPERA-study, a cutoff age of 65 years was used [10]. The results were similar to the present study, where younger patients were more often female and despite worse hemodynamic profile at baseline, also had a lower FC, better NT-proBNP, 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 worse adaptive mechanisms for increased right ventricle pressure load in elderly, who probably develop right ventricle failure at lower PAP levels. 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, the 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 outcome than those in the intermediate age group (46-64 years), with a five-year survival rate of almost 90%. In a report from the pulmonary hypertension registry of the United Kingdom and Ireland [26] the median age was 50 years and the estimated five-year survival rate for the patients <50 years was lower than in the present study; similarly, the median survival time was estimated to 2.8 years, in the study by D'Alonzo *et al* [1]. The discrepancy between the results of these studies and our results 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 randomized controlled trials including patients with idiopathic and associated PAH were presented in a meta-analysis [27]. The results indicated that older patients were more often in NYHA class III-IV, 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 for the IPAH population, according to present definition.

The improvement in risk score from baseline to follow-up was greater for the younger than for the older patients. Since 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 kind of comorbidity did; ischemic heart disease and kidney dysfunction were strongly associated with poor prognosis. Among patients above 75 years, ischemic 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 the group 64-75 years. Thus, the clinical improvement, estimated as change in risk category from baseline to follow-up, was smaller and the 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. Of course, it is very important to take into account the difference in treatment strategies, since 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 may affect the course of many underlying disease states, data relating comorbidity to outcome in IPAH patients are scarce [10, 12, 30]. Trip *et al* reported that a severely reduced DLCO in IPAH is associated with advanced age and a greater tobacco exposure and it relates to worse exercise performance and decreased survival [31], while 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, such as atrial fibrillation, ischemic heart disease, stroke, and reduced kidney function were not included in this analysis. This might be explained by the mean age being below 50 years in the REVEAL registry study [7].

Previously, serum creatinine has 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 may be influenced by other biological factors. Moreover, few studies have investigated the impact of renal function on outcome in IPAH patients and those studies [33, 34] included heterogeneous populations, with pulmonary hypertension of mixed etiologies. In the present work, ischemic heart disease and kidney dysfunction (estimated GFR< 60 ml/min x1.73m^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 incident IPAH patients from 2008 and forward, thus giving an insight into an etiologically homogenous group at a time with

modern treatment strategies. All PAH-centers in Sweden participate in SPAHR allowing for a national coverage of 89% (2015). Registry data reflect patients seen in the clinical practice and offer a real-life perspective as compared to data collected in randomized clinical trials. Categorizing 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 typically associated with observational registry studies, such as selection bias, lack of standardization of registered variables and missing follow-up data. Another limitation is the relative small size of the study population; however, in the 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 PAH-targeted therapy at baseline and had a poorer outcome. Ischemic heart disease and kidney dysfunction independently predicted poor outcome. 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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Conflicts of interest

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advisory boards for Actelion Pharmaceuticals Sweden AB, Bayer Health Care, NordicInfu Care and Glaxo-SmithKline.

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Figure legends

Figure 1. Risk assessment presented by age. Panel A – baseline, Panel B – follow-up, and Panel C - change in risk group from baseline to follow-up

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

Figure 1

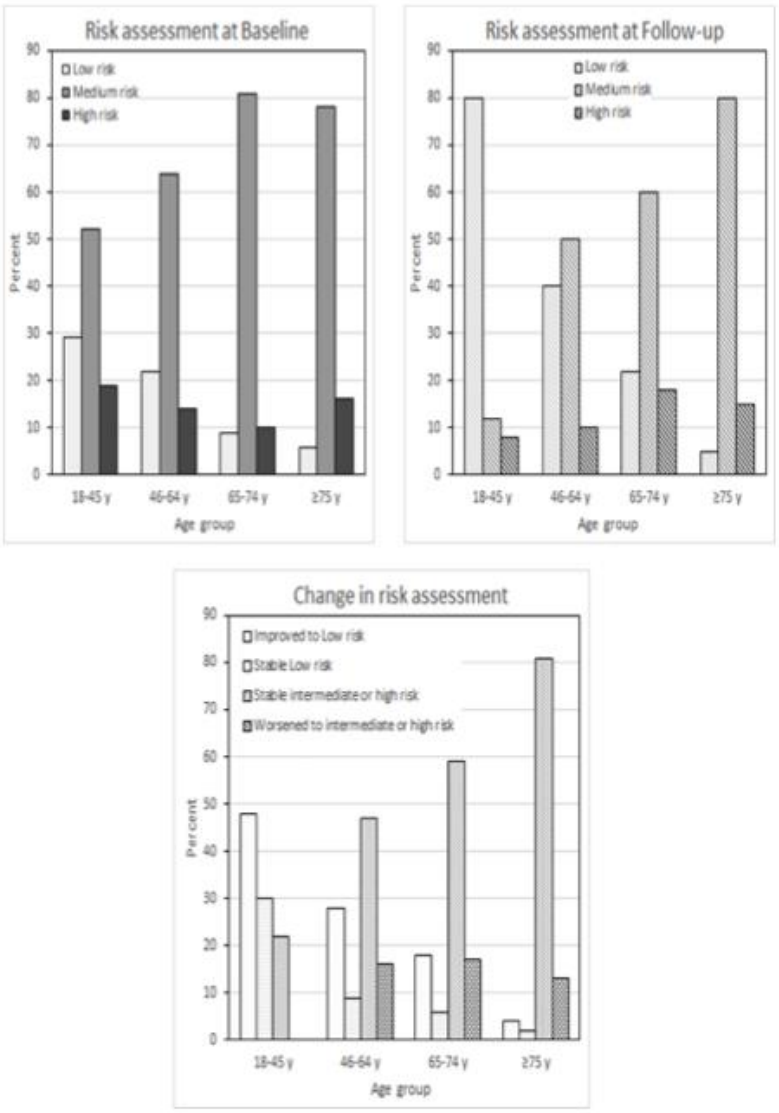
Risk assessment at Baseline
Low risk
Medium risk
High risk
Percent
0
10
20
30
40
50
60
70
80
90
18-45 y
46-64 y
65-74 y
≥75 y
Age group
Risk assessment at Follow-up
Low risk
Medium risk
High risk
Percent
Age group
Change in risk assessment
Improved to Low risk
Stable Low risk
Stable intermediate or high risk
Worsened to intermediate or high risk
Percent
Age group

Figure 2

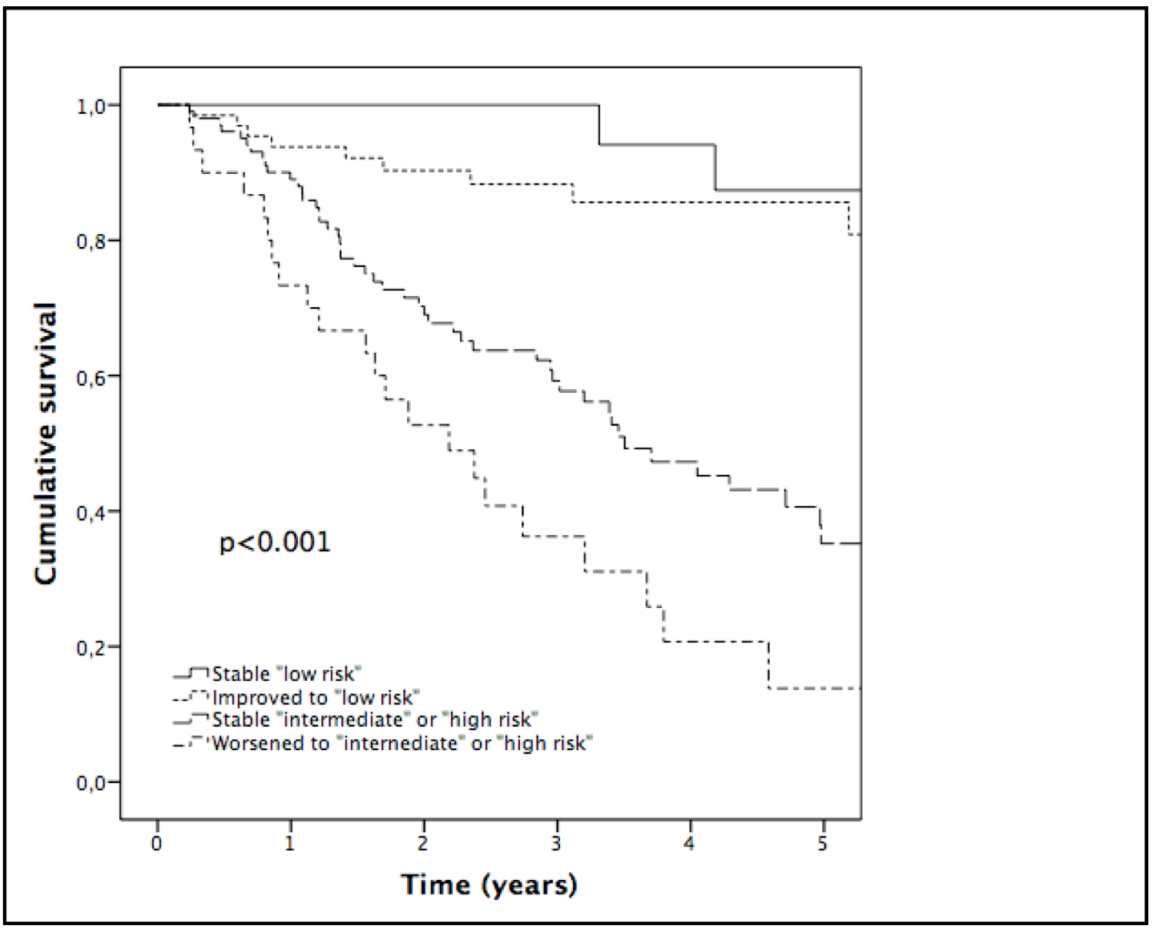
Cumulative survival
1,0
0,8
0,6
0,4
0,2
0,0
p<0.001
Stable "low risk"
Improved to "low risk"
Stable "intermediate" or "high risk"
Worsened to "internediate" or "high risk"
0
1
2
3
4
5
Time (years)

Table 1. Baseline characteristics of the study population by age.
Data are presented as mean (SD) or %, unless otherwise indicated.

Age group (years)	[18, 45) (n=48)	[45, 65) (n=59)	[65, 75) (n=90)	≥75 years (n=67)	Total (n=264)	*p-value*
Demography and clinical data						
Age in years, median (IQR)	36 (14)	59 (11)	70 (5)	78 (4)	68 (22)	***<0.001***
Female gender, %	65	70	52	43	56	***0.013***
Smoking active/previous, %	10/27	11/60	1/71	0/60	5/58	***<0.001***
BMI (kg/m^2)	25 (4.9)	29 (7.3)	28 (5.1)	26 (4.1)	27 (5.5)	***0.003***
WHO-FC (I/II/III/IV), %	0/30/48/22	0/24/66/10	0/9/85/6	0/10/82/8	0/17/73/10	***<0.001***
6MWD (m)	405 (145)	311 (148)	248 (109)	221 (115)	282 (140)	***<0.001***
DLCO, % 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/1.73 m^2)	97 (38)	75 (30)	55 (18)	43 (16)	64 (32)	***<0.001***
Hb (g/L)	150 (17)	146 (18)	147 (19)	144 (19)	146 (18)	0.520
NTproBNP in ng/L, median (IQR)	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***
Ischemic stroke	0	4	9	13	7	0.063
Ischemic 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, %						
no comorbidities	65	21	4	0	19	***<0.001***
1-3 comorbidities	35	72	76	76	67	***0.006***
4-7 comorbidities	0	7	20	24	14	***0.003***
Hemodynamics						
MRAP, mm Hg	8 (6)	8 (6)	8 (5)	8 (4)	8 (5)	0.735
MPAP, mm Hg	56 (11)	48 (10)	47 (9)	46 (9)	49 (10)	***<0.001***
PAWP, mm Hg	8 (3)	9 (6)	9 (4)	9 (3)	9 (4)	0.337
CI (L/min/m2)	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***
SaO2, %	94 (3)	92 (6)	88 (7)	87 (8)	90 (7)	***<0.001***
SvO2, %	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						
Low/medium/high, %	29/52/19	22/64/14	9/81/10	6/78/16	15/71/14	***0.002***

BMI indicates body mass index; WFO-FC, functional class; 6MWD, 6-minute walking distance; DLCO, lung diffusing capacity for CO; SBP, systolic blood pressure; DBP, diastolic blood pressure; MRAP, mean right atrial pressure; MPAP, mean pulmonary artery wedge pressure; CI, cardiac index; PVR, pulmonary vascular resistance; SaO2 systemic arterial oxygen saturation; SvO2, mixed venous oxygen saturation.

* PAH-targeted therapy started within 3 months from diagnosis

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

Explanatory variable	HR	95% CI	P-value
Gender	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***