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ORIGINAL RESEARCH ARTICLE

Longitudinal changes in risk status in pulmonary arterial hypertension

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Abstract

Aims Low-risk status in pulmonary arterial hypertension (PAH) predicts better survival. The present study aimed to describe changes in risk status and treatment approaches over multiple clinical assessments in PAH, taking age and comorbidity burden into consideration.

Methods and results The study included incident patients from the Swedish PAH registry, diagnosed with PAH in 2008–2019. Group A (n = 340) were ≤75 years old with <3 comorbidities. Group B (n = 163) were >75 years old with ≥3 comorbidities. Assessments occurred at baseline, first-year (Y1) and third-year (Y3) follow-ups. The study used an explorative and descriptive approach. Group A: median age was 65 years, 70% were female, and 46% had no comorbidities at baseline. Baseline risk assessment yielded low (23%), intermediate (66%), and high risk (11%). Among patients at low, intermediate, or high risk at baseline, 51%, 18%, and 13%, respectively, were at low risk at Y3. At baseline, monotherapy was the most common therapy among low (68%) and intermediate groups (60%), while dual therapy was the most common among high risk (69%). In patients assessed as low, intermediate, or high risk at Y1, 66%, 12%, and 0% were at low risk at Y3, respectively. Of patients at intermediate or high risk at Y1, 35% received monotherapy and 13% received triple therapy. In low-risk patients at Y1, monotherapy (40%) and dual therapy (43%) were evenly distributed. Group B: median age was 77 years, 50% were female, and 44% had ≥3 comorbidities at baseline. At baseline, 8% were at low, 80% at intermediate, and 12% at high risk. Monotherapy was the most common therapy (62%) in Group B at baseline. Few patients maintained or reached low risk at follow-ups.

Conclusions Most patients with PAH did not meet low-risk criteria during the 3 year follow-up. The first year from diagnosis seems important in defining the longitudinal risk status.

Keywords Pulmonary arterial hypertension; Risk Assessment; Treatment; Longitudinal analysis

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Introduction

In pulmonary arterial hypertension (PAH), the small pulmonary arteries are subjected to vasoconstriction and remodelling, impacting right ventricular function.[1] These pathological changes yield an array of unspecific symptoms, including dyspnoea and fatigue.[1] Effective medical treatment strategies have led to improved symptom control and survival.[2] Targeted therapies in PAH include endothelin receptor antagonists, phosphodiesterase 5 inhibitors, a soluble guanylate cyclase stimulator (s-GCs), as well as prostacyclin analogues and a prostacyclin receptor agonist.[1] These drugs address the overexpressed endothelin, as well as the under-expressed nitric oxide and prostacyclin vaso-regulatory pathways.

Based on the patient's risk class, which predicts the risk for early mortality, current European Society of Cardiology (ESC) and European Respiratory Society (ERS) pulmonary hypertension (PH) guidelines recommend an upfront treatment strategy with monotherapy or combination therapy.[1] In the latter, two or more drug groups are combined to target multiple vaso-regulatory pathways, aiming for a more effective treatment response. The risk stratification strategy uses a multi-parametric approach to stratify patients into low-risk, intermediate-risk, or high-risk groups[1] and has been validated at baseline and early follow-up for predicting 1 year mortality.[3–5]

The ESC/ERS PH guidelines recommend treatment escalation when clinical response is inadequate at follow-up.[1] This is further emphasized in recent reports from the 2018 World Symposium on Pulmonary Hypertension, where there is an urge for a treat-according-to-risk approach, and patients not reaching low-risk status at follow-up are recommended escalation to combination therapy.[6] Previous reports suggest that most patients do not reach a low-risk profile at their first follow-up assessment after PAH diagnosis.[3–5]

The proportion of patients achieving or remaining in low-risk status over longer periods of time remains unclear. Moreover, there is a lack of knowledge on risk assessment in relation to elderly and/or patients with a high comorbidity burden, a group that has been excluded from major randomized controlled clinical PAH trials.[7] The present study aims to describe changes in risk status and treatment approaches in patients with PAH over multiple clinical assessments, taking age and comorbidity burden into consideration.

Method

The Swedish pulmonary arterial hypertension registry

The Swedish pulmonary arterial hypertension registry (SPAHR) is a national quality registry that was initiated in 2008 and includes more than 90% of all incident Swedish patients diagnosed with PAH.[8] The aim of SPAHR is to ensure that all patients with PAH receive a common standard of care in Sweden as well as provide a database for population-based research in this area. All PAH centres in Sweden participate in SPAHR, allowing for the high national coverage.

For each patient, clinical, haemodynamic, and laboratory data were recorded in SPAHR after the diagnosis of PAH was confirmed by right heart catheterization, according to the ESC/ERS guidelines available at the time of diagnosis.[9,10] All patients were informed locally about their participation in SPAHR and had the right to decline. The present study complies with the Declaration of Helsinki and is approved by the local ethics committee in Lund (Dnr-2010/114, Dnr-2010/248, Dnr-2019-01033).

Inclusion and exclusion criteria

In the present study, all incident adult patients registered in SPAHR and diagnosed with idiopathic PAH (IPAH), familial PAH (FPAH), or PAH associated with connective tissue disease (CTD-PAH) between January 2008 and June 2019 were considered for inclusion (n = 582). Patients treated with study drugs at any point during the duration of the study (n = 39) or with an incalculable SPAHR risk score at baseline (n = 1) were excluded. Patients without clinical follow-ups and who had not died within the first year after baseline were considered as lost to follow-up and were excluded (n = 39).

Main and secondary cohorts

Included patients (n = 503) were dichotomized based on age and comorbidities. Patients aged $\leq$75 years with $<$3 comorbidities at baseline (n = 340) constituted the focus for the primary analysis and will be referred to as the 'main cohort'. Remaining patients (n = 163), being $>$75 years old and/or exhibiting $\geq$3 comorbidities at baseline, constituted an additional cohort that will be referred to as the 'secondary cohort'. The following comorbidities were available for analysis: hypertension, ischemic heart disease, stroke, diabetes mellitus, atrial fibrillation, obesity, and renal dysfunction.

Definitions and parameters

Baseline was defined as the day of diagnosis, confirmed by right heart catheterization. One-year follow-up was defined as the visit registered closest to 12 months in a window of 6–18 months after baseline. The 2 year follow-up was the visit closest to 24 months in a window of 18–30 months after baseline. The 3 year follow-up was the visit closest to 36 months in a window of 30–42 months after baseline.

Among patients with missing first-year follow-ups (n = 62), five had not reached 6 months since diagnosis. Among the 97 patients with missing second-year follow-ups, 38 had not reached 18 months since diagnosis. Similarly, among patients with missing third-year follow-up (n = 132), more than half (n = 68) had not reached 30 months since diagnosis.

The SPAHR includes information relevant for PH management including demographics, comorbidities, World Health Organization functional class, right heart catheterization and echocardiography data, pulmonary function tests, 6 min walk distance, blood biochemistry, PAH treatment, and other relevant medications. PAH treatment initiated within 3 months from diagnosis was considered baseline treatment. Treatment with calcium channel blockers (CCB) was only regarded

as a PAH-targeted therapy in patients with IPAH/FPAH that had a positive vasoreactive test at baseline and who did not receive any other PAH-targeted treatment at the observational point in question. In the present study, CCB treatment was not included in the monotherapy group.

Creatinine levels were used to estimate glomerular filtration rate (GFR) according to the revised Lund-Malmö GFR estimating equation.[11] Renal dysfunction was defined as an estimated GFR <30 mL × min^{-1} × 1.73 m^{-2}. Obesity was defined as a body mass index ≥ 30 kg × m^{-2}.

Study design and risk assessment

Patients were stratified by baseline or first-year follow-up using the SPAHR risk assessment method.[4,9] The risk groups were followed over time, in relation to changes in risk and PAH treatment.

Risk assessment was based on specific variables, according to the risk assessment instrument from the ESC/ERS guidelines[9,10]: World Health Organization functional class, 6 min walk distance, N-terminal prohormone of brain natriuretic peptide, right atrial area, mean right atrial pressure, pericardial effusion, cardiac index, 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 the SPAHR risk assessment method have previously been published.[4] Incalculable risk at follow-ups was regarded as a missing risk score value.

Statistics

R 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical and graphical computing. The R package alluvial was used. In the present study, a descriptive analysis approach was pursued; thus, no formal hypothesis nor statistical testing was performed. Continuous values are presented as median (lower–upper quartile), unless otherwise stated.

Results

Main cohort (age ≤75 years with <3 comorbidities)

The main cohort included 340 patients with PAH (IPAH/FPAH = 56% and APAH-CTD = 44%). The median (lower–upper quartile) time from baseline for the main cohort, was 11 (9–13) months to the first-year follow-up, 24 (22–25) months to the second year, and 36 (33–37) months to the third year.

Baseline characteristics, risk assessment, and treatment

Median age was 65 (49–70) years and 70% were female (*Table 1*). Patients with no comorbidities constituted 46%, while 30% had one and 24% had two comorbidities. The most prevalent comorbidities were systemic hypertension (34%) and obesity (14%) (*Table 1*). Additional demographic and clinical characteristics collected at time of diagnosis are described in *Table 1*. Baseline risk assessment yielded 23% assessed as low, 66% as intermediate, and 11% as high risk.

Baseline treatment was distributed as 58% on monotherapy, 28% on dual, and 3% on triple PAH therapy, while those treated with standalone CCB or no PAH-targeted therapy constituted 6% each. When observing each risk group separately, monotherapy, dual, or triple PAH therapy was distributed as 68%, 15%, and 0% for low-risk; 60%, 26%, and 4% for intermediate-risk; and 23%, 69%, and 3% for high-risk populations, respectively.

Longitudinal changes in risk and treatment

In the results from the longitudinal changes only patients with available risk score, lung transplantation, and mortality data at the analysed follow-ups were included.

The proportion at low, intermediate, and high risk were 30%, 44%, and 10% at first year; 29%, 33%, and 5% at second year; and 24%, 24%, and 4% at third year, respectively (*Figure 1*). Lung transplanted and deceased cumulatively constituted 1% and 15% at first year, 2% and 30% at second year, and 4% and 44% at third year, respectively. Among those assessed as low, intermediate, or high risk at baseline, the proportion of patients at low risk at third-year follow-up was 51%, 18%, and 13%, respectively (*Figure 1*).

Figures 2–4 show patients grouped based on first-year risk status and depict changes in risk at second-year and third-year follow-ups. Among the patients with a low risk at the first year (*Figure 2*), 66% remained at low risk, 27% deteriorated to intermediate or high risk, and 7% were lung transplant or deceased at third-year follow-up. The distribution of PAH therapy was evenly divided between monotherapy (40%) and dual therapy (43%) in patients at low risk at first year, whereas 3% were on triple therapy and 8% on standalone CCB (*Figure 2*).

In those assessed as intermediate risk at first year (*Figure 3*), 38% remained at intermediate risk, 12% had improved to low risk, and 7% deteriorated to high risk at third year. At first-year mono and dual PAH therapies were administered to 35% and 48%, respectively, while 12% were on triple therapy and 1% on standalone CCB (*Figure 3*). Patients that had undergone lung transplant or were deceased at the third year constituted 43%.

For patients at high risk at first year (*Figure 4*), the proportions at intermediate or high risk at third-year were 11%,

Table 1 Baseline characteristics shown by baseline risk group and for all. Patients ≤75 years with <3 comorbidities (n = 340)

	Low risk (n = 78)	Intermediate risk (n = 223)	High risk (n = 39)	All (n = 340)
Age (years)	63 (42–68)	66 (54–70)	63 (46–70)	65 (49–70)
Gender, female	79	65	79	70
BMI (kg m^{-2})	24 (21–27)	25 (23–28)	27 (25–30)	25 (23–28)
6MWD (m)	456 (375–500)	270 (189–368)	180 (133–258)	308 (200–416)
MAP (mmHg)	97 (86–104)	91 (81–104)	90 (84–100)	93 (83–103)
eGFR (mL min^{-1} 1.73 m^{-2})	73 (65–89)	65 (54–82)	61 (50–72)	67 (56–82)
DLCO (% pred.)	46 (38–65)	39 (30–53)	38 (29–60)	42 (31–58)
Hb (g L^{-1})	137 (128–151)	142 (126–156)	134 (124–146)	139 (126–153)
NT-proBNP (ng L^{-1})	232 (156–390)	1,555 (848–3,206)	3,620 (2,474–4,988)	1,370 (426–3,126)
Haemodynamics				
mPAP (mmHg)	36 (29–49)	44 (37–52)	54 (50–59)	44 (36–53)
mRAP (mmHg)	4 (3–5)	7 (3–10)	15 (10–18)	6 (4–10)
PAWP (mmHg)	7 (6–9)	8 (5–11)	10 (8–13)	8 (6–11)
CI (L min^{-1} m^{-2})	2.8 (2.5–3.2)	2.3 (2.0–2.7)	1.6 (1.4–1.8)	2.4 (1.9–2.8)
PVR (Wood units)	5.3 (4.2–8.5)	8.7 (6.3–11.6)	14.1 (11.5–17.0)	8.4 (5.7–11.6)
SvO_2 (%)	71 (66–74)	61 (56–66)	50 (43–53)	62 (55–68)
SaO_2 (%)	95 (91–97)	92 (88–95)	91 (84–94)	92 (89–96)
Echocardiography				
RA area (cm^2)	16 (14–19)	23 (21–27)	30 (24–32)	22 (19–26)
Pericardial fluid % present	1	10	71	15
WHO-FC (%)				
I	6	0	0	2
II	56	11	0	20
III	36	81	49	67
IV	1	7	51	11
Comorbidities (%)				
Systemic hypertension	32	36	24	34
Diabetes mellitus	5	13	21	12
Atrial fibrillation	4	10	12	9
Ischemic stroke	1	2	6	3
Ischemic heart disease	7	11	9	10
Obesity	12	13	25	14
Renal dysfunction	1	4	8	4
Supplemental treatment (%)				
Anticoagulants	27	51	54	46
Supplemental oxygen	8	23	45	22
Diuretics	24	60	85	55

Continuous values are presented in median (lower–upper quartile), and categorical values in per cent, unless otherwise stated.
6MWD, 6 min walk distance; BMI, body mass index; CI, cardiac index; DLCO, diffusing capacity for carbon monoxide; eGFR, estimated glomerular filtration rate; Hb, Haemoglobin; MAP, mean arterial pressure; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RA, right atrial; SaO_2, arterial oxygen saturation; SvO_2, mixed venous oxygen saturation; WHO-FC, World Health Organization functional class.

whereas none reached low risk at third year. At first year, 34% were on monotherapy, 48% on dual, and 14% on triple PAH therapy. Eighty-nine per cent had undergone lung transplantation or were deceased at third year.

Secondary cohort (>75 years and/or ≥3 comorbidities)

The secondary cohort included 163 patients with PAH (IPAH/FPAH = 71% and APAH-CTD = 29%). The median (lower–upper quartile) time from baseline for the secondary cohort, was 11 (9–13) months to the first-year follow-up, 24 (22–26) months to the second year, and 36 (35–38) months to the third year.

Baseline characteristics, risk and treatment

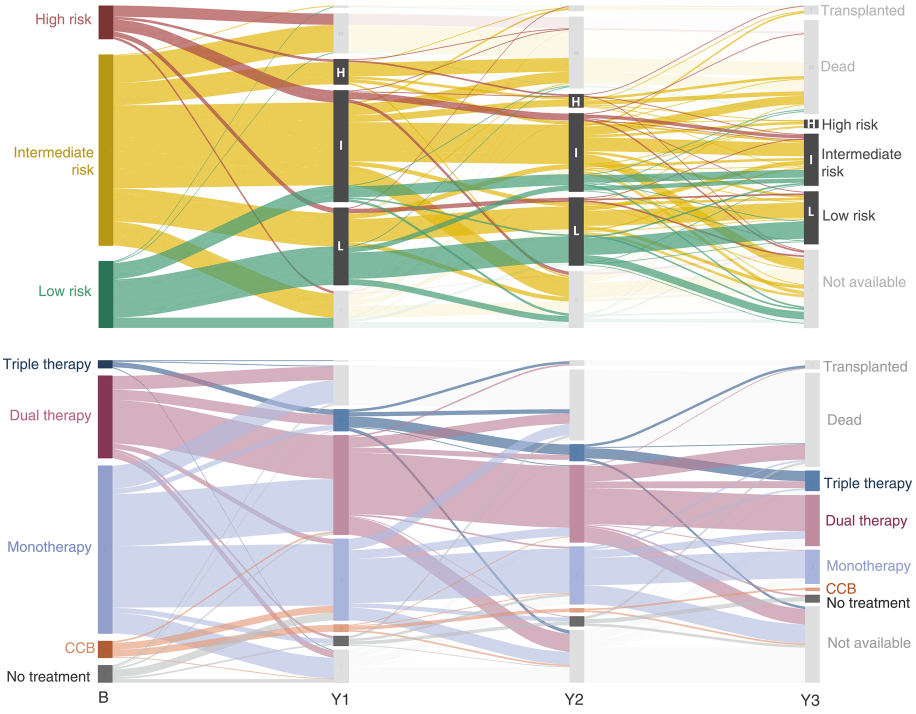
Median age was 77 (73–80) years and 50% were female (*Table 2*). Patients with no comorbidities constituted 21%, while those having one or two comorbidities were 36%, and those with three or more comorbidities were 44%. The most prevalent comorbidities were systemic hypertension (70%) and diabetes mellitus (37%) (*Table 2*). More pertinent characteristics collected at time of diagnosis can be found in *Table 2*.

Baseline risk assessment yielded 8% in low, 80% in intermediate, and 12% at high risk (*Figure 5*). Upfront PAH treatment with monotherapy was most common (62%) while 28% received dual therapy, 2% triple therapy, 3% standalone CCB treatment, and 6% no treatment (*Figure 5*). When observing each baseline risk group separately, 69% of patients at low risk received monotherapy, 8% standalone CCB, and 23% no treatment. The distribution of monotherapy, dual, or triple PAH therapy was 62%, 28%, and 2% in the intermediate-risk and 55%, 45%, and 0% in the high-risk patients, respectively.

Longitudinal changes in risk

In the secondary cohort, the proportion of patients at low, intermediate, and high risk were 9%, 54%, and 11% at first

Figure 1 Longitudinal trends for the main cohort (patients aged ≤75 years with <3 comorbidities, *n* = 340) shown at baseline (B) and at 1 (Y1), 2 (Y2), and 3 (Y3) years follow-up. In the upper panel, individual patients are shown by baseline risk status and followed throughout follow-ups. In contrast, the lower panel shows changes in treatment at each follow-up and does *not* follow individual patients. Data for transplanted or dead patients, as well as not available values, are shown in pale colours. Details of treatment and patients lost to follow-up are shown in Table S1. B, baseline; CCB, calcium channel blocker; H, high risk; I, intermediate risk; L, low risk; Y1, first-year follow-up; Y2, second-year follow-up; Y3, third-year follow-up.



year; 10%, 31%, and 5% at second year; and 6%, 24%, and 5% at third year, respectively (*Figure 5*). The cumulative shares of deceased patients were 25% at first-year, 54% at second-year, and 65% third-year follow-up. Detailed analyses regarding longitudinal risk were not performed in the secondary cohort due to small numbers of patients in each risk group at and after the first-year follow-up. No patients were lung transplanted during the 3 year follow-up.

Discussion

In the present study, longitudinal risk assessment according to the ESC/ERS 2015 guidelines using the SPAHR model,[4] revealed that most patients with PAH did not meet the low-risk criteria across the 3 year follow-up. In addition, whereas patients at low risk at the first-year follow-up tended to continue at low-risk long term, those who maintained or deteriorated into intermediate or high risk at first-year follow-up tended to remain at those risk classes long term. The study also indicated that there was room for treatment escalation in patients that had not reached a low-risk status at the first-year follow-up, which may partly be related to that many patients were treated before implementation of the 2015 ESC/ERS PH guidelines.[9]

Maintaining or achieving a low-risk status has been linked to improved survival in PAH.[3–5] Prior studies have, however, shown that most PAH patients do not reach low-risk status at an early follow-up within 3 months to 2 years after diagnosis.[3–5] While the present study supports these prior results, it also adds a long-term dimension where the first year from diagnosis seems to be important for defining the longitudinal risk in patients with PAH. This part of the analyses, based on the risk assessment at the first-year follow-up, might provide an understanding on risk status after PAH treatment initiation. If patients were at low risk at first-year follow-up, they largely remained on low risk for the remainder of the study. On the other hand, if not at low risk at the first-year follow-up, patients tended to remain in intermediate or high risk, if they had not received a lung transplant or were deceased during the follow-up time. One might speculate that more effective treatment strategies might have yielded an increased proportion of patients reaching low-risk long term.

Most patients in the present cohorts received monotherapy at baseline and a large proportion continued on monotherapy at first-year follow-up. Among the two third of patients who were at intermediate or high risk at first year,

Figure 2 In the upper graph, patients at low risk at first-year follow-up (Y1) constitute an entity that is followed throughout second- (Y2) and third-year (Y3) follow-ups. The lower graph depicts the pulmonary arterial hypertension-targeted treatment for the patients in the upper graph. B, baseline; CCB, calcium channel blocker; H, high risk; I, intermediate risk; L, low risk; Y1, first-year follow-up; Y2, second-year follow-up; Y3, third-year follow-up.

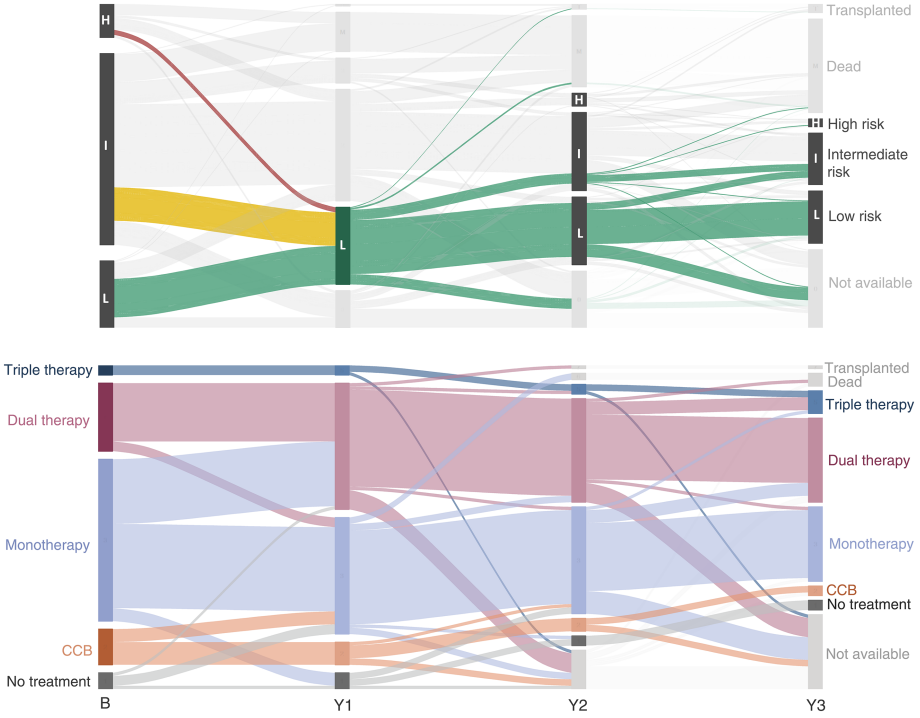


Figure 3 In the upper graph, patients at intermediate risk at first-year follow-up (Y1) constitute an entity that is followed throughout second-year (Y2) and third-year (Y3) follow-up. The lower graph depicts the pulmonary arterial hypertension-targeted treatment for the patients in the upper graph. B, baseline; H, high risk; I, intermediate risk; L, low risk; Y1, first-year follow-up; Y2, second-year follow-up; Y3, third-year follow-up.

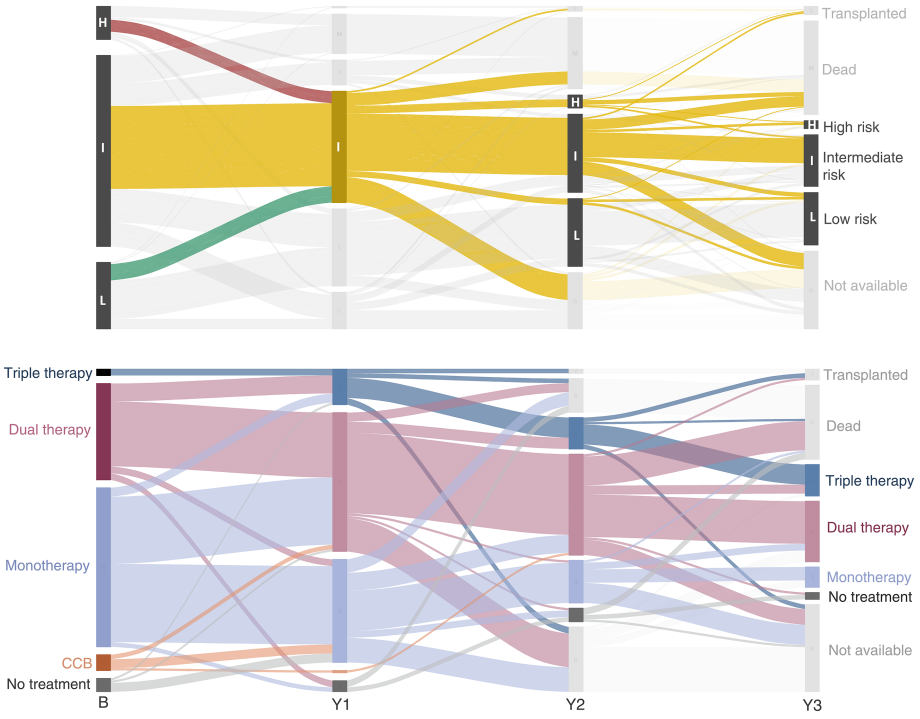


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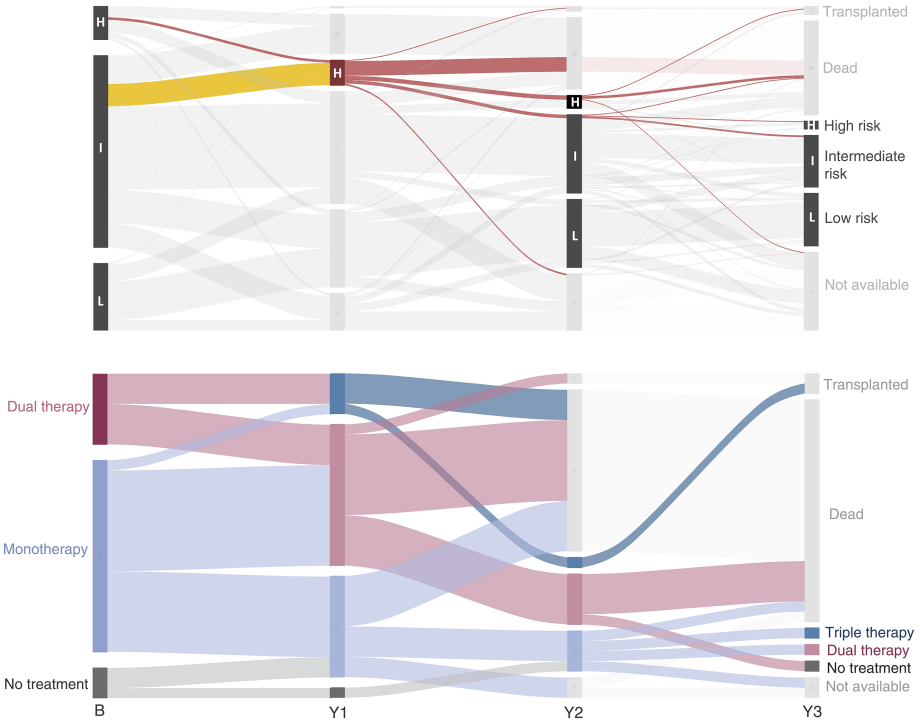
Figure 4 In the upper graph, patients at high risk at first-year follow-up (Y1) constitute an entity that is followed throughout second- (Y2) and third-year (Y3) follow-up. The lower graph depicts the pulmonary arterial hypertension-targeted treatment for the patients in the upper graph. B, baseline; H, high risk; I, intermediate risk; L, low risk; Y1, first-year follow-up; Y2, second-year follow-up; Y3, third-year follow-up.



more than a third received monotherapy, and only a tenth received triple combination therapy. Taken together, this indicates that there might have been room for a more aggressive therapy approach in the present study population.[7,12,13] Most patients in the present cohort received a sequential treatment approach in accordance to the 2009 ESC/ERS PAH guidelines[10] and might therefore seem to be undertreated according to the 2015 guidelines.[9] More upfront combination therapy and treatment escalation at first follow-up might have resulted in a more beneficial outcome. From 2015 and in concordance with results from clinical trials, the proportion of patients receiving combination therapy has been growing.[14,15] For example, in Sweden, the proportion receiving upfront dual treatment has increased from 10% in 2010 to 50% in 2018.[8]

One might also speculate that more frequent assessment of patients during the first year might have resulted in additional treatment escalations and better outcome. Decreasing the pulmonary artery pressure and resistance early in disease progress seems to be instrumental for survival.[16] Although some patients are stable over time, changes in functional class and risk profile are frequent and likely detrimental for the patient in the long term.[17] Other aspects that need to be taken into account are that some patients might be more or less responsive to treatment and the possible effect of treatment non-adherence.[18] To identify these patients, frequent and regular visits or other contacts with the patients are instrumental.[17–19]

Patients older than 75 years, which inherently can carry a high comorbidity burden, embodied a third of the study population, a representative proportion of the Swedish PAH population of today.[8] In a previous study based on SPAHR data, age and specific comorbidities were shown to be important prognostic markers of outcome in addition to established risk assessment algorithms.[20] In the present study, patients older than 75 years and/or those with a high comorbidity burden were analysed separately, to reflect the populations often excluded from major clinical trials.[7] This approach may also provide a better understanding of risk status patterns and treatment strategies in the younger patients with few comorbidities.

In the group of patients who were older and/or exhibited a greater comorbidity burden, about eight out of 10 were at intermediate risk at baseline, and the majority was on monotherapy. Patients assessed as low risk were few across the three yearly follow-ups. These findings might merely mirror that advanced age and multiple comorbidities are related to worse outcome, which is also underlined in the present study. It can also reflect that current measures used for risk assessment might not be applicable to the patient's clinical status and prognosis, as inherent limitations may prevent them from reaching low risk status. Finally, PAH-targeted

Table 2 Baseline characteristics shown by baseline risk group and for all. Patients >75 years and/or with ≥3 comorbidities (n = 163)

	Low risk (n = 13)	Intermediate risk (n = 130)	High risk (n = 20)	All (n = 163)
Age (years)	76 (69–78)	78 (73–80)	77 (76–79)	77 (73–80)
Gender, female	54	49	50	50
BMI (kg m^{-2})	31 (27–32)	26 (24–30)	25 (23–28)	27 (24–30)
6MWD (m)	320 (278–452)	211 (164–300)	90 (56–116)	210 (143–300)
MAP (mmHg)	106 (96–119)	94 (85–104)	73 (68–90)	94 (82–105)
eGFR (mL min^{-1} 1.73 m^{-2})	65 (57–73)	50 (40–60)	44 (32–54)	50 (39–61)
DLCO (% pred.)	40 (33–56)	40 (31–51)	39 (26–52)	40 (30–53)
Hb (g L^{-1})	143 (129–149)	143 (128–157)	134 (116–144)	142 (127–155)
NT-proBNP (ng L^{-1})	234 (102–412)	2,317 (1,030–5,020)	6,069 (4,078–10,472)	2,346 (915–5,389)
Haemodynamics				
mPAP (mmHg)	34 (29–39)	44 (37–51)	47 (45–50)	45 (37–50)
mRAP (mmHg)	3 (2–5)	7 (5–10)	12 (9–16)	7 (5–11)
PAWP (mmHg)	9 (5–12)	9 (6–12)	9 (7–12)	9 (6–12)
CI (L min^{-1} m^{-2})	2.8 (2.6–3.1)	2.2 (1.8–2.6)	1.6 (1.5–1.8)	2.2 (1.8–2.6)
PVR (Wood units)	4.2 (3.0–5.8)	8.4 (6.5–11.5)	13.9 (11.5–17.4)	8.6 (6.3–11.8)
SvO_2 (%)	69 (67–70)	58 (54–65)	52 (50–54)	58 (53–66)
SaO_2 (%)	94 (92–96)	90 (86–93)	89 (81–91)	91 (86–94)
Echocardiography				
RA area (cm^2)	12 (11–15)	24 (21–27)	34 (25–41)	24 (20–28)
Pericardial fluid % present	0	8	53	12
WHO-FC (%)				
I	0	0	0	0
II	31	8	0	9
III	69	87	53	81
IV	0	5	47	10
Comorbidities (%)				
Systemic hypertension	77	70	63	70
Diabetes mellitus	38	38	32	37
Atrial fibrillation	15	31	37	30
Ischemic stroke	8	12	17	12
Ischemic heart disease	15	31	28	29
Obesity	62	28	10	29
Renal dysfunction	0	10	20	11
Supplemental treatment (%)				
Anticoagulants	46	55	70	56
Supplemental oxygen	23	35	70	38
Diuretics	54	78	95	78

Continuous values are presented in median (lower–upper quartile), and categorical values in per cent, unless otherwise stated.
6MWD, 6 min walk distance; BMI, body mass index; CI, cardiac index; DLCO, diffusing capacity for carbon monoxide; eGFR, estimated glomerular filtration rate; Hb, Haemoglobin; MAP, mean arterial pressure; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RA, right atrial; SaO_2, arterial oxygen saturation; SvO_2, mixed venous oxygen saturation; WHO-FC, World Health Organization functional class.

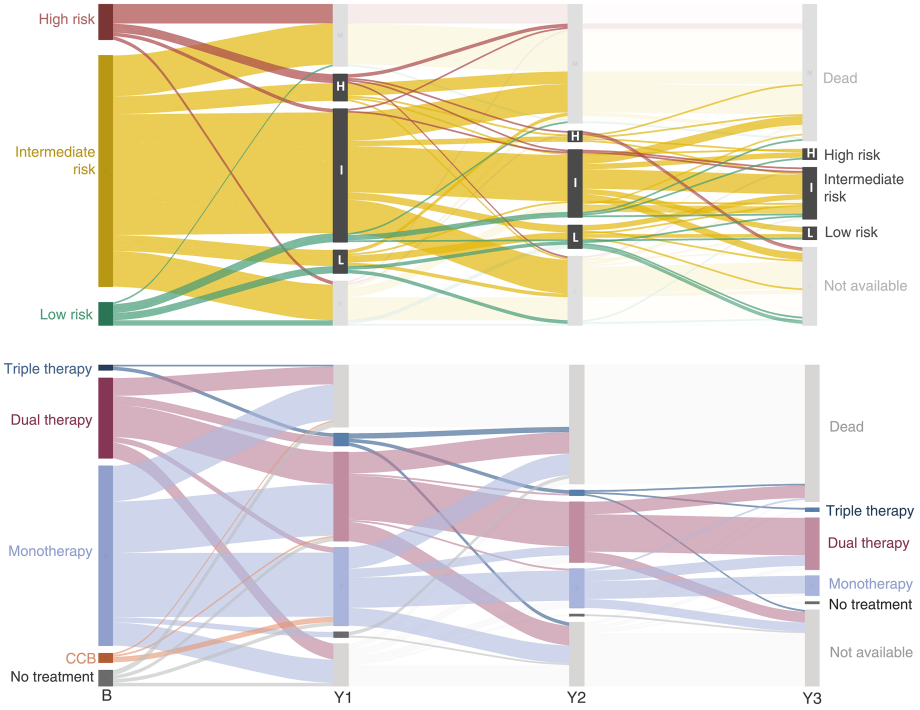
treatments have not been investigated in these patients in clinical trials. Elderly patients indeed show diminished response to PAH treatment,[21] and thus, clinicians may want to select a more cautionary approach. Hence, it is important that future studies address characteristics and clinical measures as well as treatment goals and response in these patients.

Strengths and limitations

A strength of the present study is that the analyses include only incident patients diagnosed with IPAH/FPAH or CTD-PAH after 2008, providing a homogenous study group. All PAH centres in Sweden participate in SPAHR, and more than 90% of all patients diagnosed with PAH in Sweden since 2008 are included. Thus, data from this national register reflect a real-life patient population, as seen in clinical practice, compared with data collected in clinical trials. This is particularly reflected in the secondary cohort of elderly patients with a high comorbidity burden.

When interpreting results and trends in the present study, some limitations should be taken into account. First, this is a retrospective registry study with an exploratory design. Limitations typically associated with observational registry studies, such as lack of standardization of registered variables and missing data exist in the presented study. Patients in SPAHR are somewhat older than what is regarded to be the typical age for PAH.[22] Nonetheless, the main cohort was selected to be younger and with fewer comorbidities. In some subgroups, the sample size was too small to draw firm conclusions. Across follow-ups, some patients had incomplete or missing data, partly due to diagnosis being too close to follow-up. For instance, nearly half of those with no available

Figure 5 Longitudinal trends for the secondary cohort (patients aged >75 years and/or with ≥3 comorbidities, *n* = 163), shown at baseline (B) and at 1 (Y1), 2 (Y2), and 3 (Y3) years follow-up. In the upper panel, individual patients are shown by baseline risk status and followed throughout follow-ups. In contrast, the lower panel shows changes in treatment at each follow-up and does *not* follow individual patients. Data for transplanted or dead patients, as well as not available values, are shown in pale colours. Details of treatment and patients lost to follow-up are shown in Table S2. B, baseline; H, high risk; I, intermediate risk; L, low risk; Y1, first-year follow-up; Y2, second-year follow-up; Y3, third-year follow-up.



data at the third-year follow-up had not reached that time point yet. In addition, stable patients might be seen less often in clinic and thus fall outside one of the follow-up windows used in the present study design. Finally, the present study included patients diagnosed between 2008 and 2019, and during this time, changes to PAH treatment landscape, including availability of treatments and changes in guidelines, have occurred, which might have influenced the interpretation of the results.

Conclusions

The first year from diagnosis appears to be critical for the patient with PAH and defines the risk status the patient will reach long term. A majority of patients was treated according to the 2009 PH guidelines, and this less aggressive treatment approach appears to not have succeeded in moving a substantial portion of the patients to a low risk status. Future research should look at the impact of the newly introduced guidelines on treatment approach and outcomes.

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Conflict of interest

HB reports personal lecture fees from Actelion Pharmaceuticals Sweden AB and unrestricted research grants from the Swedish Society of Pulmonary Hypertension on behalf of GlaxoSmithKline. GR reports unrestricted research grants from Actelion Pharmaceuticals Sweden AB and GlaxoSmithKline and personal lecture fees from Actelion Pharmaceuticals Sweden AB, Bayer HealthCare, GlaxoSmithKline, NordicInfu Care, and Sandoz/Novartis. GR is, and has been, primary or co-investigator in clinical PAH trials for GlaxoSmithKline, Actelion Pharmaceuticals Sweden AB, Pfizer, Bayer HealthCare, and United Therapeutics and has

been involved in research advisory boards for Actelion Pharmaceuticals Sweden AB, Bayer HealthCare, Eli Lilly, and Sanofi-Aventis. OB is an employee of Bayer AG (Berlin, Germany). RH reports personal lecture fees from Actelion Pharmaceuticals Sweden AB, Janssen-Cilag AB, AnaMar, Boehringer-Ingelheim, Celgene, Gesynta, Lilly, and Roche. CH reports personal lecture fees from Actelion, a Janssen Pharmaceutical Company of Johnson & Johnson, outside the submitted work. CH is, and has been, primary or co-investigator in clinical PAH trials for Actelion and United Therapeutics and has been involved in research advisory boards for Actelion, a Janssen Pharmaceutical Company of Johnson & Johnson. KH is an employee of Bayer AG (Berlin, Germany). KJ has been primary or co-investigator in clinical PAH trials for GlaxoSmithKline, Actelion Pharmaceuticals Sweden AB, Pfizer, and Bayer HealthCare. RK is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. SS reports unrestricted research grants from Actelion Pharmaceuticals Sweden AB and Pfizer, as well as personal lecture fees from Actelion and Bayer HealthCare. SS is, and has been, primary or co-investigator in clinical PAH trials for GlaxoSmithKline, Actelion Pharmaceuticals Sweden AB, Pfizer, and Bayer HealthCare and has been involved in research advisory boards for Actelion Pharmaceuticals Sweden AB, Bayer HealthCare, GlaxoSmithKline, and Eli Lilly. BK reports unrestricted research grants from Actelion Pharmaceuticals Sweden AB and is the receiver of the grant from MSD related to the study.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. PAH treatment in the main cohort shown by baseline risk group and for all

Table S2. PAH treatment in the secondary cohort shown by baseline risk group and for all.

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