Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension

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ABSTRACT Current European guidelines recommend periodic risk assessment for patients with pulmonary arterial hypertension (PAH). The aim of our study was to determine the association between the number of low-risk criteria achieved within 1 year of diagnosis and long-term prognosis.

Incident patients with idiopathic, heritable and drug-induced PAH between 2006 and 2016 were analysed. The number of low-risk criteria present at diagnosis and at first re-evaluation were assessed: World Health Organization (WHO)/New York Heart Association (NYHA) functional class I or II, 6-min walking distance (6MWD) >440 m, right atrial pressure <8 mmHg and cardiac index ⩾2.5 L·min^{-1}·m^{-2}.

1017 patients were included (mean age 57 years, 59% female, 75% idiopathic PAH). After a median follow-up of 34 months, 238 (23%) patients had died. Each of the four low-risk criteria independently predicted transplant-free survival at first re-evaluation. The number of low-risk criteria present at diagnosis ($p<0.001$) and at first re-evaluation ($p<0.001$) discriminated the risk of death or lung transplantation. In addition, in a subgroup of 603 patients with brain natriuretic peptide (BNP) or N-terminal pro-brain natriuretic peptide (NT-proBNP) measurements, the number of three noninvasive criteria (WHO/NYHA functional class, 6MWD and BNP/NT-proBNP) present at first re-evaluation discriminated prognostic groups ($p<0.001$).

A simplified risk assessment tool that quantifies the number of low-risk criteria present accurately predicted transplant-free survival in PAH.

Introduction

Pulmonary arterial hypertension (PAH) is an obliterative vasculopathy that results in high pulmonary arterial pressure and without treatment ultimately leads to right ventricular failure and death [1–3]. Over the past few decades, the development of effective medical therapies and the use of combination therapy have substantially improved the prognosis of patients with PAH [4–8]. The currently available therapies are effective in improving symptoms, functional capacity and haemodynamics; however, many patients have persistent symptoms or develop right heart failure despite treatment [9, 10].

Previous international guidelines have recommended the longitudinal periodic evaluation of PAH patients to assess disease severity and prognosis [11–14]. The recent 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines for the diagnosis and treatment of pulmonary hypertension recommend a risk assessment for patients using a multidimensional stratification according to clinical, echocardiographic, exercise and haemodynamic variables with known prognostic significance [2, 3]. Certain low-risk features are associated with better prognosis in PAH, such as a modified New York Heart Association (NYHA)/World Health Organization (WHO) functional class I or II, a 6-min walking distance (6MWD) >440 m, a right atrial pressure (RAP) <8 mmHg and cardiac index $\geqslant$2.5 $L \cdot min^{-1} \cdot m^{-2}$ [2, 3]. Additionally, brain natriuretic peptide (BNP) or N-terminal pro-brain natriuretic peptide (NT-proBNP) levels <50 $ng \cdot L^{-1}$ or <300 $ng \cdot L^{-1}$, respectively, are considered to be low-risk features. Patients with low-, intermediate- and high-risk features have an estimated 1-year risk of death of <5%, 5–10% and >10%, respectively [2, 3]. These risk stratification groups are meant to be applicable at the time of diagnosis and during follow-up for prognostication, and low-risk criteria can be used as treatment goals. However, the accuracy of this risk assessment during follow-up has not yet been fully established and cut-offs for many of the variables used in risk assessment are based on expert opinion, with low levels of evidence [2, 3]. Patients may have several low-risk criteria but other intermediate- or high-risk criteria, and it is not known how many low-risk criteria must be attained in order to identify a particular patient as truly low risk.

The objective of the current study was to apply the risk assessment criteria from the 2015 ESC/ERS guidelines to an incident cohort of patients with PAH from the French pulmonary hypertension registry. We aimed to determine survival according to the number of low-risk criteria at diagnosis and the number achieved during the first year of treatment. We hypothesised that survival would be better in patients achieving all low-risk criteria compared to those patients who achieved fewer criteria.

Methods

This was a retrospective study which complied with the Declaration of Helsinki. French law does not require ethics committee or institutional review board approval or informed consent for retrospective data collection; however, all data were anonymised and compiled according to the requirements of the Commission Nationale Informatique et Liberté, the organisation dedicated to privacy, information technology and civil rights in France. The committee approved the methods used to collect and analyse registry data on May 24, 2003 (approval number 842063).

Patient selection

We retrospectively reviewed all incident (*i.e.* newly diagnosed) patients aged $\geqslant$18 years with idiopathic, heritable or drug- and toxin-induced PAH who were enrolled in the French registry between January 1, 2006 and March 30, 2016. Inclusion required a baseline right heart catheterisation (RHC) confirming PAH, defined as a mean pulmonary arterial pressure $\geqslant$25 mmHg, pulmonary arterial wedge pressure $\leqslant$15 mmHg and pulmonary vascular resistance >3 Wood units [2, 3]. Patients were excluded if they lacked a calculable follow-up time or a complete re-evaluation with WHO/NYHA functional class assessment, a 6-min walk test and RHC within 1–12 months of diagnosis.

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Risk assessment

Risk assessment was performed according to the 2015 ESC/ERS pulmonary hypertension guidelines [2, 3]. We evaluated the presence of four low-risk criteria which were defined as 1) WHO/NYHA functional class I or II, 2) 6MWD >440 m, 3) RAP <8 mmHg and 4) cardiac index $\geqslant$2.5 L·min^{-1}·m^{-2} [2, 3]. Patients were classified according to the number of low-risk criteria present at baseline (*i.e.* at the time of PAH diagnosis) and at the time of re-evaluation. As exploratory analyses, we examined the additive value of the BNP <50 ng·L^{-1} or NT-proBNP <300 ng·L^{-1} low-risk criteria and the addition of the mixed venous oxygen saturation (S_{vO_2}) >65% low-risk criterion, in the subsets of patients for whom these data were available.

Statistical analysis

Data were collected from the web-based French Registry (PAH Tool; Inovultus, Santa Maria da Feira, Portugal) and were stored in a personal computer-based data spreadsheet. Analysis was performed using the StatEL statistical package in Microsoft Excel (Ad Science, Paris, France). Continuous variables were expressed as mean±SD and categorical variables as n (%). Changes between baseline and follow-up variables were assessed using the paired t-test and Chi-squared test where appropriate. Transplant-free survival time was calculated from the date of diagnostic RHC to the date of last follow-up, death or lung transplantation for the baseline and first re-evaluation survival analyses. Univariable and multivariable forward stepwise Cox proportional hazards regression models were performed to assess the risk of death or lung transplantation according to baseline and follow-up risk-criteria variables. A p-value threshold of <0.10 was used for entry into the multivariable model and p>0.05 was the threshold for variable removal. Survival according to the number of low-risk criteria was represented using the Kaplan–Meier method, truncated at 5 years, and compared using the log-rank test. All comparisons were two-sided and a p-value <0.05 considered statistically significant.

Results

Patients

Between January 1, 2006 and March 30, 2016, 1591 incident patients with idiopathic, heritable or drug-induced PAH were enrolled in the French registry. We identified 1017 patients who had both baseline and re-evaluation with documentation of WHO/NYHA functional class, 6MWD and a RHC within 1 year of diagnosis. Among this population, 603 patients had BNP or NT-proBNP measurements documented within 1 year of diagnosis (figure 1). Baseline characteristics are shown in table 1. The majority of patients had a diagnosis of idiopathic PAH (75%), with a mean age of 57 years and 598 (59%) were female. Most patients were in WHO/NYHA functional class III (61%) or IV (13%) at baseline, whereas 26% were in functional class I–II. Initial treatment consisted of monotherapy in approximately half of the patients and combination therapy for the other half (online supplementary table S1). Transplant-free survival in the overall population (n=1591) is shown in online supplementary figure S1. For the analysis cohort with a follow-up assessment (n=1017), over a median (interquartile range (IQR)) follow-up duration of 34 (16–56) months, 238 (23%) died and 31 (3%) underwent lung transplantation.

Risk assessment at the time of PAH diagnosis

At diagnosis, 25.5%, 36.5%, 21%, 11% and 6% of patients had no, one, two, three or four low-risk criteria, respectively (figure 2). In univariable Cox regression analysis, baseline WHO/NYHA functional class III–IV, 6MWD $\leqslant$440 m, RAP $\geqslant$8 mmHg and cardiac index <2.5 L·min^{-1}·m^{-2} were associated with a higher risk of death or transplantation (table 2). In multivariable analysis of baseline criteria, only a 6MWD $\leqslant$440 m independently predicted death or transplantation (p<0.001). Transplant-free survival according to the number of low-risk criteria present at baseline is shown in figure 3a, with significant differences between criteria groups (log-rank test, p<0.001).

Risk assessment at first follow-up

Median (IQR) interval between diagnosis and first re-evaluation was 4.4 (3.6–6.4) months. There were significant improvements in WHO/NYHA functional class, 6MWD and haemodynamic parameters (table 3). Similarly, there were greater proportions of patients attaining two, three or four low-risk criteria and a lesser proportion of patients with no or one low-risk criterion (p<0.001; figure 2). In univariable and multivariable Cox regression analysis of low-risk criteria at first re-evaluation, all were significantly and independently associated with death or transplantation (table 2). Figure 3b shows transplant-free survival according to the number of low-risk criteria achieved at first follow-up. There were significant differences in transplant-free survival between all criteria groups (log-rank test, p<0.001). Within the group achieving three low-risk criteria at first re-evaluation (n=247), there was no significant difference in survival according to which three of the four criteria were achieved.

Patients who had fewer than three low-risk criteria at baseline but improved to having three or four low-risk variables at the time of re-evaluation had similar outcomes to those who maintained three or four low-risk variables from diagnosis to first re-evaluation, whereas the group of patients who had fewer than three low-risk criteria at diagnosis and at follow-up had the worst outcomes (online supplementary figure S2). Of the 95 patients who had zero variables in the low-risk range at follow-up, patients who had one of these variables in the high-risk range (WHO/NYHA functional class IV, 6MWD <165 m, RAP >14 mmHg or cardiac index <2.0 $L \cdot min^{-1} \cdot m^{-2}$) had 1- and 2-year transplant-free survival rates of 87% and 67%, respectively, while those with more than one variable in the high-risk range had 1- and 2-year survival rates of 70% and 42%, respectively (online supplementary figure S3).

When we considered the subset of patients with BNP or NT-proBNP measurements available at follow-up (n=603), the low-risk BNP/NT-proBNP thresholds were predictive of transplantation-free survival in univariable and multivariable analyses (table 4). Haemodynamic variables were no longer significant in this multivariable model including BNP/NT-proBNP. Using three noninvasive low-risk criteria (WHO/NYHA functional class I–II, 6MWD >440 m, BNP <50 $ng \cdot L^{-1}$ or NT-proBNP <300 $ng \cdot L^{-1}$) assessed at follow-up (figure 4), there were significant differences in transplant-free survival according to the number of criteria achieved (log-rank test, p<0.001). In the univariable and multivariable analyses of 606 patients with a SvO_2 measurement available at first re-evaluation, the presence of SvO_2 >65% was an independent predictor of transplant-free survival (online supplementary table S2). The cardiac index ⩾2.5 $L \cdot min^{-1} \cdot m^{-2}$ criterion was no longer significant in this multivariable model, whereas WHO/NYHA functional class I–II, 6MWD >440 m and RAP <8 mmHg remained significant. Survival according to the number of low-risk criteria including SvO_2 >65% is shown in online supplementary figure S4.

Discussion

The main finding of this study was that the risk assessment criteria proposed in the 2015 ESC/ERS guidelines accurately predicted the risk of death or lung transplantation in incident PAH patients at the time of diagnosis and during the first year of treatment. The number of low-risk criteria achieved during the first year of follow-up discriminated patients at low risk better than the number of criteria present at baseline. In our analysis, patients attaining only one or two low-risk criteria at follow-up had a worse long-term prognosis than those who attained three or four low-risk criteria. Furthermore, patients achieving or maintaining all four low-risk criteria had a better long-term prognosis than those with three low-risk criteria at re-evaluation.

Our results demonstrate that a simplified version of the 2015 ESC/ERS risk assessment, using only four modifiable variables, could be a valid method to assess prognosis in patients with idiopathic, drug-induced

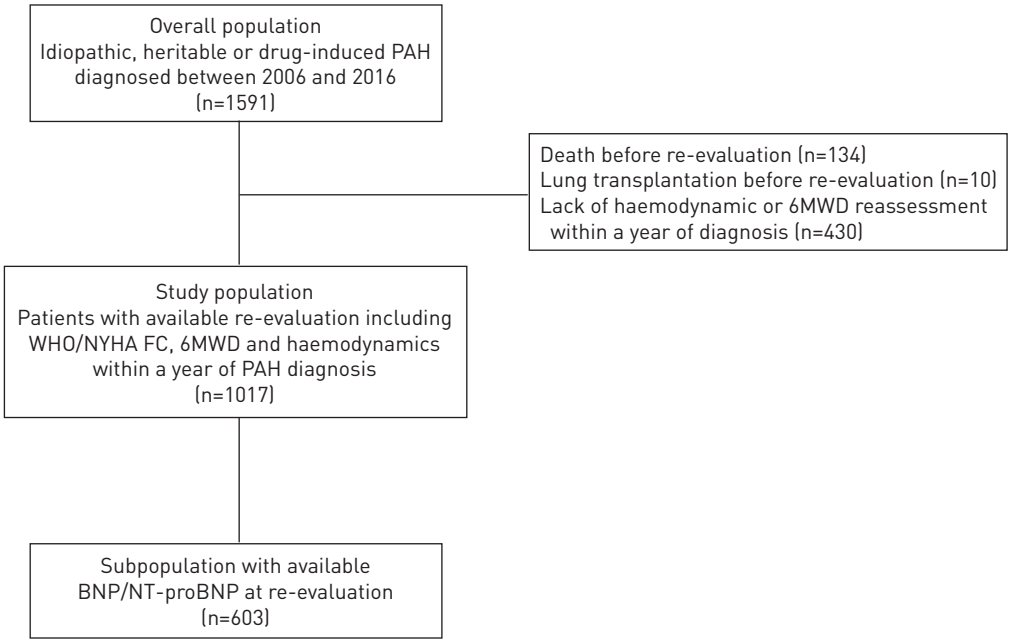


FIGURE 1 Patient selection flow chart. PAH: pulmonary arterial hypertension; 6MWD: 6-min walking distance; WHO: World Health Organization; NYHA: New York Heart Association; FC: functional class; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-brain natriuretic peptide.

TABLE 1 Demographics and baseline characteristics of overall and study populations of patients with newly diagnosed idiopathic, heritable and drug-induced pulmonary arterial hypertension (PAH)

	Overall population	Study population
Subjects	1591	1017
Female/male	924 (58)/667 (42)	598 (59)/419 (41)
Age years	60±17	57±17
BMI kg·m^{-2}	27.8±7.0	27.7±6.4
BMI >30 kg·m^{-2}	474 (30)	291 (29)
PAH diagnosis		
Idiopathic	1228 (77)	762 (75)
Heritable	109 (7)	94 (9)
Drug-induced	254 (16)	161 (16)
Acute vasodilator responder	139 (8.7)	97 (9.5)
WHO/NYHA functional class		
I–II	441 (28)	261 (26)
III	925 (58)	624 (61)
IV	225 (14)	132 (13)
6-min walking distance m	307±142	311±145
Haemodynamics		
RAP mmHg	8.8±5.2	8.6±5.0
mPAP mmHg	48±13	50±13
PAWP mmHg	10±4	9±4
Cardiac output L·min^{-1}	4.4±1.5	4.4±1.4
Cardiac index L·min^{-1}·m^{-2}	2.4±0.8	2.4±0.7
PVR Wood units	9.9±5.6	10.5±5.9
Mean blood pressure mmHg	96±18	95±17
Heart rate beats·min^{-1}	80±16	80±15
Sv_{O_2} %	63±10	63±9[#]

Data are presented as n, n (%) or mean±SD. BMI: body mass index; WHO: World Health Organization; NYHA: New York Heart Association; RAP: right atrial pressure; mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance; Sv_{O_2}: mixed venous oxygen saturation. [#]: n=606.

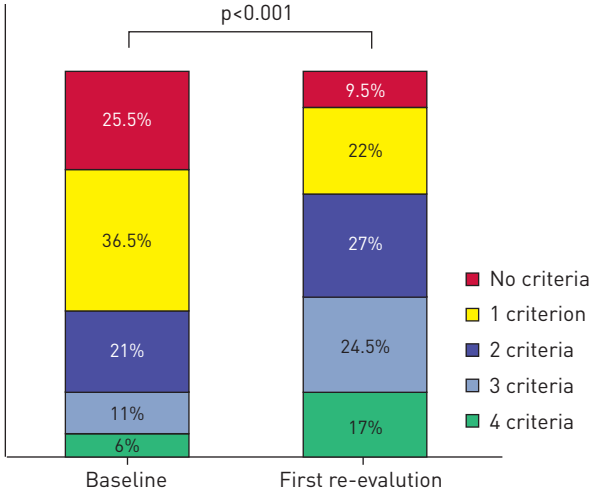


FIGURE 2 Number of low-risk criteria (World Health Organization/New York Heart Association functional class I–II; 6-min walking distance >440 m; right atrial pressure <8 mmHg; cardiac index ⩾2.5 L·min^{-1}·m^{-2}) present at baseline and first re-evaluation within the first year after diagnosis.

TABLE 2 Univariable and multivariable Cox regression analysis of low-risk criteria assessed at baseline and first re-evaluation

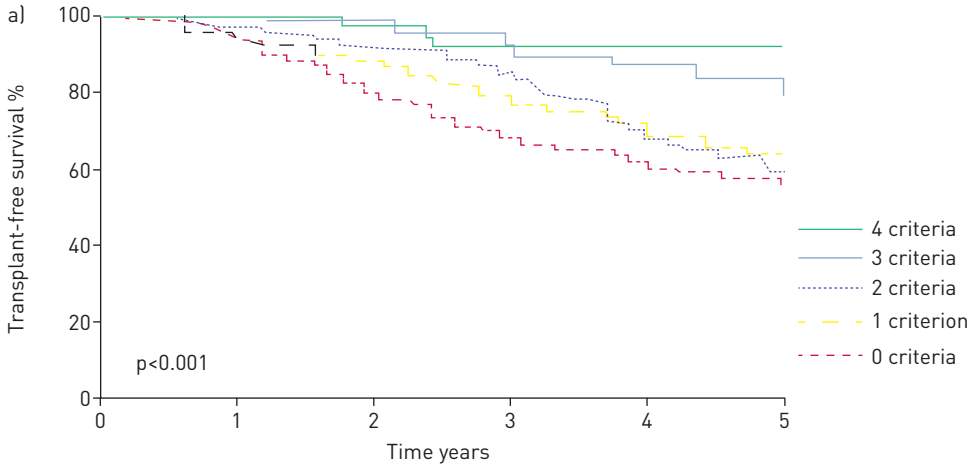
	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
At baseline				
WHO/NYHA FC I–II	0.59 (0.43–0.82)	0.001		
6-min walking distance >440 m	0.29 (0.18–0.46)	<0.001	0.31 (0.19–0.50)	<0.001
Right atrial pressure <8 mmHg	0.71 (0.55–0.92)	0.009		
Cardiac index ⩾2.5 $L \cdot min^{-1} \cdot m^{-2}$	0.76 (0.59–0.97)	0.029		
At first re-evaluation				
WHO/NYHA FC I–II	0.30 (0.23–0.39)	<0.001	0.44 (0.34–0.58)	<0.001
6-min walking distance >440 m	0.24 (0.17–0.34)	<0.001	0.37 (0.26–0.55)	<0.001
Right atrial pressure <8 mmHg	0.51 (0.40–0.64)	<0.001	0.74 (0.57–0.94)	0.016
Cardiac index ⩾2.5 $L \cdot min^{-1} \cdot m^{-2}$	0.51 (0.40–0.65)	<0.001	0.64 (0.50–0.82)	<0.001

WHO: World Health Organization; NYHA: New York Heart Association; FC: functional class.

and heritable PAH. Similarly to a previous study of idiopathic PAH patients, we observed that clinical variables in response to initial management predicted long-term prognosis better than baseline values [15]. In a study of 109 patients, NICKEL *et al.* [15] demonstrated that response to therapy was at least as important as baseline values in terms of known prognostic factors such as WHO/NYHA functional class, cardiac index, SvO_2 and NT-proBNP. We extended these findings to a much larger population and have demonstrated the importance of the absolute number of low-risk criteria present at baseline and during follow-up, whereas the study by NICKEL *et al.* only assessed prognosis according to changes in each variable individually. Although limited to a subset of patients (n=606) with SvO_2 measured at first re-evaluation, the presence of SvO_2 >65% predicted survival independently of WHO/NYHA functional class, 6MWD, RAP and cardiac index, again extending the results of NICKEL *et al.* [15]. The REVEAL (Registry to Evaluate Early and Long-term PAH Disease Management) score is another validated risk assessment tool that can be applied serially during follow-up in PAH patients to predict the risk of death during the following 12 months; however, this calculated score uses 13 different variables, some of which are nonmodifiable, such as age, sex and aetiology of PAH [16–19].

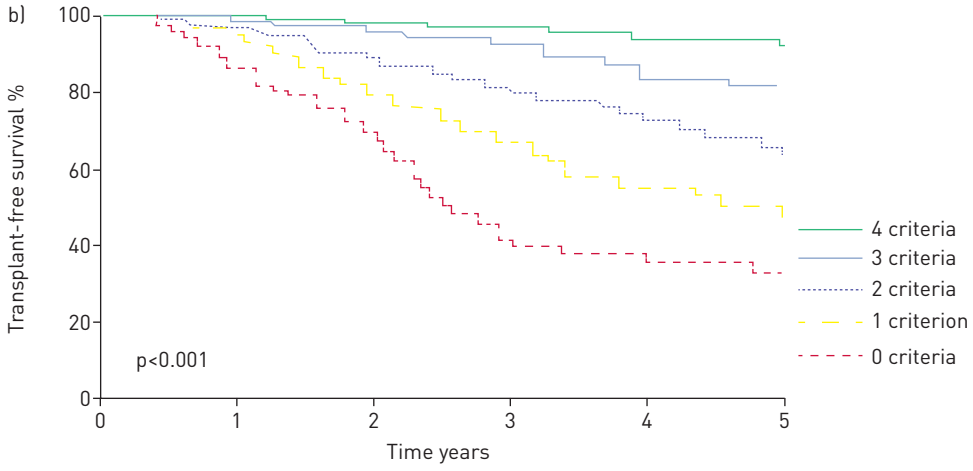
Our study evaluated only four modifiable clinical and haemodynamic variables, which were useful both at diagnosis and during the first year of treatment, but our approach has the advantage of being simpler and uses fewer variables, which might be easier to apply in clinical practice than the REVEAL score. However, we did not directly compare our approach to the REVEAL prognostication score in this population and therefore do not claim that our approach discriminates as well as or better than the REVEAL score. Even without considering the presence of certain intermediate-risk or high-risk criteria from the 2015 ERS/ESC guidelines, we found that the mere absence of low-risk criteria at baseline or follow-up identified patients with a particularly poor prognosis. Patients who had zero low-risk features and one or more variable in the high-risk range had a 1-year mortality risk between 13% and 30%, which corresponds with a high-risk profile (online supplementary figure 3). Patients with one or two low-risk criteria at follow-up had 1-year mortality rates of 4% (figure 3b), which is not consistent with an intermediate-risk profile [2, 3]. It remains unclear how to best define an intermediate-risk profile based on our results. A low-risk profile was apparent for patients with three or four low-risk criteria at follow-up, which reflected a 1-year mortality risk of 0–1% (figure 3b).

Another important finding in our study was that the total number of low-risk criteria achieved in the first year was related to long-term prognosis, reflecting the importance of individual responses to PAH therapy. Similarly to NICKEL *et al.* [15], we found that patients who improved to having three or four low-risk criteria at re-evaluation had a similar prognosis to those patients who maintained three or four low-risk criteria from baseline to first re-evaluation, confirming that follow-up assessments may discriminate prognosis better than baseline factors (online supplementary figure 2). We observed that patients attaining only one or two low-risk criteria in the first year of treatment had worse outcomes than patients who achieved three or four low-risk criteria and those who did not achieve any low-risk criteria had a dismal prognosis. Nevertheless, 49% of patients had still achieved only one or two low-risk criteria within the first year of treatment, which reflects the limitations of current treatment options and strategies. Although patients who achieved three criteria within the first year had a transplant-free survival of 93% at 3 years, the 5-year transplant-free survival was 78%, which was considerably lower than the 91% 5-year survival



Patients at risk n

4 criteria	59	52	46	35	26	20
3 criteria	112	94	74	59	36	26
2 criteria	217	173	149	104	63	45
1 criterion	371	302	233	176	128	89
0 criteria	258	212	158	117	76	53



Patients at risk n

4 criteria	175	153	128	102	63	48
3 criteria	247	204	175	140	102	72
2 criteria	275	219	171	122	78	49
1 criterion	225	183	128	91	62	45
0 criteria	95	61	44	22	18	14

FIGURE 3 Transplant-free survival according to the number of low-risk criteria (World Health Organization/New York Heart Association functional class I–II I; 6-min walking distance >440 m; right atrial pressure <8 mmHg; cardiac index ⩾2.5 L·min^{-1}·m^{-2}) present at a) time of pulmonary arterial hypertension diagnosis; b) first re-evaluation within the first year after diagnosis.

among the patients who achieved four criteria. Interestingly, prognosis did not differ according to which three low-risk criteria were present at follow-up. Only 20% of patients with four low-risk criteria at follow-up were acute responders to vasoreactivity testing compared to 9% in the group with three low-risk criteria. Therefore, the group achieving four criteria were not particularly enriched with a patient phenotype known to have a better prognosis [19]. An ideal treatment objective could be to obtain the maximum number of low-risk criteria possible, even in patients without acute vasoreactivity. Thus, use of a simplified multidimensional risk assessment and an ambitious treatment strategy of maximising the

TABLE 3 Change in functional class (FC), exercise capacity and haemodynamics between baseline and first re-evaluation

	Baseline	First re-evaluation#	p-value
WHO/NYHA FC			
I–II	261 (26)	595 (59)	<0.001
III	624 (61)	349 (34)	
IV	132 (13)	73 (7)	
6-min walking distance m	311±145	354±145	<0.001
Haemodymamics			
RAP mmHg	8.6±5.0	7.5±4.8	<0.001
mPAP mmHg	50±13	44±13	<0.001
Cardiac output $L \cdot min^{-1}$	4.4±1.4	5.3±1.6	<0.001
Cardiac index $L \cdot min^{-1} \cdot m^{-2}$	2.4±0.7	2.9±0.8	<0.001
PVR Wood units	10.5±5.9	7.1±4.6	<0.001
S_{vO_2} %	63±10	67±8	<0.001

Data are presented as n (%) or mean±SD, unless otherwise stated. n=1017. WHO: World Health Organization; NYHA: New York Heart Association; RAP: right atrial pressure; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; S_{vO_2}: mixed venous oxygen saturation. #: 5.6±3.4 months after baseline.

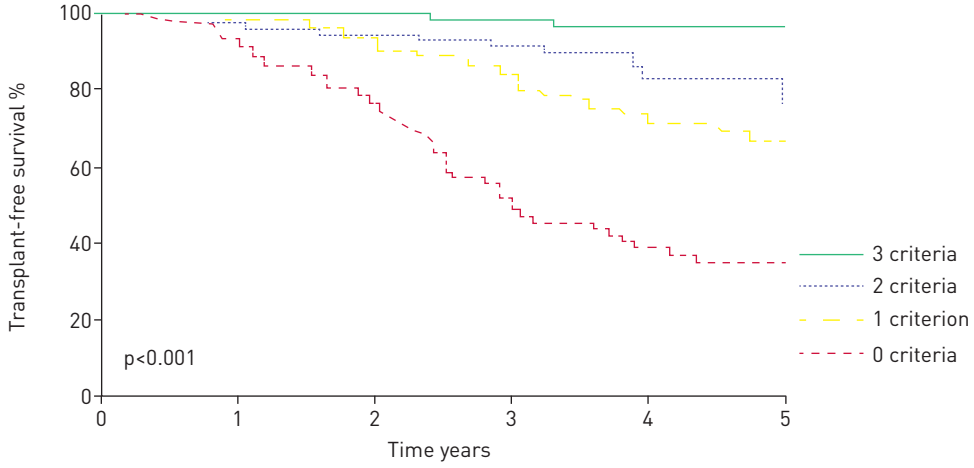
number of low-risk criteria could translate to a better long-term prognosis for newly diagnosed patients with PAH.

Serial follow-up assessments of PAH patients using noninvasive variables would be preferable if such a method provided comparable or superior prognostic utility compared to risk assessment tools that incorporate invasive haemodynamic variables. Interestingly, in a subset of 603 patients who had WHO/NYHA functional class, 6MWD, haemodynamics and either BNP or NT-proBNP measured at follow-up, only the three noninvasive variables were independently associated with transplant-free survival. Although invasive haemodynamic measurements with right heart catheterisation are necessary to confirm the diagnosis of PAH, the number of noninvasive low-risk criteria present at follow-up identified groups of patients with different long-term outcomes (figure 4). This may be partially explained by the fact that BNP and NT-proBNP are related to right ventricular function, and thus reflect both RAP and cardiac index. In our cohort, a normal BNP/NTpro-BNP level had 98% sensitivity to exclude the presence of either RAP >8 mmHg, cardiac index <2.5 $L \cdot min^{-1} \cdot m^{-2}$ or both. Most importantly, patients with all three noninvasive low-risk criteria had a 2-, 3- and 5-year survival of 100%, 99% and 97%, respectively, while patients without any noninvasive low-risk criteria at follow-up had a dismal prognosis. This suggests that routine haemodynamic follow-up may not be necessary for all patients, particularly those who attain and maintain all three noninvasive low-risk criteria (WHO/NYHA functional class I or II, 6MWD >440 m and either BNP <50 $ng \cdot L^{-1}$ or NT-proBNP <300 $ng \cdot L^{-1}$). Certainly, a management strategy relying on only noninvasive risk assessment variables would need to be replicated and confirmed in a prospective study. However, it must also be noted that the haemodynamic risk assessment criteria were still independent

TABLE 4 Univariable and multivariable Cox regression analysis of low-risk criteria assessed at first re-evaluation in the subset of patients with available brain natriuretic peptide (BNP) or N-terminal pro-brain natriuretic peptide (NT-proBNP) measurements

	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	**p-value**	**Hazard ratio (95% CI)**	**p-value**
WHO/NYHA FC I–II	0.28 (0.19–0.42)	<0.001	0.47 (0.32–0.71)	<0.001
6-min walking distance >440 m	0.17 (0.09–0.31)	<0.001	0.32 (0.17–0.60)	<0.001
BNP <50 $ng \cdot L^{-1}$ or NT-proBNP <300 $ng \cdot mL^{-1}$	0.21 (0.13–0.34)	<0.001	0.31 (0.19–0.52)	<0.001
Right atrial pressure <8 mmHg	0.45 (0.31–0.65)	<0.001		
Cardiac index ⩾2.5 $L \cdot min^{-1} \cdot m^{-2}$	0.44 (0.30–0.65)	<0.001		

WHO: World Health Organization; NYHA: New York Heart Association; FC: functional class.



Patients at risk n						
3 criteria	115	97	81	63	38	26
2 criteria	145	116	95	72	36	21
1 criterion	175	136	101	62	38	24
0 criteria	168	117	76	39	23	11

FIGURE 4 Transplant-free survival according to the number of noninvasive low-risk criteria (World Health Organization/New York Heart Association functional class I–II; 6-min walking distance >440 m; brain natriuretic peptide <50 ng·L^{-1} or N-terminal pro-brain natriuretic peptide <300 ng·mL^{-1}) present at first re-evaluation (n=603).

predictors of transplant-free survival in the overall analysis population and provide important diagnostic and prognostic information in PAH patients with signs of clinical worsening. It remains unknown whether the addition of other noninvasive modalities, such as echocardiography or cardiopulmonary exercise testing to the three noninvasive criteria assessed in our study could further improve the prognostic utility of a noninvasive risk assessment tool.

The major strengths of our study were the large cohort size and the availability of complete data for invasive haemodynamic and noninvasive variables at diagnosis and during the first year of treatment. As nearly half of our cohort received initial combination therapy, we were able to validate the 2015 ERS/ESC risk assessment criteria in a real-world cohort managed according to contemporary strategies endorsed in these same guidelines. We intentionally limited our analysis to patients with idiopathic, heritable or drug-induced PAH to avoid the potentially confounding effect of disease aetiology on prognosis. Furthermore, most of the risk assessment criteria cut-points suggested in the guidelines were derived from studies of predominantly idiopathic, anorexigen and heritable PAH [14]. However, we recognise that our study did not attempt to apply the risk assessment criteria in patients with PAH due to other aetiologies (such as connective tissue diseases, portopulmonary hypertension or congenital heart disease), which limits the generalisability of our results to other PAH aetiologies. We recognise that there are certain other limitations inherent to the retrospective nature of this study and that we considered only the absolute number of low-risk criteria present, but not the prognostic significance of the intermediate- or high-risk values for the risk assessment variables. We were only able to assess certain risk assessment variables due to absent data for echocardiographic parameters, S_{vO_2} and cardiopulmonary exercise testing for many patients. Finally, patients were actively managed after the first year of follow-up and clinical response to treatment changes beyond the first year were not assessed in our analysis, which limits generalisability to prevalent patients who are >1 year from PAH diagnosis. Because the first follow-up between 1 month and 1 year is somewhat arbitrary, some individuals may still have achieved three or four low-risk criteria at the second post-treatment re-evaluation within the first year or later than 1 year, particularly if therapy was intensified within that interval. This could be a potential explanation for the reasonably good outcomes for patients achieving two low-risk criteria (figure 3b). Thus, our results only reflect initial treatment responses and not subsequent responses to changes in PAH therapy.

In conclusion, this study helps validate the multidimensional approach to risk assessment recommended in the 2015 ERS/ESC guidelines in a large cohort of incident patients with PAH. Long-term prognosis was accurately determined using a simple quantification of the number of low-risk criteria present at diagnosis and after treatment initiation for WHO/NYHA functional class, 6MWD, RAP and cardiac index. Patients

who maintained or achieved three or four low-risk criteria had excellent long-term transplant-free survival, whereas prognosis was worse among patients with fewer low-risk criteria. Our results suggest that a goal-oriented management strategy using ambitious treatment targets should be further studied for incident patients with PAH. Noninvasive risk assessment was useful in identifying patients at very low risk of death or lung transplantation and may obviate the need for routine invasive haemodynamic follow-up assessment in selected patients.

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