Risk assessment in pulmonary arterial hypertension

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ABSTRACT Regular patient assessment is essential for the management of chronic diseases, such as pulmonary arterial hypertension (PAH). Comprehensive patient assessment and risk stratification in PAH are important to guide treatment decisions and to monitor disease progression as well as patients' response to treatment. Approaches for assessing risk in PAH patients include the use of risk variables, as recommended in the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) pulmonary hypertension (PH) guidelines, and the application of risk equations and scores, such as the French registry risk equation and the REVEAL registry risk score. Risk stratification and risk scores are both useful predictors of survival on a population basis, and provide an estimate for individual patients' risk. The 2015 ESC/ERS PH guidelines recommend regular assessment of multiple variables at an expert centre. The respective merits and limitations of different risk assessment methods in PAH are discussed in this article, as well as some considerations that can be taken into account in the future development of risk assessment tools.

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Regular risk assessment with multiple parameters evaluates PAH disease progression and treatment response http://ow.ly/Nq0I305kgpU

Introduction

Patient risk assessment is essential in the management of many chronic diseases such as asthma, heart failure and cancer [1–4]. Comprehensive patient assessment allows clinicians to determine the patient's prognosis, monitor disease progression and the patient's response to treatment, and impacts treatment decisions. In pulmonary arterial hypertension (PAH), the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) pulmonary hypertension (PH) guidelines recommend that risk assessment should be conducted regularly (3–6 monthly in stable patients) using multiple parameters to evaluate disease progression and patients' response to treatment [5–7]. Risk assessment in these patients should include a range of clinical, haemodynamic and exercise parameters, as there is no single variable that provides definitive prognostic information [6, 7].

Currently, there are different approaches to assessing risk in PAH; these include the use of risk variables according to the 2015 ESC/ERS PH guidelines [6, 7], a risk equation such as the French registry equation [8] or National Institutes of Health (NIH) equation [9], or the use of a risk score such as the REVEAL (Registry to Evaluate Early And Long-term PAH Disease Management) registry risk score [10]. In this

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article we will discuss parameters of prognostic relevance in PAH, the different approaches to risk assessment and how the outcomes of risk assessment can influence PAH management.

Risk assessment in PAH

Patient demographics

As with many diseases, patient demographics can influence patient outcomes. However, a number of parameters that affect survival rates in PAH cannot be influenced by therapy. One of these parameters is patient sex. Male sex was shown to be an indicator of poor prognosis in the French risk registry [8, 11], and older male patients (aged >60 years) also showed an increased risk of mortality in the REVEAL registry [12]. Another prognostic parameter that cannot be influenced by therapy is the aetiology of PAH, such as PAH-associated with systemic sclerosis (SSc) or bone morphogenetic protein receptor 2 (BMPR2) mutation status. PAH-SSc patients have a worse prognosis compared with patients with idiopathic PAH [13–15]. PAH-SSc patients also have markedly worse prognoses and survival rates when compared with patients with other forms of PAH-associated connective tissue disease [14, 16]. BMPR2 loss-of-function mutations are the most common genetic cause of PAH. Patients with these mutations have been shown to have higher mean pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR), and reduced cardiac index at presentation compared with patients with no BMPR2 mutations, indicating a more severe disease phenotype and worse prognosis [17].

Signs and symptoms

Clinical signs of right heart failure are indicative of a poor prognosis in PAH [6, 7] and include lower limb oedema, ascites, S3 gallop and elevated jugular venous pressure. Syncope has prognostic relevance in PAH and is an indicator of disease severity. Occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope, can be observed in an otherwise stable PAH patient. Repeated episodes of syncope, even with little or regular physical activity, is usually observed in patients with high risk PAH and overt right heart failure [6, 7].

Functional class

Another clinical parameter of prognostic relevance is New York Heart Association/World Health Organization functional class (WHO FC). WHO FC is a powerful predictor of survival, with increasing numbers for WHO FC (I–IV) representing a scale to measure severity of PAH [6, 7]. Studies have shown that poorer WHO FC status at presentation is associated with worse 5-year survival [18, 19]. Furthermore, improvements and deteriorations in WHO FC at follow-up have been associated with increases and decreases in survival rates, respectively [18–21]. However, WHO FC is a subjective measurement and inter-observer variability has been observed amongst clinicians [22]. While the variation observed in WHO FC assessments does not negate the value of WHO FC as a prognostic tool [22], this potential limitation should be considered when evaluating it as a prognostic indicator.

Exercise capacity measures

At least one measurement of exercise capacity, such as 6-minute walk distance (6MWD) or cardiopulmonary exercise testing (CPET), should be conducted as part of the regular assessment of PAH patients [6, 7]. The 6MWD is a widely used and simple method for assessing patients' exercise capacity [6, 7]. Patients presenting with a high 6MWD had improved survival rates at 3 years compared with patients presenting with a lower 6MWD [11]. In one study, patients with a 6MWD >380 m (median value) at baseline showed significantly greater survival than those with a 6MWD less than the median at baseline. Similar results were demonstrated using a median 6MWD at follow-up of 418 m [20]. A lower threshold was calculated from the REVEAL registry, which showed that a 6MWD of <165 m at enrolment was significantly associated with mortality risk [12]. The REVEAL registry also demonstrated that a ⩾15% worsening of 6MWD was strongly and significantly associated with poor prognosis [23]. However, several studies have shown that change in 6MWD from baseline is not associated with long-term outcomes [19, 20, 24–27].

Maximal exercise testing of patients with PAH using CPET is thought to be useful in identifying early signs of disease progression, such as reduced right ventricular reserve in the presence of normal resting PAP [28]. Data gathered from CPET include peak oxygen uptake (V'_{O_2}), anaerobic threshold and the degree of ventilatory inefficiency. PAH patients show reduced peak V'_{O_2} compared with the expected values for healthy individuals, and peak V'_{O_2} values during exercise at baseline are considered to have the strongest correlation with survival rates [29], with values <15 mL·min^{-1}·kg^{-1} suggesting increased mortality risk [6, 7]. PAH patients also show increased volume of minute volume (V'_E) and carbon dioxide production (V'_{CO_2}) slope, which is representative of ventilatory insufficiency. V'_E/V'_{CO_2} slope values >36 are a marker of poor prognosis [6, 7].

Echocardiography and cardiac magnetic resonance imaging

Echocardiography allows quantitative assessment of measures of right ventricular function (*e.g.* TAPSE (tricuspid annular plane systolic excursion)), right ventricular global longitudinal strain and right ventricular fractional area change. TAPSE values of <1.8 cm have been associated with reduced 2-year survival rates in PAH [30]. Furthermore, other simple echocardiographic surrogates of right heart function have been shown to have prognostic significance in PAH, such as right atrial area and pericardial effusion. Patients who present with a right atrial area >18 cm^2, either at baseline or follow-up, are considered to be at an increased risk of mortality *versus* patients with a right atrial area <18 cm^2 [6, 7]. Pericardial effusion at baseline is a strong predictor of mortality in PAH patients [5] and is an indicator of a high-risk patient [18].

Cardiac magnetic resonance imaging (MRI) has emerged as a reliable and reproducible imaging method for assessing right heart morphology and function [6, 7], including ejection fraction [31], longitudinal shortening [32], mass index [31] and work [33]. Of these parameters, ejection fraction, as assessed by cardiac MRI, has a strong prognostic value [31, 34], with low right ventricular ejection fraction (RVEF) (<35%) being associated with poor survival, independent of PVR, and increases in RVEF after 12 months being predictive of improved 6-year survival [34]. Another study showed that after 12 months of disease-targeted therapy, there were significant increases in both RVEF and left ventricular ejection fraction [31].

Haemodynamic parameters

The 2015 ESC/ERS PH guidelines recommend that right heart catheterisation (RHC) should be considered 3–6 months after a change in a patient's treatment regimen or in case of clinical worsening, indicating the importance of RHC during follow-up, despite its invasive nature. RHC measures are very informative, and some respected centres perform RHC at regular intervals during follow-up in stable patients; in these centres, yearly RHC is usually considered [6, 7]. RHC enables monitoring of right atrial pressure, elevations of which are associated with poorer survival rates [6, 7]. Low mixed venous oxygen saturation and cardiac index at baseline, and deteriorations in these parameters, have been significantly associated with poor outcomes [27].

BNP and NT-proBNP

Brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are biomarkers that are commonly studied in clinical trials in PAH. Absolute levels of NT-proBNP [35] and BNP are correlated with haemodynamic parameters and clinical outcome, both at baseline and at follow-up. NT-proBNP levels are thought to have a superior prognostic value than BNP levels [36], and reduced levels of NT-proBNP after 1 year are associated with improved 3-year [20] and 5-year survival rates [27].

Approaches to risk assessment: comprehensive assessment using the 2015 ESC/ERS PH guidelines

The PAH risk assessment approach described in the 2015 ESC/ERS PH guidelines is the first to be proposed in European PH guidelines [6, 7]. The 2015 ESC/ERS PH guidelines strongly recommend regular assessment of patients with PAH and highlight the role of expert centres in these assessments. Based on the evaluation of multiple variables, PAH patients can be categorised as low, intermediate or high risk with estimated 1-year mortality of <5%, 5–10% and >10%, respectively (table 1) [7]. However, the use of multiple variables brings with it complexity. An individual patient is unlikely to have all variables indicative of low, medium or high risk. Good clinical judgement is essential, as patients are likely to present with some variables that are indicative of low risk, and some indicative of intermediate or high risk. The main treatment goal for patients with PAH is to achieve a low risk status [6, 7]. Low risk patients are typically WHO FC I/II with good exercise capacity and normal or near-normal right ventricular function (the latter is assessable using a number of different parameters) [6, 7]. Patients with an intermediate or high risk are typically WHO FC III/IV, with poor exercise capacity and poor right ventricular function. Improving or maintaining many of the variables listed in the 2015 ESC/ERS PH guidelines [6, 7] may be associated with improved survival and/or better quality of life [27, 37]. Comprehensive risk assessment based on multiple variables can also be used to guide therapeutic decisions [6, 7]. The 2015 ESC/ERS PH guidelines recommend initial monotherapy or initial oral combination therapy for low or intermediate risk patients, whereas an initial combination therapy regimen, including intravenous prostacyclin analogues, should be considered for high-risk patients [6, 7]. The risk assessment approach according to the 2015 ESC/ERS PH guidelines has broader implications for patients, such as the timing of listing of patients for lung transplantation.

Approaches to risk assessment: risk scores and equations

A number of registries have been established to collect data on patients with PAH and analyse the course of the disease in the current treatment era [38–43]. Data from these registries have led to the development of risk scores and equations, which combine assessments of multiple parameters into a single score to

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TABLE 1 Risk assessment in patients with pulmonary arterial hypertension

Determinants of prognosis[#] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[¶]	Repeated syncope[+]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak V'_{O_2}>15 mL·min^{-1}·kg^{-1} (>65% pred)	Peak V'_{O_2} 11–15 mL·min^{-1}·kg^{-1} (35–65% pred)	Peak V'_{O_2} <11 mL·min^{-1}·kg^{-1} (<35% pred)
	V'_E/V'_{CO_2} slope <36	V'_E/V'_{CO_2} slope 36–44.9	V'_E/V'_{CO_2} slope ⩾45
NT-proBNP plasma levels	BNP <50 ng·L^{-1}	BNP 50–300 ng·L^{-1}	BNP >300 ng·L^{-1}
	NT-proBNP <300 ng·L^{-1}	NT-proBNP 300–1400 ng·L^{-1}	NT-proBNP>1400 ng·L^{-1}
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2	RA area 18–26 cm^2	RA area >26 cm^2
	No pericardial effusion	No or minimal, pericardial effusion	Pericardial effusion
Haemodynamics	RAP <8 mmHg	RAP 8–14 mmHg	RAP >14 mmHg
	CI ⩾2.5 L·min^{-1}·m^{-2}	CI 2.0–2.4 L·min^{-2}·m^{-2}	CI <2.0 L·min^{-1}·m^{-2}
	S_{vO_2} >65%	S_{vO_2} 60–65%	S_{vO_2} <60%

WHO: World Health Organization; 6MWD: 6-min walking distance; NT-proBNP: N-terminal pro-brain natriuretic peptide; CMR: cardiac magnetic resonance; V'_{O_2}: oxygen uptake; V'_E/V'_{CO_2}: ventilatory equivalents for carbon dioxide; BNP: brain natriuretic peptide; RA: right atrium; RAP: right atrial pressure; CI: cardiac index; S_{vO_2}: mixed venous oxygen saturation. [#]: most of the proposed variables and cut-off values are based on expert opinion. They may provide prognostic information and may be used to guide therapeutic decisions, but application to individual patients must be done carefully. One must also note that most of these variables have been validated mostly for idiopathic pulmonary arterial hypertension and the cut-off levels used above may not necessarily apply to other forms of pulmonary arterial hypertension. Furthermore, the use of approved therapies and their influence on the variables should be considered in the evaluation of the risk. [¶]: occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in an otherwise stable patient. [+]: repeated episodes of syncope, even with little or regular physical activity. Reproduced from [7] with permission from the publisher.

predict prognosis in PAH patients. The first of these registries was the US-based NIH registry, data from which were used to investigate how haemodynamic, pulmonary and demographic factors affected survival rates in patients [9]. Of note, this early registry was established in 1981 and patients were enrolled and followed up in an era when PAH-specific therapies were not available. Two more recent ongoing PAH registries are the US-based REVEAL registry [43, 44] and the French Pulmonary Hypertension Network (FPHN) registry [38]. REVEAL (established in 2006) and FPHN (established in 2002) are both observational, prospective registries of patients diagnosed with PAH. They were implemented during the same era of disease knowledge, patient management and treatment, but were developed independently with different enrolment criteria, data collection and timing of follow-up. REVEAL enrolled adult and paediatric patients with WHO group 1 PH who met haemodynamic criteria (mean PAP >25 mmHg at rest or >30 mmHg with exercise, mean pulmonary arterial wedge pressure or left ventricular end-diastolic pressure of ⩽18 mmHg and PVR of >3 Wood units), and were receiving treatment for PAH at the time of enrolment. The FPHN registry enrolled all group 1 PH patients irrespective of aetiology, and included newly diagnosed patients (incident cases) and patients for whom a PAH diagnosis had been established before enrolment in the registry (prevalent cases).

The FPHN initiated the national prospective registry to investigate real-world survival of patients with PAH during a 3-year follow-up period [11, 38]. Based on the data collected in this registry, factors such as sex, 6MWD at diagnosis and cardiac output at diagnosis were identified as being independent prognostic markers at baseline for determining PAH disease severity [8, 38]. These factors were then incorporated into the development of the French registry risk equation, $\exp(-0.02–0.28xt)^{A(x,y,z)}$, which estimates the chance of survival from diagnosis after a given period of time. Predicted survival is calculated from the function $A^{(x,y,z)}$, which was determined using a Cox proportional hazards model, where x is the distance walked in metres at diagnosis, y is a sex function (1=female, 0=male) and z is the cardiac output in L·min^{-1} at diagnosis [8]. It is important to note that the French registry risk equation was designed to have prognostic value at baseline, but was not designed for serial assessment. The equation has also been used to determine the effectiveness of a dual combination treatment regimen [45]. Expected survival of newly diagnosed WHO FC II–IV patients on initial dual oral combination therapy, consisting of an endothelin receptor antagonist and a phosphodiesterase type 5 inhibitor, was calculated using the French registry risk equation [45]. Actual survival rates in this group of patients were 97%, 94% and 83% at 1, 2 and 3 years, respectively, compared with the calculated expected survival rates of 86%, 75% and 66%,

respectively [45]. Similarly, another study determined the effectiveness of a triple combination treatment regimen using this equation. Expected survival in newly diagnosed WHO FC III/IV PAH patients, initiated on upfront triple combination therapy consisting of intravenous epoprostenol, bosentan and sildenafil was calculated [46]. Overall survival estimates in these patients were 100% at 1, 2 and 3 years compared with an expected survival, calculated from the French registry equation, of 75%, 60% and 49%, respectively [46].

Data from the REVEAL registry have been used to develop a predictive model for survival in PAH. One of the pre-specified objectives of the REVEAL registry was to identify predictors of survival in a PAH population, in the context of treatment at the time and clinical variables [43]. This registry subsequently highlighted a number of factors, including WHO FC, haemodynamic and echocardiographic parameters and other criteria, that were indicative of a mortality risk in PAH patients [12]. A quantitative equation for predicting survival was developed [10, 12] and was prospectively validated in a cohort of newly diagnosed PAH patients from the REVEAL registry [10]. A simplified risk score (figure 1) based on the prognostic equation was developed, which was designed to be simple and easy enough to be adopted in everyday

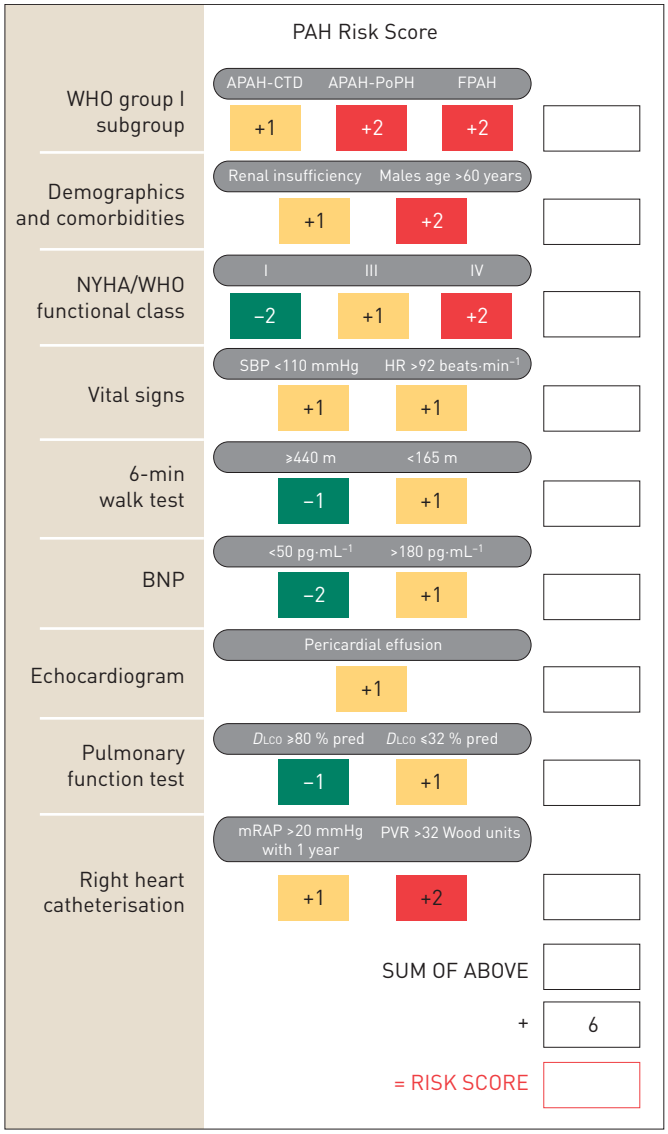

FIGURE 1 Simplified REVEAL (Registry to Evaluate Early And Long-term PAH Disease Management) risk score. PAH: pulmonary arterial hypertension; WHO: World Health Organization; NYHA: New York Heart Association; BNP: brain natriuretic peptide; APAH; associated PAH; CTD: connective tissue disease; PoPH: portopulmonary hypertension; FPAH: familial PAH; SBP: systolic blood pressure; HR: heart rate; *D*LCO: diffusing capacity of the lung for carbon monoxide; mRAP: mean right atrial pressure; PVR: pulmonary vascular resistance. Reproduced from [10] with permission from the publisher.

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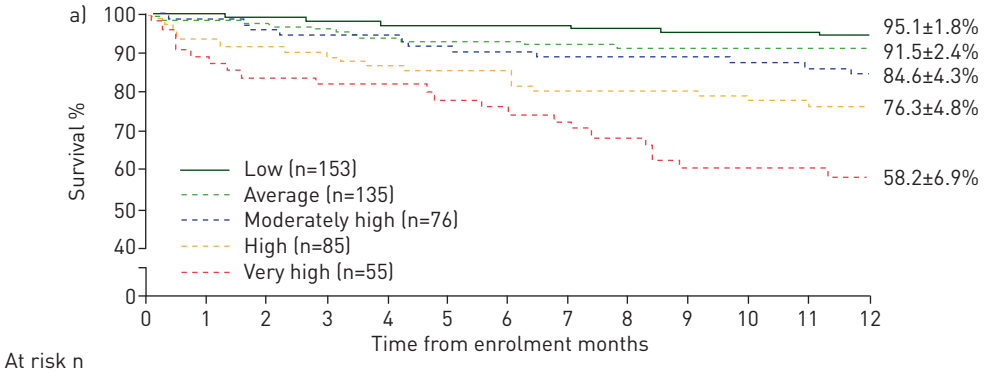
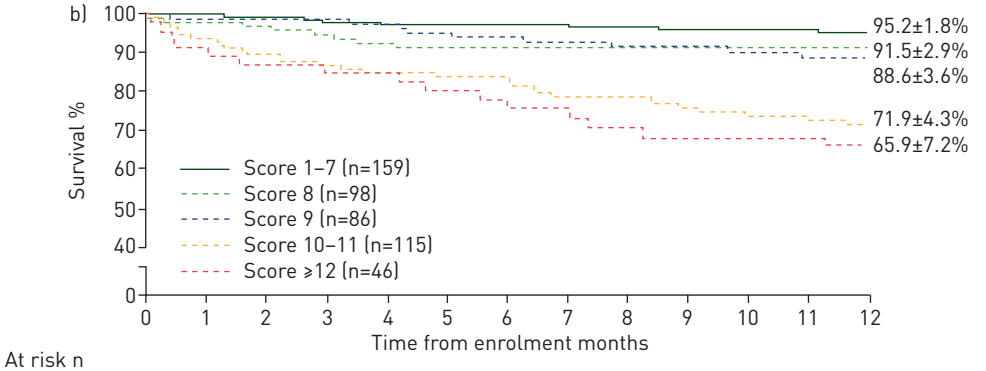
clinical practice, compared with the relatively complex REVEAL risk equation [10]. The simplified REVEAL risk score is defined by single measurements of each variable, with one point being allocated for factors that are responsible for a statistically significant increase in 1-year mortality risk and two points being allocated for factors that are responsible for a greater than two-fold increase in 1-year mortality risk (figure 1) [10]. Recent improvements to the risk score have been made by incorporating serial assessments of risk scores over 1 year, which were shown to improve survival prediction compared with using only baseline measurements [47]. This study found that alterations in WHO FC, systolic blood pressure, BNP levels, 6MWD, heart rate and pericardial effusion status were most likely to lead to a change in risk score within 1 year. No single parameter was the primary source of change, highlighting the need for multifactorial risk assessment [47]. The simplified REVEAL risk score has been shown to have comparable performance in predicting survival rates when validated against the REVEAL risk equation (figure 2) [10]. This score was also validated in an independent US single-centre PAH cohort, which included patients with similar baseline characteristics to those in the REVEAL registry cohort, although the former cohort included more patients with severe disease [48].

Both the simplified REVEAL risk score and French registry risk equation have been independently validated in a recent collaborative analysis [49]. This was conducted by retrospectively applying the French registry risk equation parameters to the REVEAL cohort data and the REVEAL risk score to the French registry cohort. Only data that met the inclusion criteria for both equations were included in the analysis, and the survival scores derived using each equation were compared with those obtained from their



At risk n													
Low	153	150	149	145	144	144	144	135	134	133	117	117	116
Average	135	130	128	125	122	121	121	115	114	114	98	98	98
Mod. high	76	74	72	69	69	67	66	62	62	62	58	57	56
High	85	79	77	75	72	71	71	63	63	63	55	55	54
Very high	55	49	46	44	44	42	41	36	34	30	28	28	27



At risk n													
Score 1–7	159	156	155	151	150	150	150	141	140	139	120	120	119
Score 8	98	93	91	89	87	86	86	84	81	81	71	71	71
Score 9	86	84	84	81	80	78	77	73	72	72	65	64	64
Score 10–11	115	107	102	99	96	95	95	85	85	82	74	74	72
Score ≥12	46	42	40	38	38	36	35	31	29	28	26	26	25

FIGURE 2 1-year survival in the REVEAL (Registry to Evaluate Early And Long-term PAH Disease Management) validation cohort as predicted according to the a) risk prognostic equation and b) simplified risk score. PAH: pulmonary arterial hypertension. Reproduced from [10] with permission from the publisher.

"native" populations. The REVEAL risk score and the French registry risk equation appear accurate and well calibrated in the French registry and REVEAL validation cohorts, respectively [49], suggesting their generalisability in different PAH populations. Application of the French registry risk equation parameters to REVEAL and REVEAL risk scores to the French registry cohort demonstrated estimated hazard ratios that were consistent between studies and had high probabilities of concordance [49].

Practical considerations for risk assessment

There are several considerations that should be taken into account regarding risk assessments. All risk assessments should be considered in terms of the individual patient and their pertinent history and current PAH-specific therapy. For example, data from national PAH registries in the USA and Europe have shown improved survival rates amongst prevalent patients compared with incident patients [8], and a recent comparison of outcomes of these subgroups in a randomised controlled PAH trial showed that incident patients have a higher risk of disease progression [50]. Therefore, an incident patient in an intermediate or high-risk category might be considered to have a worse prognosis than a prevalent patient in the same risk category, if on similar PAH-specific therapies. However, a patient's prognosis may also be affected by their previous exposure to therapy. For example, a newly diagnosed, treatment-naïve incident patient may have the same high-risk assessment as a patient who has been on double or triple therapy for some time and has been clinically declining. In this situation the treatment-naïve patient may respond to initial therapy [6, 7], whereas the patient with a high-risk profile despite treatment with double or triple therapy will be coming to the end of medical treatment options and should, therefore, be considered as a priority case for lung transplantation if eligible. The rate of disease progression should be considered as an important part of risk assessment, with rapid deterioration being indicative of high risk [6, 7]. Another important consideration regarding risk assessment is that patients should not calculate their risk themselves, as this increases the possibility of misinterpretation. As with any other medical test, it is essential that healthcare professionals be present to discuss the results of risk assessment to ensure that they are put into appropriate context for a given patient and to consider the next steps with regards to treatment strategy.

In PAH in general, risk assessment allows the determination of patient prognosis and the monitoring of responses to therapy, and can aid decision-making with respect to treatment choices. It can also provide confirmation to physicians that their impression of how well a patient is doing is correct. This approach of regular risk assessment is strongly recommended within the current ESC/ERS guidelines [6, 7]. However, it should be noted that the tools and parameters discussed in this article have mainly been evaluated in the context of baseline risk assessment and very few data are available on their use in the on-going assessment of risk. Tools for dynamic assessment at multiple follow-up time-points would benefit evaluation of the impact of time-dependent variables on clinical outcomes [51].

In addition to the general considerations regarding risk assessment, there are specific advantages and limitations to be taken into account. When taking the approach of risk assessment according to the 2015 ESC/ERS PH guidelines, an important advantage is that it can be used at follow-up as well as at baseline. This approach also has the advantage of being multifactorial, using clinical, imaging and haemodynamic findings that are easily and routinely obtained at PH centres. It also allows more flexibility for a clinician to use their own judgement. However, the comprehensive approach according to the 2015 ESC/ERS PH guidelines means that it can be complex and relies on good clinical judgement, particularly when considering a difficult case. The 2015 ESC/ERS PH guidelines approach lacks validation as to whether risk stratification correlates with prognosis. Furthermore, this approach may increase the potential for inter-clinician variation: if a patient shows a range of risks across the variables, the physician's decision on the overall risk is subjective and the assessment could vary between different physicians.

The REVEAL risk score is straightforward to use and provides quantitative outcome measurements rather than qualitative outputs obtained from clinicians, which is an important advantage since the latter may vary substantially between physicians [52]. While the REVEAL risk equation and risk score have prognostic value at baseline, a limitation is that there has only been one analysis that has evaluated the prognostic implications of changes in the risk score after 12 months [47]. This analysis found that changes in REVEAL risk scores occurred in most patients over a 12-month period and were predictive of survival [47]. Further data are required to support the use of the risk equations and risk score to assess subsequent risk. It is also important to note that the REVEAL risk score and the French risk equation are population-based, and cannot precisely predict what will happen in an individual patient. In addition, some of the variables in the REVEAL risk score, such as age and PAH aetiology, are not modifiable. Variables may change over a 12-month period, suggesting that a patient's condition has improved or deteriorated; however, this may be offset by non-modifiable variables, potentially leading to an inaccurate evaluation of the patient's prognosis. With this in mind, non-modifiable variables should be discounted at

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follow-up assessments to provide a more accurate estimation of the patient's condition. A further point to consider is the potential for the under-use of all risk scores amongst some clinicians, who rely more on their own clinical judgement and opinion.

Conclusion

Risk assessment forms an essential part of disease management in PAH and should be performed on a regular basis using a combination of parameters. Regular and consistent multifactorial follow-up is vital to ascertain a patient's response to treatment and to analyse symptom and disease progression. The latest 2015 ESC/ERS PH guidelines include updated recommendations for patient assessment, risk stratification and treatment goals in PAH [6, 7]. Data from patient registries have provided evidence for a number of prognostic factors in PAH [38–43]. Such data have led to the development of two independent risk scoring systems, the French registry equation [8] and the REVEAL risk score [12]. The REVEAL risk score has since been refined further to develop it for use in serial assessments [47] and to make it more useful in general practice. These risk assessment tools have proven to be effective in accurately predicting survival in multiple patient cohorts [10, 46, 49], indicating their prognostic generalisability in different PAH populations. The ability of current tools to evaluate risk over time needs to be validated, and the possible limitations should be taken into consideration in the development of future risk assessment tools. It is important to acknowledge the limitations of the PAH risk assessment methods that are currently available, such as the lack of data to support the use of these tools to assess risk over time. Finally, it is important that risk assessment is considered in conjunction with the patient's current treatment as it provides the framework for continuous re-evaluation and re-adjustment of treatment strategies so that the best outcome for the individual patient can be achieved.

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References

1 Wells BJ, Kattan MW, Cooper GS, *et al.* Colorectal cancer predicted risk online (CRC-PRO) calculator using data from the multi-ethnic cohort study. *J Am Board Fam Med* 2014; 27: 42–55.
2 Stelloo E, Bosse T, Nout RA, *et al.* Refining prognosis and identifying targetable pathways for high-risk endometrial cancer: a TransPORTEC initiative. *Mod Pathol* 2015; 28: 836–844.
3 Cazzoletti L, Corsico AG, Albicini F, *et al.* The course of asthma in young adults: a population-based nine-year follow-up on asthma remission and control. *PLoS One* 2014; 9: e86956.
4 Drazner MH, Velez-Martinez M, Ayers CR, *et al.* Relationship of right- to left-sided ventricular filling pressures in advanced heart failure: insights from the ESCAPE trial. *Circ Heart Fail* 2013; 6: 264–270.
5 McLaughlin VV, Gaine SP, Howard LS, *et al.* Treatment goals of pulmonary hypertension. *J Am Coll Cardiol* 2013; 62: D73–D81.
6 Galiè N, Humbert M, Vachiery JL, *et al.* 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J* 2016; 37: 67–119.
7 Galiè N, Humbert M, Vachiery JL, *et al.* 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2015; 46: 903–975.
8 Humbert M, Sitbon O, Yaici A, *et al.* Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. *Eur Respir J* 2010; 36: 549–555.
9 D'Alonzo GE, Barst RJ, Ayres SM, *et al.* Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med* 1991; 115: 343–349.
10 Benza RL, Gomberg-Maitland M, Miller DP, *et al.* The REVEAL registry risk score calculator in patients newly diagnosed with pulmonary arterial hypertension. *Chest* 2012; 141: 354–362.
11 Humbert M, Sitbon O, Chaouat A, *et al.* Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation* 2010; 122: 156–163.
12 Benza RL, Miller DP, Gomberg-Maitland M, *et al.* Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). *Circulation* 2010; 122: 164–172.
13 Launay D, Sitbon O, Le PJ, *et al.* Long-term outcome of systemic sclerosis-associated pulmonary arterial hypertension treated with bosentan as first-line monotherapy followed or not by the addition of prostanoids or sildenafil. *Rheumatology (Oxford)* 2010; 49: 490–500.
14 Mathai SC, Hassoun PM. Pulmonary arterial hypertension in connective tissue diseases. *Heart Fail Clin* 2012; 8: 413–425.
15 Fisher MR, Mathai SC, Champion HC, *et al.* Clinical differences between idiopathic and scleroderma-related pulmonary hypertension. *Arthritis Rheum* 2006; 54: 3043–3050.
16 Condliffe R, Kiely DG, Peacock AJ, *et al.* Connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era. *Am J Respir Crit Care Med* 2009; 179: 151–157.
17 Evans JD, Girerd B, Montani D, *et al.* BMPR2 mutations and survival in pulmonary arterial hypertension: an individual participant data meta-analysis. *Lancet Respir Med* 2016; 4: 129–137.
18 Farber HW, Miller DP, Poms AD, *et al.* Five-year outcomes of patients enrolled in the REVEAL Registry. *Chest* 2015; 148: 1043–1054.
19 Sitbon O, Humbert M, Nunes H, *et al.* Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol* 2002; 40: 780–788.

20 Ghofrani HA, Grimminger F, Grunig E, *et al.* Predictors of long-term outcomes in patients treated with riociguat for pulmonary arterial hypertension: data from the PATENT-2 open-label, randomised, long-term extension trial. *Lancet Respir Med* 2016; 4: 361–371.
21 Barst RJ, Chung L, Zamanian RT, *et al.* Functional class improvement and three-year survival outcomes in patients with pulmonary arterial hypertension in the REVEAL registry. *Chest* 2013; 144: 160–168.
22 Taichman DB, McGoon MD, Harhay MO, *et al.* Wide variation in clinicians' assessment of New York Heart Association/World Health Organization functional class in patients with pulmonary arterial hypertension. *Mayo Clin Proc* 2009; 84: 586–592.
23 Farber HW, Miller DP, McGoon MD, *et al.* Predicting outcomes in pulmonary arterial hypertension based on the 6-minute walk distance. *J Heart Lung Transplant* 2015; 34: 362–368.
24 Fritz J, Blair C, Oudiz R, *et al.* Baseline and follow-up six minute walk distance and BNP predict 2-year mortality in pulmonary arterial hypertension. *Chest* 2013; 143: 315–323.
25 Savarese G, Paolillo S, Costanzo P, *et al.* Do changes of 6-minute walk distance predict clinical events in patients with pulmonary arterial hypertension? A meta-analysis of 22 randomized trials. *J Am Coll Cardiol* 2012; 60: 1192–1201.
26 Gabler NB, French B, Strom BL, *et al.* Validation of six-minute-walk distance as a surrogate endpoint in pulmonary arterial hypertension trials. *Circulation* 2012; 126: 349–356.
27 Nickel N, Golpon H, Greer M, *et al.* The prognostic impact of follow-up assessments in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J* 2012; 39: 589–596.
28 Chia EM, Lau EM, Xuan W, *et al.* Exercise testing can unmask right ventricular dysfunction in systemic sclerosis patients with normal resting pulmonary artery pressure. *Int J Cardiol* 2016; 204: 179–186.
29 Blumberg FC, Arzt M, Lange T, *et al.* Impact of right ventricular reserve on exercise capacity and survival in patients with pulmonary hypertension. *Eur J Heart Fail* 2013; 15: 771–775.
30 Forfia PR, Fisher MR, Mathai SC, *et al.* Tricuspid annular displacement predicts survival in pulmonary hypertension. *Am J Respir Crit Care Med* 2006; 174: 1034–1041.
31 Peacock AJ, Crawley S, McLure L, *et al.* Changes in right ventricular function measured by cardiac magnetic resonance imaging in patients receiving pulmonary arterial hypertension-targeted therapy: the EURO-MR study. *Circ Cardiovasc Imaging* 2014; 7: 107–114.
32 Swift AJ, Rajaram S, Capener D, *et al.* Longitudinal and transverse right ventricular function in pulmonary hypertension: cardiovascular magnetic resonance imaging study from the ASPIRE registry. *Pulm Circ* 2015; 5: 557–564.
33 Han QJ, Witschey WR, Fang-Yen CM, *et al.* Altered right ventricular kinetic energy work density and viscous energy dissipation in patients with pulmonary arterial hypertension: a pilot study using 4D flow MRI. *PLoS One* 2015; 10: e0138365.
34 van de Veerdonk MC, Kind T, Marcus JT, *et al.* Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. *J Am Coll Cardiol* 2011; 58: 2511–2519.
35 Harbaum L, Hennigs JK, Baumann HJ, *et al.* N-terminal pro-brain natriuretic peptide is a useful prognostic marker in patients with pre-capillary pulmonary hypertension and renal insufficiency. *PLoS One* 2014; 9: e94263.
36 Leuchte HH, El Nounou M, Tuerpe JC, *et al.* N-terminal pro-brain natriuretic peptide and renal insufficiency as predictors of mortality in pulmonary hypertension. *Chest* 2007; 131: 402–409.
37 Halank M, Einsle F, Lehman S, *et al.* Exercise capacity affects quality of life in patients with pulmonary hypertension. *Lung* 2013; 191: 337–343.
38 Humbert M, Sitbon O, Chaouat A, *et al.* Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med* 2006; 173: 1023–1030.
39 Thenappan T, Shah SJ, Rich S, *et al.* A USA-based registry for pulmonary arterial hypertension: 1982–2006. *Eur Respir J* 2007; 30: 1103–1110.
40 Jing ZC, Xu XQ, Han ZY, *et al.* Registry and survival study in Chinese patients with idiopathic and familial pulmonary arterial hypertension. *Chest* 2007; 132: 373–379.
41 Thenappan T, Shah SJ, Rich S, *et al.* Survival in pulmonary arterial hypertension: a reappraisal of the NIH risk stratification equation. *Eur Respir J* 2010; 35: 1079–1087.
42 Peacock AJ, Murphy NF, McMurray JJ, *et al.* An epidemiological study of pulmonary arterial hypertension. *Eur Respir J* 2007; 30: 104–109.
43 McGoon MD, Krichman A, Farber HW, *et al.* Design of the REVEAL registry for US patients with pulmonary arterial hypertension. *Mayo Clin Proc* 2008; 83: 923–931.
44 Badesch DB, Raskob GE, Elliott CG, *et al.* Pulmonary arterial hypertension: baseline characteristics from the REVEAL registry. *Chest* 2010; 137: 376–387.
45 Sitbon O, Sattler C, Bertoletti L, *et al.* Initial dual oral combination therapy in pulmonary arterial hypertension. *Eur Respir J* 2016; 47: 1727–1736.
46 Sitbon O, Jais X, Savale L, *et al.* Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study. *Eur Respir J* 2014; 43: 1691–1697.
47 Benza RL, Miller DP, Foreman AJ, *et al.* Prognostic implications of serial risk score assessments in patients with pulmonary arterial hypertension: a Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL) analysis. *J Heart Lung Transplant* 2015; 34: 356–361.
48 Kane GC, Maradit-Kremers H, Slusser JP, *et al.* Integration of clinical and hemodynamic parameters in the prediction of long-term survival in patients with pulmonary arterial hypertension. *Chest* 2011; 139: 1285–1293.
49 Sitbon O, Benza RL, Badesch DB, *et al.* Validation of two predictive models for survival in pulmonary arterial hypertension. *Eur Respir J* 2015; 46: 152–164.
50 Simonneau G, Channick RN, Delcroix M, *et al.* Incident and prevalent cohorts with pulmonary arterial hypertension: insight from SERAPHIN. *Eur Respir J* 2015; 46: 1711–1720.
51 Rubin LJ, Simonneau G, Badesch D, *et al.* The study of risk in pulmonary arterial hypertension. *Eur Respir Rev* 2012; 21: 234–238.
52 Lee KL, Pryor DB, Harrell FE Jr, *et al.* Predicting outcome in coronary disease. Statistical models *versus* expert clinicians. *Am J Med* 1986; 80: 553–560.

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