Development of prognostic tools in pulmonary arterial hypertension: Lessons from modern day registries

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Summary
Pulmonary arterial hypertension (PAH), classified as group 1 pulmonary hypertension (PH), is characterised by proliferative and fibrotic changes in the small pulmonary arteries, leading to increased resistance and pressure, vessel obstruction, right-sided ventricular failure, and death. Identification of factors that affect patient survival is important to improve patient management and outcomes. The first registry to evaluate survival and develop a prognostic model was the National Institutes of Health (NIH) registry in 1981. Importantly this prognostic model is based on data collected prior to availability of PAH-targeted therapies and does not reflect survival rates for treated patients. Since the 1980s, however, four modern registries of PAH now exist which compensate for the NIH equations shortcomings and include the French National registry, Pulmonary Hypertension Connection registry, the Mayo registry, and the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL). The similarities and differences in these registries are highlighted in this review and although similar in many respects, the four registries vary in patient population, including the numbers of newly and previously diagnosed patients, as well as the era of observation, period of survival, and timing of assessment of potential predictive factors. Despite this, the predictive factors identified in each registry and described in detail within the body of this manuscript share surprising homology in that disease aetiology, patient gender and factors reflective of right heart failure are integral in depicting survival. Future modifications of modern prognostic equations should be an ongoing goal of the PAH community in order to provide increased accuracy with identification of novel risk factors and prediction of disease course.

Keywords
Prognosis, pulmonary arterial hypertension, REVEAL, risk calculator, survival prediction

Introduction
Pulmonary arterial hypertension (PAH), classified as group 1 pulmonary hypertension (PH), is characterised by proliferative and fibrotic changes in the small pulmonary arteries, leading to increased resistance and pressure, vessel obstruction, right-sided ventricular failure, and death (1). Despite recent progress in the treatment of PAH, patient outcomes remain poor (2). Consequently, improvements in the diagnosis and management of patients with PAH are essential. Interestingly, subtypes of PAH share a similar underlying pathology, suggesting that parameters capable of measuring disease progression might be applicable across PAH subgroups, allowing the development of comprehensive therapeutic tools. Documentation of clinical changes and outcomes associated with PAH permits the development of models that predict disease progression and survival.

The ability to identify and evaluate factors that affect survival in patients with PAH remains of critical interest to clinicians because it facilitates clinical care and directs research. With this as a key objective, the first of several registries was initiated in 1981, the ground-breaking Patient Registry for the Characterization of Primary Pulmonary Hypertension supported by the National Institutes of Health (NIH) and the National Heart, Lung, and Blood Institute (NHLBI) – known as the NIH registry (3). The NIH registry enrolled patients with primary PH, which, at that time, included patients with idiopathic PAH (IPAH), familial PAH (FPAH), or anorexigen-induced PAH (anorexigen-APAH) (3). NIH registry data were used to predict outcomes in those patients, resulting in the development of a prognostic equation that has facilitated the individualisation and implementation of treatment regimens (4). Simply put, the ability to predict a patient’s morbidity or imminent mortality provides a prompt for the clinician to escalate therapy or to refer for transplant and forewarns the patient and his/her family. Although shown to be a powerful tool for improving our understanding of PAH, interpretations of data from the NIH registry have become limited by the era in which these
data were collected, i.e. 30 years ago and prior to the availability of approved pulmonary vascular-targeted therapies. In addition, due to changes in PAH classification since the NIH registry, the NIH prognostic equation (4) may not be applicable to the present classification of group 1 PH as a whole (5) and may not accurately reflect current survival rates (6). The NIH equation should no longer be the gold standard to predict survival nor used as a basis for assessing drug efficacy. Thus, the PAH community has sought to improve epidemiologic data with newer registries, with the aim of producing a prognostic equation that can be used in all patients with PAH at any time during their disease history.

Among a number of important national PAH registries (7–12), four modern registries acquiring data on the management and treatment of patients with PAH have evaluated and developed improved prognostic equations as suggested by the original NIH data (3). The largest of these modern registries is the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) (6, 13). Three others include the ItinerAir-HTAP French Network on Pulmonary Hypertension registry (French registry) (14–16), the Pulmonary Hypertension Connection registry (PHC registry) (17, 18), and most recently, the Mayo Clinic PAH registry (Mayo registry) (19). The objective of this article is to review recent improvements in the methods and tools employed to predict survival outcomes and risk in patients with PAH by comparing REVEAL with the other three modern registries.

Modern registries

The major purposes of disease registries are to describe the population (phenotype and/or genotype), disease frequency (incidence/prevalence), outcome (morbidity/mortality) and risk factors for that outcome. The latter two factors — outcome/survival and the development of methods of assessing risk of adverse outcome are of increasing interest as treatment options for patients have increased. There are therefore several registries which have generated predictive models that are suitable for the modern management era. Table 1 shows the characteristics of the four largest modern registries evaluating patients with group 1 PH: the French registry, a 55-centre registry initiated in 2002 (14, 15), the PHC registry, a single-centre registry initiated in 2004 (18), REVEAL, a 55-centre, observational, US-based registry initiated in 2006 (6, 13), and the Mayo clinic single-centre, retrospective registry (19). These registries differ in size, duration of recruitment (the PHC registry has accrued patients since 1986), site (local registry PHC; US-wide REVEAL; European /French). Differences in these registries and their assessment of outcomes therefore can reflect all these variables. What is needed is a reliable survival/outcome prediction model that is generalisable to all populations and also one that maintains its validity (reliably predicts what it is supposed to predict) even in populations that differ by nationality, and general physical characteristics.

The registries differ from one another in patient population, period of survival, and timing of assessment of predictive factors (Table 1). Irrespective of differences in analyses and predictive factors identified, modern registries have demonstrated an improvement in the survival of patients with PAH compared with that reported at the time of the NIH registry (6, 14, 18).

Registry demographics

French Registry

The French National Registry spearheaded by Humbert et al reported results that were obtained for 674 patients with PAH comprising 17 pulmonary vascular centres (14, 15). To maintain a homogenous population, the registry was restricted to PAH and excluded patients with severe pulmonary function abnormalities (denoted as forced vital capacity, total lung capacity, or forced expiratory volume in 1 second [s] <60%). This registry has made a more comprehensive analysis of the subgroup of 354 patients with IPAH, FPAH, or anorexigen-APAH. Patients who were diagnosed >3 years prior to enrolment were excluded from the final analysis cohort (n=164). In the French registry, PAH was defined as mean pulmonary artery pressure (mPAP) ≥25 mmHg at rest and pulmonary capillary wedge pressure (PCWP) ≤15 mmHg during right-sided heart catheterisation (RHC). Patients were followed-up prospectively for three years after enrolment, and survival at one, two, and three years was evaluated in the newly diagnosed (diagnosed within three months of study inclusion, n=54) and in the combined newly and previously diagnosed (diagnosed within three years of study entry, n=190) populations, with diagnostic RHC serving as the baseline time point (14). Left truncation was employed to mitigate any survivor bias introduced by the inclusion of previously diagnosed patients.

PHC Registry

The PHC registry initiated in 2004 in Chicago comprised 576 patients with newly and previously diagnosed IPAH, FPAH, or anorexigen-APAH (Fig. 3; Table 2) (18). This longitudinal registry was formulated to collect specific variables on every patient in the authors’ practice, which was established sequentially at three university medical centres in Chicago, since 1982. Consequently, from 1982–2004, patients were entered into the database retrospectively; from 2004–2007, they were entered into the database prospectively. The analysis included adult patients (aged ≥18 years at referral) diagnosed with PAH defined as mPAP >25 mmHg at rest with PCWP <15 mmHg. Other categories of PAH were excluded via clinical evaluation and objective tests. To facilitate comparison to the NIH registry, 52 patients on approved PAH therapy at referral were excluded from the study population. Additionally, 26 patients who were diagnosed with PAH prior to 1991 were excluded due to their potential inclusion in the NIH registry. In the final study population, one-, three-, and five-year survival were evaluated.
REVEAL (13) provides current information regarding demographics and treatment in 3,515 patients with PAH enrolled from March 2006 to December 2009, with follow-up planned to 2014 (6, 13, 20). Eligible patients met the following catheterisation criteria: mPAP >25 mmHg at rest or >30 mmHg with exercise; PCWP or left ventricular end-diastolic pressure (LVEDP) ≤15 mmHg; and pulmonary vascular resistance (PVR) ≥240 dynes•cm⁻⁵ (i.e. ≥3.0 Wood units). In addition, the wedge criteria were expanded to include patients with PCWP or LVEDP of 16–18 mmHg to permit analyses of both patients with traditional PAH (PCWP or LVEDP ≤15 mmHg) and patients meeting a wider definition (PCWP or LVEDP of 16–18 mmHg) (13, 20, 21). The classification of PAH used in REVEAL is broader than that used at the time of the NIH registry (20). Although REVEAL included pulmonary veno-occlusive disease and pulmonary capillary haemangiomatosis, these conditions were subsequently removed from the classification of group 1 PH to standardise the group (5). Both incident and prevalent patients were included in REVEAL. Although the majority of patients were prevalent, a sufficient number were incident to allow assessment of prediction models in both groups.

Mayo Registry

The Mayo registry, which was designed to evaluate survival patterns in PAH and to identify clinical and haemodynamic factors that influence survival (19), retrospectively enrolled all sequential adult (218 years) patients diagnosed with group 1 PH (mPAP ≥25 mmHg in the setting of increased PVR) seen between January 1, 1995 and December 31, 2004 at the Mayo Clinic specialty PH clinic (19).

Table 1: Characteristics of the populations used for prognostic assessment in the four modern registries of patients with PAH.
Use of modern registry data to predict survival

French Registry

In the French registry, patients with previously diagnosed “prevalent” IPAH, FPAH, and anorexigen-PAH had better long-term survival compared with newly diagnosed “incident” patients, emphasizing the relevance of survivor biases in prevalent PAH populations (16). In the combined newly and previously diagnosed patient population (n=190), with diagnostic RHC serving as the baseline time point, individual survival analysis identified female sex, New York Heart Association (NYHA) functional class (FC) III/II, greater 6 minute walk distance (6MWD), lower mean right-sided atrial pressure (mRAP), and higher cardiac output (CO) as significantly and positively associated with survival (14). Stepwise-forward multivariable Cox proportional hazard analysis was used to examine the independent effect on survival of selected variables (those with p≤0.20 from individual analysis), controlling for possible confounders. The stepwise addition of covariates was established via examinations of significant (p<0.05) differences in log likelihoods between models. The multivariable analysis also investigated the prognostic effect of potential, clinically important two-way interactions (NYHA FC with 6MWD and age with sex). Multivariable analysis showed that female sex, greater 6MWD, and higher CO were jointly significantly associated with improved survival, whereas male sex, reduced right-sided ventricular haemodynamic function, and exercise limitation demonstrated a close association with mortality (Fig. 2; Table 2). French registry studies resulted in development of a new prognostic equation. From a statistical standpoint, it is important to note inclusion in the combined analysis cohort of factors with an independent effect on survival (sex, CO, and 6MWD) (16).

PHC Registry

In the PHC registry, survival rates were calculated using Kaplan-Meier methodology and standard analyses. The date of baseline RHC was denoted the date of enrolment. For patients who did not undergo initial RHC, the date of referral was considered the date of enrolment.

Differences were assessed before and after 2002 because bosentan, the first oral therapy for PAH, was approved for use in the US in November 2001. Prior to the approval of bosentan, treatment of PAH consisted of conventional therapy and intravenous epoprostenol. In the total PHC PAH cohort, the subgroup of patients with IPAH, FPAH, or anorexigen-PAH was used as the reference group to which all other aetiologies of PAH were compared (18). For the final multivariable analyses, variables with p≤0.1 according to the univariate analysis were retained. A likelihood ratio (LR) analysis was performed versus the model regarding age, CTD aetiology, and NYHA FC alone, and multivariate analysis identified a combination of age, CTD aetiology, FC, and mRAP as the best model to predict survival (Fig. 3; Table 2). FC and exercise capacity were significantly correlated (correlation coefficient = 0.73; p<0.0001); thus, only FC was retained in the final models to avoid multicollinearity. Separate models were created for each haemodynamic variable.

PHC registry studies resulted in development of a new prognostic equation using a Weibull model first (which assumes that the cumulative hazards ratio is a linear function of time), followed by an exponential regression model for ease of use (22). Since the PHC data was considered adequate for only a ten-year survival period, and the exponential model yielded similar results, the exponential model was adopted to allow for an indefinite survival prediction time.

From a statistical standpoint, it is important to note that the group predetermined a priori that the three haemodynamic predictors (mPAP, mRAP, and cardiac index [CI]) from the NIH model were clinically relevant for inclusion in the model. Variables that demonstrated statistical significance in a univariate analysis compared with these three haemodynamic variables were used to complete the model. Following backward elimination analyses similar to those used to derive the final NIH equation, only mPAP, mRAP, and CI were retained in the final model; all three were statistically significant. The predicted survival calculated using the new equation was similar to the survival reported in other PAH cohorts (18).

REVEAL

Predictors of 1-year survival in patients enrolled in REVEAL were determined using data from 2,716 consecutively enrolled patients (6). Multivariable analysis using a Cox proportional hazard model demonstrated an independent association of the following variables with a >2-fold increase in the hazard ratio (HR): PoPH, family history of PAH, male sex, age >60 years, modified NYHA FC IV, and PVR >32 Wood units (Fig. 1) (6). Four variables were also associated with an increased likelihood of one-year survival: modified NYHA/WHO FC I, 6MWD ≥440 m, brain natriuretic peptide (BNP) <50 pg/ml, and percent-predicted diffusion capacity of carbon monoxide (DLCO) ≥80%. Nineteen independent predictors of survival were identified (Fig. 1) and used to generate a prognostic equation based on the Cox proportional hazard multivariable analysis. Multiple sensitivity analyses were conducted (1) using β levels of 0.2, 0.1, 0.01, and 0.001 for model entry, (2) censoring at time of transplantation, and (3) modelling survival from time of diagnosis rather than time of enrolment. Parameters significantly associated with one-year survival only in univariable analyses included the Borg dyspnoea scale, right-sided ventricular dysfunction, PVR index, PCWP, CI, mPAP, and total serum bilirubin. Candidate predictor variables that were not significant at the univariable level included the Tei index, vasoreactivity, race, newly diagnosed PAH, and income. Missing Borg scale and missing PVR index data were both associated with lower-than-average observed survival.
survival and were therefore considered candidate predictor vari-
ables. The inclusion of multiple, incremental clinical measures in
the equation make it a better predictor of survival compared with
the assessment of each measure individually. The final prognostic
equation contains 19 predictive factors (Fig. 1; Table 2). Each
of these factors was found to be a significant predictor of patient
outcome, even after adjusting for the other 18 terms included
in the model. Because the average patient had data available for 16
of the 19 potential risk factors, patients with missing data were in-
cluded in the reference category for that specific risk factor. This
strategy allowed inclusion of all patients in the model, making it
possible to extrapolate the findings to clinical practice (6, 19).

Mayo Registry

In the Mayo registry, the REVEAL risk score was utilised to evaluate
prognosis (19). Survival estimates and comparisons among groups
were performed using Kaplan-Meier methodology; and predictors
of mortality were evaluated using Cox proportional hazards regres-
sion models (19). Age- and sex-adjusted predictors of overall mor-
tality included male sex (HR, 0.77; 95% confidence interval [CI],
0.58–0.99; p < 0.05), increasing age (mortality increased 27% with
every decade [HR, 1.27; 95% CI, 1.16–1.39; p < 0.0001]), and pres-
ence of CTD (two-fold higher risk of death than IPAH or PAH
[HR, 2.08; 95% CI, 1.57–2.73; p < 0.0001]). NYHA FC was also sig-
nificantly associated with mortality; there was a 69% increase in risk
per class (HR, 1.69; 95% CI, 1.39–2.06). Furthermore, serum creati-
nine levels ≥1.5 mg/dl were associated with a 3.64-fold higher mor-
tality compared with levels <1.0 mg/dl and a 2.70-fold higher mor-
tality compared with levels between 1 and 1.4 mg/dl. Other cor-
relates of mortality included right atrium enlargement, right-sided
ventricular (RV) dysfunction, haemodynamic findings at RHC, CI,
and RAP. After adjustment for age, sex, PAH aetiology, and FC, only
RAP and severe right-sided atrial enlargement, RV enlargement or
dysfunction, or severe tricuspid valve regurgitation remained sig-
nificant predictors of mortality (19).

Incremental modelling was performed to produce an index
with the highest predictive capability: the highest c-index achieved
was 0.84 using the following factors: FC, age, sex, PAH aetiology,
6MWD, haemoglobin and serum creatinine, %DLCO, and echocardi-
ogram (19).

Comparison of registries

A comparison of the 4 registries revealed remarkable similarities
among the findings, including the identification of FC (6, 17, 19)
and 6MWD (6, 14, 19) as strong prognostic factors and the import-
ance of haemodynamic parameters (6, 14, 18, 23). The French
and PHC registries limited the analysis to IPAH, FPAH, and anor-
exigen-APAH, whereas the Mayo registry and REVEAL included
all types of PAH. There were some notable differences observed be-
tween patients enrolled in REVEAL and the population studied in
the NIH registry; at diagnosis, REVEAL patients were older, more
likely to be female, and more likely to be obese (21).

A comparison of the French registry and REVEAL analyses (23)
showed that, despite differences between the two registries (23),
there were remarkable similarities in the findings, including the
identification of FC and 6MWD as strong prognostic factors and
the acknowledgement of the importance of haemodynamic pa-
rameters. Similar to the NIH registry, REVEAL also comprised a
higher proportion of obese patients compared with the French
registry, although the prevalence of obesity in each registry re-
lected that seen in the general US and French populations, re-
spectively (21).

Excluding the Mayo registry, all of the registries included a large
proportion of patients who were enrolled well into their disease
course (previously diagnosed patients). For example, the com-
bined analysis population of 190 patients in the French registry
included only 56 newly diagnosed patients defined as patients with
a diagnosis of PAH that was confirmed by RHC during the recruit-
ment phase of the study; in contrast, 70% (134/190) were pre-
viously diagnosed patients (defined as those who were diagnosed
before the start of the study but ≤36 months before) (14).

In the Mayo registry, overall disease severity was greater than
that observed in the other registries including REVEAL (71% WHO
FC II/III in Mayo (19) vs. 53.7% in REVEAL) (6), resulting in
lower one-year survival rates (77.3% in Mayo vs. 84.7% in RE-

Table 2: Prognostic equations for probability of survival in PAH.

<table>
<thead>
<tr>
<th>Registry</th>
<th>Equation</th>
<th>C-Index</th>
</tr>
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<tbody>
<tr>
<td>NIH(4)</td>
<td>$P(t) = \exp\left(\alpha + \beta \cdot \text{AGE} + \gamma \cdot \text{Sex} + \delta \cdot \text{PAH Aetiology} + \omega \cdot \text{6MWD} + \eta \cdot \text{Hemoglobin} + \zeta \cdot \text{Serum Creatinine} + \xi \cdot \text{DLCO} + \chi \cdot \text{Echocardiogram}\right)$</td>
<td>0.588</td>
</tr>
<tr>
<td>French(14)</td>
<td>$P(t) = \exp\left(\alpha + \beta \cdot \text{AGE} + \gamma \cdot \text{Sex} + \delta \cdot \text{PAH Aetiology} + \omega \cdot \text{6MWD} + \eta \cdot \text{Hemoglobin} + \zeta \cdot \text{Serum Creatinine} + \xi \cdot \text{DLCO} + \chi \cdot \text{Echocardiogram}\right)$</td>
<td>0.57</td>
</tr>
<tr>
<td>PHC(18)</td>
<td>$P(t) = 1 - \exp\left(-\text{FC} \cdot \text{AGE} \cdot \text{Sex} \cdot \text{PAH Aetiology} \cdot \text{6MWD} \cdot \text{Hemoglobin} \cdot \text{Serum Creatinine} \cdot \text{DLCO} \cdot \text{Echocardiogram}\right)$</td>
<td>Not calculated</td>
</tr>
<tr>
<td>REVEAL(6)</td>
<td>$P(1-year) = 1 - \exp\left(-\text{FC} \cdot \text{AGE} \cdot \text{Sex} \cdot \text{PAH Aetiology} \cdot \text{6MWD} \cdot \text{Hemoglobin} \cdot \text{Serum Creatinine} \cdot \text{DLCO} \cdot \text{Echocardiogram}\right)$</td>
<td>0.772</td>
</tr>
<tr>
<td>Mayo registry(19)</td>
<td>Incremental modelling $P(t) = \exp\left(\alpha + \beta \cdot \text{AGE} + \gamma \cdot \text{Sex} + \delta \cdot \text{PAH Aetiology} + \omega \cdot \text{6MWD} + \eta \cdot \text{Hemoglobin} + \zeta \cdot \text{Serum Creatinine} + \xi \cdot \text{DLCO} + \chi \cdot \text{Echocardiogram}\right)$</td>
<td>0.84</td>
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</table>
VEAL). This discrepancy was not surprising because the Mayo registry included all patients seen at a single tertiary referral centre (6, 19). A higher mortality was also expected in the Mayo registry because it included only newly diagnosed patients and was not subject to the survival bias inherent in the other three registries (19).

**Discriminatory power of prognostic equations**

The discriminatory power of the prognostic equation can be shown by calculating the probability of concordance (c-index), which is defined as the probability that a randomly chosen survivor has a lower predicted risk of death than a randomly chosen in-

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**Figure 1:** Cox proportional hazards estimates for multivariable model of survival, limited to terms in the final stepwise model. Reproduced with permission from Benza et al. (6). 6MWD, 6-minute walk test distance; CTD-APAH, connective tissue disease associated with PAH; BNP, brain natriuretic peptide; BP, blood pressure; bpm, beats per minute; DLCO, percent-predicted diffusion capacity of carbon monoxide; ECHO, echocardiogram; FPAH, familial PAH; HR, hazard ratio; mRAP, mean right-sided atrial pressure; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PoPH, portopulmonary hypertension; RHC, right-sided heart catheterisation; WHO, World Health Organization.

*Reference category: NYHA/WHO functional class II or missing. †If N-terminal proBNP is available and BNP is not, listed cut points are replaced with <300 pg/ml and >1,500 pg/ml. ‡Restricted to tests performed within 1 year of enrolment; otherwise, the indicator is set to 0.
dividual who died (24). The closer the c-index is to the maximum value of 1.0, the better the model discriminates between patients who are likely to die versus those who are likely to survive. The c-index of 0.772 reported for the total REVEAL cohort model is comparable to c-indices associated with other widely used prognostic equations. For example, the c-index reported for the Seattle Heart Failure model was 0.725 in the derivation cohort (25). In addition, in cardiac transplant candidates, Aaronson et al. reported c-indices of 0.74 and 0.69 in the derivation and validation cohorts, respectively (26). Because those studies evaluated disease conditions other than PAH, we also calculated the c-index for the NIH equation for comparison with REVEAL.

The REVEAL equation demonstrated a superior ability to discriminate low- and high-risk patients accurately compared with the NIH survival equation (c-index 0.772 vs. 0.588) (6). The results obtained for the NIH equation reflected only a small improvement (0.088) over a c-index achieved via random chance (0.5). By contrast, the REVEAL equation showed an improvement over a random chance of 0.272 – approximately three times greater than that determined for the NIH equation (6). Importantly, the REVEAL equation was capable of discriminating low- and high-risk patients in the entire cohort and in the following subgroups: maximally treated patients (i.e. on intravenous prostacyclin analogues or combination PAH therapies); newly diagnosed patients; PCWP <12 mmHg; and IPAH, FPAH, or other forms of PAH (6). Consistently, the newer model provided better risk discrimination than did the NIH equation, i.e. the resultant estimates corresponded more accurately to actual outcomes. By comparison, the c-index calculated for the French registry model was 0.57 (95% CI, 0.29–0.82) (14). The better discriminatory ability of the REVEAL model may be because it is derived from a multitude of covariates may limit some of the biases associated with its derivation in incident and prevalent cases. No c-index was calculated for the PHC equation.

To achieve an equation that is applicable to all patients at any time point during their disease progression, irrespective of the availability of data for all of the tests, cut-off points were used for continuous variables such as 6MWD and BNP. Some of the cut-off points were extreme but were driven by the data and not by clinical relevance. For example, some variables, such as mRAP or PVR, exhibited a threshold effect such that these variables only provided prognostic value (after adjustment for all other variables present in the model) after the achievement of a specific threshold. It is important to note that the cut-off points cannot be used to interpret individual tests in isolation, but analysis and weighting of all 19 factors together can determine those that are important in the context of the other 18 cut-off points. There is a possibility that some thresholds would be different if two- or three-year outcomes had been used instead of one year.

Limitations of the registries

The French, PHC, and REVEAL registries are limited by survival and immortal time biases. Immortal time, a form of survival bias, refers to a period of cohort follow-up in a time-to-event analysis during which the outcome under study could not occur, i.e. only

Figure 2: Multivariable Cox proportional hazard model of survival in the French Registry. Adapted with permission from Humbert et al. (14). HR, hazard ratio. Variables that were considered in this model (p ≤ 0.2) were age quartiles (≤39, 40–52, 53–62, and ≥63 years), sex, 6-minute walk test distance (6MWD), New York Heart Association (NYHA) functional class (FC) (I/II, III, and IV), right-sided atrial pressure, cardiac output, cardiac index, pulmonary vascular resistance, pulmonary vascular resistance index, diagnosis (idiopathic PAH, familial PAH, and anorexigen-associated PAH), and interaction covariates (6MWD x NYHA FC I, 6MWD x NYHA FC II, sex x age quartile 1, sex x age quartile 2, sex x age quartile 3). Being female, having a greater 6MWD, and having higher cardiac output were significantly associated with improved survival.
patients who survived could be enrolled into the registry (27); this is an inherent limitation in all registries that attempt to define survival from a time point prior to enrolment when patient data are gathered retrospectively and enrolment can be many months or years after diagnosis. Left truncation delayed-entry model analyses were performed to correct for immortal time from time of diagnosis (28), yielding similar results for prognostic factors available at diagnosis and enrolment (6). All of the registries excluding the Mayo registry included previously diagnosed patients. The French registry and REVEAL used left truncation to address survival bias.

Figure 3: Multivariable Cox proportional model of survival in the Pulmonary Hypertension Connection (PHC) registry. Adapted with permission from Thenappan et al. (18). CI, cardiac index; CTD, connective tissue disease; FC, functional class; LR, likelihood ratio; mPAP, mean pulmonary artery pressure; RAP, right-sided atrial pressure. 95% confidence intervals in parentheses. LR analysis was performed versus the model with age, CTD aetiology, and FC alone. Model 1, including age, CTD aetiology, FC, and RAP is the best model. Adding CI does not help discriminate further (LR test for model 1 with CI vs. model 1 without CI: p=0.47). A) Model 1 independent variables: age at diagnosis, CTD aetiology, and FC (p=0.013 on LR analysis). B) Model 2 independent variables: age at diagnosis, CTD aetiology, FC, and mPAP (p=0.35 on LR analysis). C) Model 3 independent variables: age at diagnosis, CTD aetiology, FC, and CI (p=0.013 on LR analysis).
and all registries reported a separate analysis of only newly diagnosed patients and patients with consistent results (6, 14, 18). Consequently, survival bias may have led to an underestimation of mortality in these registries due to the absence of patients who died prior to enrolment and the higher mortality rates observed in PAH during early stages of the disease (14, 23). The PHC also addressed survival bias. Since there was no information about exact duration of PH symptoms prior to catheterisation for those given a diagnosis prior to the catheterisation at the tertiary centre it was not possible to use left truncation in the analysis. But, patients who were already on a PAH treatment at referral were excluded, which in effect excluded prevalent cases.

Missing data associated with registry data collection were a limitation in all registries. In addition, many known predictors of survival were not captured, including tricuspid annular plane systolic excursion (TAPSE), serum sodium levels, and quantitative measures of renal and hepatic function. These parameters will likely require a more focused examination in future studies. In addition, serial assessments were not performed, and thus, predictions of disease trajectory over time could not be established (29).

Finally, none of the reported survival prediction models accounted for the effects of modern PAH-specific therapies – treatment type, incremental medication use, or changes in treatment – on patient survival. Nonetheless, one of the strengths of the REVEAL equation is its quite robust ability to predict outcome regardless of what treatment a patient was receiving at the time of risk calculation.

### French Registry

Additional limitations were restriction of the evaluated population to IPAH/FPAH/anorexigen-APAH and to selected pulmonary vascular centres, which may preclude generalisation of the results to the broader PAH population (14). However, it should be emphasised that PAH management in European countries like France and the United Kingdom is only conducted in specialised centres (1). Of note, survival analysis of the whole 674 patients with PAH from the French registry indicated that causes of PAH and age at PAH diagnosis were associated with outcomes (worse survival was observed in patients with CTD-APAH and age >51 years, and better survival in patients with CHD-APAH) (16).

### PHC Registry

The PHC Registry had limitations associated with retrospective data collection. This registry was initiated in 2004, and thus the majority of patients were entered into the registry retrospectively. Furthermore, a single tertiary referral practice provided the care for all of the patients, potentially impairing the generalisability of the findings (18).

### REVEAL

All relevant measurements were collected at the mandated study visits, and thus the average patient had data available for only 16 of the 19 potential risk factors. Patients with missing data for a given test associated only with an average survival were included in the reference category, and the results suggest that differences in power of the prognostic equation between patients with versus without available test data are minimal. Thus, physicians may estimate the one-year survival of patients who lack some of the predictive factor data in the equation (6).

### Mayo Registry

The Mayo registry was retrospective, based on data from a single centre, and was limited by a lack of data for some study parameters in certain patients. Therefore, an independent, prospective multicentre study is required to validate these data. Other limitations include the exclusion of patients diagnosed between 2005 and 2009 to analyse the prognostic value of factors on five-year survival and the changes in standard treatment during the enrolment period; although recently published, the Mayo cohort preceded that of REVEAL and, therefore, included both patients on intravenous prostanoid therapy and on oral therapies. The lack of oral therapies in some patients may have negatively affected outcomes.

### Development and validation of risk score calculators

The prognostic equations developed based on REVEAL, the French registry, and the PHC registry all reflect complementary algorithms that can be used concomitantly in clinical practice. For example, the French, PHC and REVEAL equations are effective tools to predict survival at time of diagnosis. In addition, the utility of the REVEAL equation for serial assessments is currently being evaluated in patients with PAH. Though capable of providing an accurate assessment of survival of patients with PAH in the era of modern treatment strategies, the prognostic equations can be challenging to apply immediately to a patient during a clinic visit. Importantly, the French registry equation is not used by clinicians from the French Network to predict individual patient outcomes but is used as a comparator for analysis of survival in novel PAH cohorts, thus assisting in the study of epidemiological trends at a national level.

The REVEAL risk score calculator is a simple calculator that has been developed for practical daily clinical use based on the multivariable Cox proportional hazard model and derived by assigning weighted values for variables that were independent prognosticators of survival in the model development cohort (Fig. 4). Validation of the calculator and comparison with the REVEAL prognostic equation for predicting survival was performed in a
validation cohort comprising 504 patients with newly diagnosed PAH who were enrolled in the registry between September 2007 and December 2009 and who met established haemodynamic criteria (30).

Compared with the model development cohort (n=2,716), the validation cohort included a greater proportion of patients who were classified as NYHA FC III or IV and a similar proportion of patients with IPAH. The risk score calculator was tested using the validation cohort and provided results consistent with the observed one-year survival rates in each of the five risk strata assessed (Fig. 5). In addition, the c-indices calculated for the survival equation were 0.726 for the overall validation cohort and 0.770 for the subgroup of patients with IPAH. The bias-corrected c-index for the risk calculator in the model development cohort was 0.735, demonstrating its similar discriminatory ability to the complete prognostic equation (0.772) (6, 30).

The c-index determined for the risk calculator in the model development cohort was 0.724 (30). To confirm the utility of the risk score calculator in all patients with PAH, its sensitivity was further analysed in a subset of 158 patients who were enrolled within three days of diagnosis and in all REVEAL patients during the second year of follow-up. The results for the former patient subset were similar to those obtained for the remainder of the cohort, thus confirming the applicability of the calculator in newly diagnosed indi-

### REVEAL PAH Risk Score

<table>
<thead>
<tr>
<th>WHO Group I Subgroup</th>
<th>APAH-CRD</th>
<th>APAH-IPAH</th>
<th>PPAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal insufficiency</td>
<td>+1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males Age 60 yrs</td>
<td>+2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NYHA/WHO Functional Class</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP&lt;110 mm Hg</td>
<td>+1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR&lt;92 BPM</td>
<td>+1</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Vital Signs</th>
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<th>&lt;140 m</th>
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</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 pg/mL</td>
<td>-1</td>
<td>+1</td>
<td></td>
</tr>
<tr>
<td>&gt;180 pg/mL</td>
<td>+1</td>
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<table>
<thead>
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<tbody>
<tr>
<td>% pred. DLco&lt;80</td>
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<tr>
<td>% pred. DLco&lt;50</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Pulmonary Function Test</th>
<th>mRAP&lt;50 mm Hg within 1yr</th>
<th>PVR&lt;32 Wood units</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+1</td>
<td>+2</td>
</tr>
</tbody>
</table>

**SUM OF ABOVE**

\[ +6 \]

**RISK SCORE**

---

**Figure 4: REVEAL PAH risk score calculator.**

Reprinted with permission from Benza et al. (30). Calculated risk scores can range from 0 (lowest risk) to 22 (highest risk). APAH, associated PAH; BNP, brain natriuretic peptide; BPM, beats per minute; CTD, connective tissue disease; DLco%, percent-predicted diffusion capacity of carbon monoxide; FPAH, familial PAH; HR, heart rate; mRAP, mean right-sided atrial pressure; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PoPH, portopulmonary hypertension; PVR, pulmonary vascular resistance; SBP, systolic blood pressure; WHO, World Health Organization.
viduals. In the latter group, patients who were predicted to have low, average, moderately high, high, or very high risk demonstrated an observed survival of 97.2%, 92.6%, 84.6%, 73.3%, and 52.3% at one year, respectively (30).

The sensitivity of the REVEAL risk score calculator has been further confirmed in the Mayo Registry (19), where it demonstrated a c-index of 0.71 in the overall population and of 0.70 in patients with IPAH/FPAH/anorexigen-APAH (19). Comparison of c-indices from a range of mortality models using the Mayo PAH data showed that, although simple and easy to use, the REVEAL score was more accurate than FC alone (c-index of 0.71 and 0.60, respectively) and only slightly less accurate than several more complicated models that incorporate all available data (19). Interestingly, the updated NIH equation was also tested using the Mayo IPAH/FPAH/anorexigen-APAH subgroup, and although it also predicted survival over the longer term, it was less accurate (c-index of 0.66) than the REVEAL risk score calculator (19).

Both the PHC equation and the French equation accurately predicted survival in IPAH/FPAH/anorexigen-APAH patients in a large prospective cohort of patients enrolled in four double-blind randomised controlled trials and their associated open-label extension arms (31). However, neither of these equations nor the NIH equation accurately predicted individual survival with strong reliability. Taken together, these validations suggest that all current models can be used to estimate cohort survival but further study is needed before they can be confidently used for individual assessment over time.

**Future directions**

Several outstanding questions remain regarding all predictive models. Further assessments are clearly needed to determine whether they are effective in predicting individual patient outcomes or whether their utility is restricted to cohort analyses. The use of these models in clinical trials as an endpoint or for risk stratification is appealing and should be investigated in future studies. All models are based on the most recent patient assessment, excluding the trajectory of the patient’s condition or any changes occurring over the course of the disease. Thus, changes in a given patient over time cannot yet be determined. For example, if the 6MWD of a patient decreases from 500 m to 400 m, the predicted survival of the patient will diminish due to the loss of the positive effect associated with a 6MWD ≥ 440 m. In this example, the 20% decline of the patient may portend future declines, and such predictive measures are not a component of the present model. Novel findings that were recently presented at the International Society for Heart and Lung Transplantation suggest that a 15% reduction in 6MWD may provide additional prognostic value beyond the most recent 6MWD value (32). Changes in other variables such as a rise in BNP from 200 pg/ml to 400 pg/ml may be hypothesised to be of prognostic importance, but at present, they do not result in any change in the risk score because both values are above the threshold for risk. The extent of change in such factors will be incorporated in future iterations of the present model as more serial data become available. In a recent report, increased survival in patients with PAH receiving subcutaneous treprostinil was associated with disease aetiology, baseline factors including FC, 6MWD, mixed venous oxygen saturation, and the dose of the drug administered (33).

Model enhancements will also need to incorporate cohort biases, biases in diagnostic and treatment availability, and to account for changes in prognosis after treatment. Development or modification of existing equations may be best done in meta-analyses of registries. In addition, the inclusion of novel predictive factors in the model such as type of treatment may also provide invaluable information concerning the clinical course of a patient, particularly with the implementation of serial assessments. Additional parameters shown to provide incremental predictive power,
such as right-sided ventricular strain, are not available in the current registry datasets and should be considered for inclusion in future registries (33). Modifications of the existing models are crucial to allow these tools to be utilised at their best in clinical practice and research.

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Conflicts of interest
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References