Predicting Survival in Pulmonary Arterial Hypertension

Insights From the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL)

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Background—Factors that determine survival in pulmonary arterial hypertension (PAH) drive clinical management. A quantitative survival prediction tool has not been established for research or clinical use.

Methods and Results—Data from 2716 patients with PAH enrolled consecutively in the US Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) were analyzed to assess predictors of 1-year survival. We identified independent prognosticators of survival and derived a multivariable, weighted risk formula for clinical use. One-year survival from the date of enrollment was 91.0% (95% confidence interval [CI], 89.9 to 92.1). In a multivariable analysis with Cox proportional hazards, variables independently associated with increased mortality included pulmonary vascular resistance >32 Wood units (hazard ratio [HR], 4.1; 95% CI, 2.0 to 8.3), PAH associated with portal hypertension (HR, 3.6; 95% CI, 2.4 to 5.4), modified New York Heart Association/World Health Organization functional class IV (HR, 3.1; 95% CI, 2.2 to 4.4), men >60 years of age (HR, 2.2; 95% CI, 1.6 to 3.0), and family history of PAH (HR, 2.2; 95% CI, 1.2 to 4.0). Renal insufficiency, PAH associated with connective tissue disease, functional class III, mean right atrial pressure, resting systolic blood pressure and heart rate, 6-minute walk distance, brain natriuretic peptide, percent predicted carbon monoxide diffusing capacity, and pericardial effusion on echocardiogram all predicted mortality. Based on these multivariable analyses, a prognostic equation was derived and validated by bootstrapping technique.

Conclusions—We identified key predictors of survival based on the patient's most recent evaluation and formulated a contemporary prognostic equation. Use of this tool may allow the individualization and optimization of therapeutic strategies. Serial follow-up and reassessment are warranted.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00370214.

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Key Words: prognosis ■ pulmonary arterial hypertension ■ risk factors ■ survival

Pulmonary arterial hypertension (PAH) is a fatal disease that has no satisfactory predictive model of survival. The only existing predictive equation, derived from the National Institutes of Health (NIH) Registry of Primary Pulmonary Hypertension (1983 to 1987),[1] may not be applicable to the broader World Health Organization (WHO) group I PAH population or accurately reflect survival in the current treatment era. Substantial advances, including safe and effective therapies[2,3] and a revised classification system,[4] necessitate a new prognostic equation.

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Although 6-minute walk distance (6MWD) and other end points are considered potential surrogates for survival of patients with PAH, they have never been thoroughly tested for their predictive abilities. However, these factors are often used to make critical decisions about the utility and efficacy of present-day therapeutics.[5] The Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) is a

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multicenter, observational, US-based registry initiated in 2006 and designed to study longitudinal clinical course and disease management in ≈3000 patients with WHO group I PAH.[6] A prespecified objective of the REVEAL Registry was to identify predictors of short- and long-term survival reflecting current treatment and clinical variables. Using these results, we assessed the prognostic value of multiple factors, enabling more accurate risk stratification, and we developed an algorithm for predicting survival in patients with PAH.

Methods

REVEAL Study Design

REVEAL is an observational prospective registry study that consecutively enrolled patients with a diagnosis of WHO group I PAH meeting prespecified hemodynamic criteria at 54 geographically diverse community and university PAH specialty care facilities in the United States.[6] Both newly and previously diagnosed patients have been enrolled and will be followed up for at least 5 years unless discontinued from the study because of withdrawal of consent, death, or loss to follow-up. There are no protocol-mandated tests, treatments, or visit schedules. Study objectives and methods were prespecified in an Institutional Review Board–approved protocol, and all participants or their legal guardians gave written informed consent.

Data from right heart catheterization were categorized as meeting traditional or expanded hemodynamic criteria for WHO group I PAH (ie, pulmonary capillary wedge pressure ≤15 versus 16 to 18 mm Hg); only patients meeting traditional hemodynamic criteria are included in the analyses to develop a prognostic equation for survival in PAH. All WHO group I subgroups were analyzed except for pulmonary hypertension of the newborn.

Patient data are collected electronically at the time of enrollment and updated quarterly as available. Demographic data include age, sex, race, and ZIP code; median income in the patient's ZIP code is used as a proxy for socioeconomic status.[7] The most recent data collected at the time of enrollment include WHO group I PAH subgroup classification, modified New York Heart Association (NYHA)/WHO functional class, 6MWD with concurrent Borg dyspnea scale, pulmonary function testing, hemodynamic measurements, and acute vasodilator test results if available. A ≥10-mm Hg decrease in mean pulmonary artery pressure to <40 mm Hg without a decrease in cardiac output defined vasoreactivity.[8] Comorbid conditions such as renal insufficiency are determined by each investigator. Blood test results are categorized as low, normal, and high; however, results for brain natriuretic peptide (BNP) levels are quantitative. Qualitative echocardiographic results (none, mild, moderate, moderate/severe, or severe) are recorded for right ventricular dysfunction and pericardial effusion (yes/no), whereas numeric results are captured for Tei index only from those who routinely perform this modality. Information on other quantitative echocardiographic parameters such as tricuspid annular plane systolic excursion were not captured in this data set.

Missing and out-of-range data are queried at the point of data entry; additional clarifications are sent as queries to sites. Onsite monitoring of source data is performed at 20% of participating sites annually.

Statistical Methods

Survival was estimated from time of enrollment with all-cause mortality as the end point. Because of the observational nature of REVEAL, survival analyses involved a large number of candidate predictor variables from a wide range of diagnostic tests. As a result of natural practice pattern variation, few patients had every test performed, and some tests were performed more recently than others.

There were 2 steps to the survival analysis. First, univariable Cox regression models were used to identify subgroups with better-than-average, worse-than-average, poor, and extremely poor 1-year survival. One-year survival of 90% to 95% was considered average on the basis of the 1-year survival estimate for the full patient cohort, and the other 4 categories were defined on the basis of 5-percentage-point increments (eg, 85% to 90% for worse than average, 80% to 85% for poor, etc).

The univariable analyses identified predicted cut points to transform continuous variables into subgroups. An indicator variable was created for every subgroup associated with better- or worse-than-average survival but not for continuous or categorical variables associated with average survival. To avoid excluding patients with missing tests, univariable analyses were also performed for the "missing" category. If the indicator variable for "missing" was associated only with an average survival, patients with missing data became part of the reference group. For time-sensitive hemodynamic data, additional models were run, restricting to tests that had been performed within the 1 or 2 years preceding study entry. To account for the possibility of interactions, we created sex-specific age and WHO group I PAH subgroup pathogenesis indicators. No other interactions were considered.

In the second step of the survival analysis, the full set of indicator variables identified in the univariable analyses were entered into a stepwise multivariable Cox regression model. Because of the way that the indicator variables were created (ie, patients with missing data were a subgroup or were part of the reference group), all patients had a complete set of covariates. An α level of 0.05 was used for model entry in the primary analysis. Proportional-hazards assumptions were confirmed with a Kolmogorov-type supremum test.[9]

The discriminatory ability of the model was assessed with the c index.[10] The assessment was repeated for subgroups of maximally treated patients and for WHO group I PAH subgroups to ensure generalizability. Cross-validation was used to compute the c index to approximate an independent validation.[11] For each of 1000 bootstrap samples, the stepwise model was refit and reassessed on the original data. Following the approach of Harrell et al,[12] optimism associated with both the c index and calibration was assessed so that a bias-corrected shrinkage factor could be included in the final predictive equation. The optimism estimates for discrimination were applied to compute corrected c indexes, and separately, optimism estimates for comparing predicted values with observed (Kaplan-Meier) values were computed for each 5-percentile increment in the distribution of predicted values.

Multiple sensitivity analyses were conducted (1) using α levels of 0.2, 0.1, 0.01, and 0.001 for model entry, (2) censoring at the time of transplantation, and (3) modeling survival from time of diagnosis rather than time of enrollment. Details of the following 3 aspects of the model development are located in the Appendix in the online-only Data Supplement: a more complete flow of the model-building process, sensitivity analyses using models of time from diagnosis, and bootstrap cross-validation.

Results

Characteristics at Enrollment

A total of 2716 consecutively enrolled patients met all analysis criteria. Mean age was 50 years; 79% were women; and 73% were white (Table 1). Forty-seven percent had idiopathic PAH (IPAH); 86% were in modified NYHA/WHO functional class II to III, and 14% were newly diagnosed by right heart catheterization within 3 months preceding enrollment. Median times from echocardiograms, hemodynamic measurements, and percent predicted carbon monoxide diffusing capacity (DLCO) to enrollment were 2.8, 11.2, and 15.4 months, respectively.

PAH therapies included prostacyclin analogs in 1092 (41.6%), endothelin receptor antagonists in 1231 (46.9%), and phosphodiesterase-5 inhibitors in 1301 (49.6%) patients. A total of 1087 (40.0%) and 687 (26.2%) patients received combination PAH therapies or an intravenous prostacyclin analog, respectively. Calcium channel blockers were used for

Table 1. Descriptive Characteristics at the Time of Enrollment

Characteristic	n	% or Mean (SD)
Age	2716	50.4 (16.8)
Women	2135	78.6
Race		
White	1969	72.5
Black	327	12.0
Hispanic	249	9.2
Other/unknown*	171	6.3
WHO group I PAH subgroup		
IPAH	1262	46.5
Familial PAH	79	2.9
Associated PAH		
CHD	319	11.8
CTD	648	23.9
Scleroderma	366	13.5
Not scleroderma	282	10.4
Portal hypertension	138	5.1
Drugs/toxins	134	4.9
HIV infection	51	1.9
Other	85	3.1
Modified NYHA/WHO functional class		
I	210	8.5
II	936	37.8
III	1194	48.2
IV	136	5.5
Newly diagnosed	367	13.5
Previously diagnosed	2349	86.5
Time from diagnosis to enrollment, mo		
Mean (SD)	2716	39.3 (45.4)
Median (interquartile range)	2716	26.4 (8.7–53.7)
6MWD, m	2173	370 (127)
Mean right atrial pressure, mm Hg	2451	8.6 (5.3)
Mean pulmonary artery pressure, mm Hg	2623	49.5 (14.8)
Cardiac index, $L \cdot min^{-1} \cdot /m^{-2}$	2105	2.6 (0.9)
Pulmonary vascular resistance, Wood units	2562	10.5 (6.6)
Pulmonary vascular resistance index, Wood units $\cdot m^2$	2087	18.6 (11.0)
Pulmonary capillary wedge pressure, mm Hg†	2598	9.6 (4.0)
BNP level, pg/mL	1340	286 (530)
N-terminal proBNP level, pg/mL	208	1455 (3296)
Predicted D_{LCO}, %	1556	59.9 (23.4)
Systolic BP, mm Hg	2582	116 (17)
Heart rate, bpm	2560	83 (15)
Borg dyspnea scale	1958	2.9 (2.0)
Tei index	187	0.6 (0.2)
Median income, $	2716	53 229 (18 493)
Right ventricular dysfunction (moderate-severe or severe)	459	21.8
Pericardial effusion (yes), n/N	532/2105	25.3
Renal insufficiency, n/N	109/2716	4.0
High total bilirubin, n/N	334/2285	14.6
Vasoreactivity, n/N	155/1535	10.1
Vasoreactivity, IPAH patients only, n/N	83/734	11.3

(Continued)

Total N=2716.

*"Other" race includes Asian or Pacific Islander, Native American or Native Alaskan, other, or unknown.

†To be included, all patients had either pulmonary capillary wedge pressure or left ventricular end-diastolic pressure measured contemporaneously with pulmonary artery pressure measurements.[6]

SD indicates standard deviation.

PAH treatment or as a concomitant therapy for 251 (9.2%) and 428 (15.8%) patients, respectively.

Survival

The mean duration of follow-up (after enrollment) among survivors was 521 days (range, 0 to 731 days); 5 patients (0.2%) had no follow-up, and 97.5% of survivors were followed up for ≥12 months. There were 340 deaths, and 33 patients underwent lung transplantation. The observed 1-year survival from the date of enrollment was 91.0% (95% confidence interval [CI], 89.9 to 92.1; Figure 1).

Predictors of Survival

Several demographic, functional, laboratory, and hemodynamic parameters were independently associated with survival in the multivariable model (Figure 2). Variables associated with a >2-fold increase in hazard ratio (HR) included PAH associated with portal hypertension (HR, 3.6; 95% CI, 2.4 to 5.4), a family history of PAH (HR, 2.2; 95% CI, 1.2 to 4.0), men >60 years of age (HR, 2.2; 95% CI, 1.6 to 3.0), modified NYHA/WHO functional class IV (HR, 3.1; 95% CI, 2.2 to 4.4), and pulmonary vascular resistance >32 Wood units (HR, 4.1; 95% CI, 2.0 to 8.3). Other variables associated with significantly increased risk of death included PAH associated with connective tissue disease (CTD), renal insufficiency, modified NYHA/WHO functional class III, resting systolic blood pressure (BP) <110 mm Hg, resting heart rate >92 bpm, 6MWD <165 m, BNP >180 pg/mL, presence of

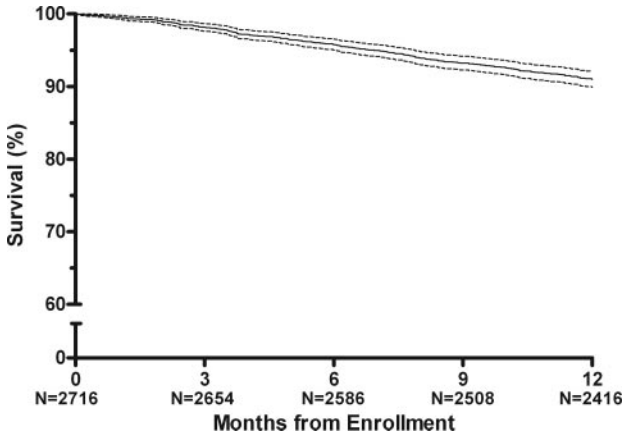

Figure 1. Kaplan-Meier estimates of 1-year survival from time of enrollment. Dashed lines represent the 95% CI for the Kaplan-Meier estimates.

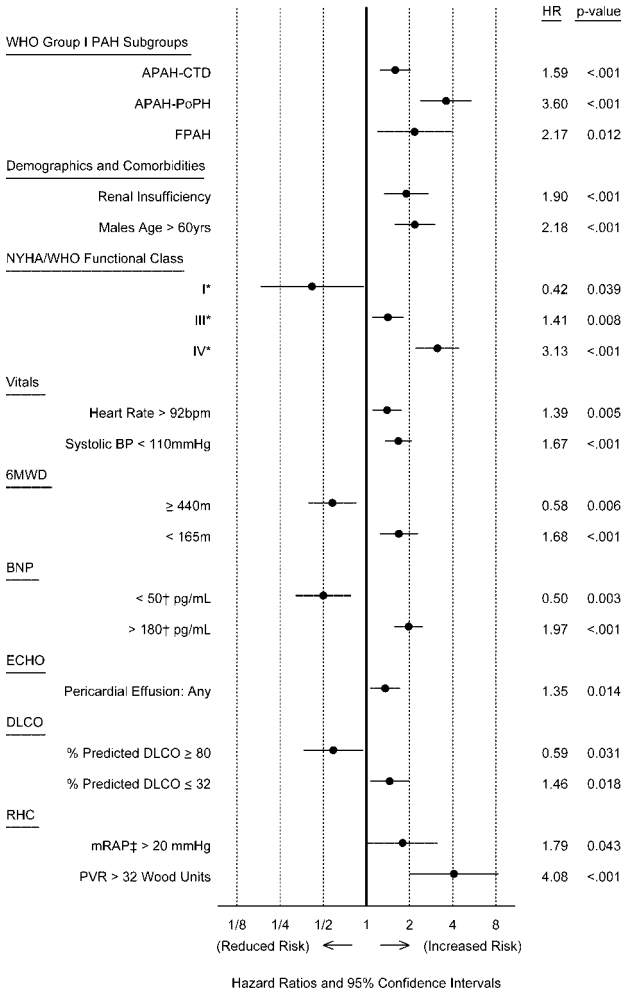

Figure 2. Cox proportional-hazards estimates for multivariable model of survival, limited to terms included in the final stepwise model. Parameters significantly associated with 1-year survival only in univariable analyses included the Borg dyspnea scale, right ventricular dysfunction, pulmonary vascular resistance (PVR) index, pulmonary capillary wedge pressure, cardiac index, mean pulmonary artery pressure, and total serum bilirubin. Candidate predictor variables that were not significant at the univariable level included Tei index, vasoreactivity, race, newly diagnosed PAH, and income. Missing Borg scale and missing PVR index were both associated with lower-than-average observed survival and were therefore considered candidate predictor variables. APAH indicates associated I PAH; ECHO, echocardiogram; FPAH, familial PAH; mRAP, mean right atrial pressure; PoPH, portopulmonary hypertension; and RHC, right heart catheterization. *Reference category: NYHA/WHO functional class (Fn) II or missing. †If N-terminal proBNP is available and BNP is not, listed cut points are replaced with <300 pg/mL and >1500 pg/mL. ‡Restricted to tests performed within 1 year of enrollment; otherwise, the indicator is set to 0.

pericardial effusion, percent predicted DLCO ≤32%, and mean right atrial pressure >20 mm Hg within the year preceding enrollment. Scleroderma and nonscleroderma CTD categories had similar coefficients and were combined in the final model. Four variables were associated with increased 1-year survival: modified NYHA/WHO functional class I, 6MWD ≥440 m, BNP <50 pg/mL, and percent predicted DLCO ≥80%.

Time from diagnosis was not independently associated with survival. Without adjustment for other variables, patients newly diagnosed within 90 days of enrollment had a nonsignificant elevated risk (HR=1.20; P=0.24) compared with patients diagnosed >90 days before enrollment, and no difference was present after adjustment for the multivariable model (HR=0.93; P=0.63). Without adjustment for other variables, years from diagnosis was significantly associated with a decreased risk (HR=0.94 per year; P=0.002); however, this difference did not persist after adjustment (HR=1.01 per year; P=0.53).

Sensitivity Analysis: Censoring at Transplant

Results of censoring patients at the time of lung transplant were consistent with those in the primary analysis. All terms remained in the model using the prespecified α=0.05 criterion.

Prognostic Equation

Based on the Cox proportional-hazard multivariable analysis, a preliminary prognostic equation was derived from the independent prognosticators of survival. Patients were divided into 20 equally sized groups (half-deciles) stratified by predicted survival. The Kaplan-Meier estimates for each group were compared with the preliminary predicted survival (Figure 3A), showing good apparent calibration. Optimism-corrected Kaplan-Meier estimates (Figure 3B) suggested a need for a small shrinkage adjustment, primarily because the optimism-corrected Kaplan-Meier estimate for the lowest half-decile demonstrated slightly better survival than predicted (58.8% versus 54.4%). After application of a shrinkage correction to develop a final prognostic equation, the calibration was nearly perfect (Figure 3C).

Predicted 1-year survival is computed as follows: $S0(1)^{\exp(Z'\beta\gamma)}$ where S0(1) is the baseline survivor function (0.9698), $Z'\beta$ is the linear component, and γ is the shrinkage coefficient (0.939). The core of the prognostic equation is $Z'\beta$, the linear component of the Cox model presented in Figure 2. Starting with a base value of 0, the linear component is increased or decreased according to the variable coefficients summarized in Table 2.

To further summarize the mortality risk stratification produced by the final prognostic equation, 5 risk groups were defined. The predicted risk, after shrinkage correction, was classified as low (>95% 1-year survival) for 1374 patients. Patients in the low risk category had a median of 1 of a possible 15 risk factors and a median of 1 of 4 possible protective factors. The average risk (90% to 95% 1-year survival), moderately high risk (85% to 90% 1-year survival), high risk (70% to 85% 1-year survival), and very high risk (<70% 1-year survival) strata had a median of 2, 3, 4, and 6 risk factors, respectively, and a median of 0 protective factors. Because of the nature of the formula, patients within the same strata with more risk factors than the median were more likely to have ≥1 protective factors. Patients in higher risk categories had proportionately lower observed 1-year survival (Figure 4). Table 3 describes a sample patient for each of the 5 strata.

In addition to calibration and shrinkage, discrimination was assessed. The c index, defined as the probability that a randomly chosen survivor has a lower risk estimate than a

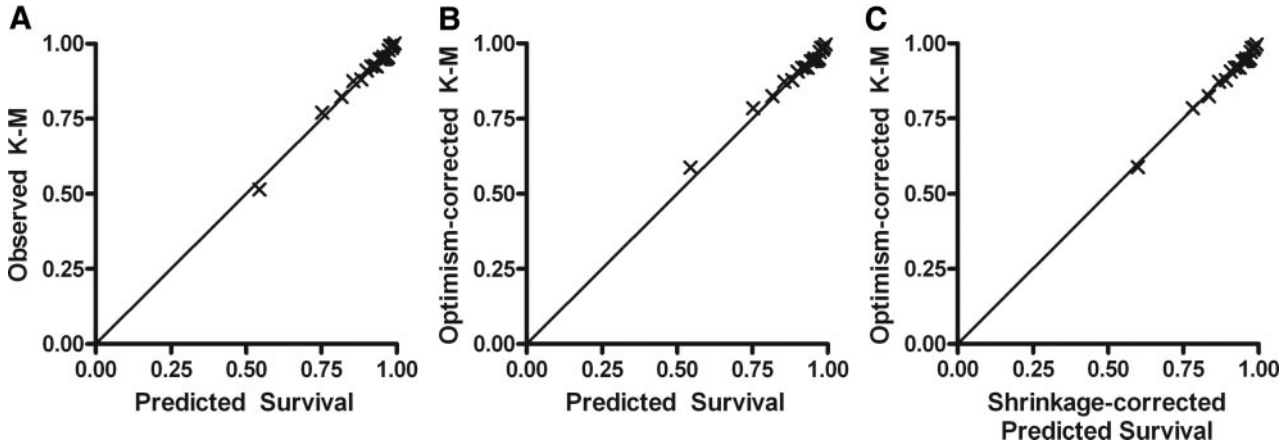

Figure 3. Model calibration before and after shrinkage adjustment. A, Observed Kaplan-Meier (K-M) estimates vs preliminary predicted survival for each half-decile. B, Optimism-corrected Kaplan-Meier estimates vs preliminary predicted survival for each half-decile. C, Optimism-corrected Kaplan-Meier estimates vs shrinkage-corrected predicted survival.

randomly chosen death, was calculated for estimates from the NIH survival equation and for the REVEAL multivariable model, before and after bootstrap correction for optimism (Table 4). The ability of the REVEAL multivariable model to discriminate between low- and high-risk patients was considerably greater than that of the NIH survival equation (0.772 versus 0.588), even after correcting for the optimism bias inherent in using the same data set for developing and assessing the model (corrected c index=0.744). The model was also able to accurately discriminate between higher- and lower-risk patients in these specific subgroups: (1) maximally treated patients (ie, on intravenous prostacyclins or combination PAH therapies), (2) newly diagnosed patients, (3) pulmonary capillary wedge pressure <12 mm Hg, and (4) IPAH/familial PAH or other forms of PAH. Estimates were consistently greater than those from the NIH survival equation for IPAH/familial PAH even when many of the tests associated with the indicator variables in the model were unavailable.

Discussion

One of the major goals of the REVEAL Registry was to design a widely applicable, contemporary, clinically relevant model to predict outcome in patients with WHO group I PAH. Through analysis of multiple prognostic factors in 2716 consecutively enrolled patients with PAH, we developed a prognostic equation that predicts 1-year survival. Multiple, incremental clinical measures in the equation make it a more valuable predictor of survival compared with each measure assessed individually.

Assessment of prognosis guides individual therapeutic decisions. Using information commonly obtained in patients with WHO group I PAH, one can calculate the risk and estimate 1-year survival from time of assessment (regardless of when the patient was diagnosed). The prognostic equation was developed to be applicable at any point in the course of the disease based on the patient's most recent evaluation. The ability of the equation to discriminate between lower- and higher-risk patients was demonstrated in the entire cohort and in several clinical subsets (listed in Table 4). Patients with more protective factors than risk factors (n=396) exhibited 1-year survival of 98.7%, and patients in the lowest risk decile had a predicted 1-year survival of 99.0%, similar to the age-adjusted estimated survival rate for the general US population in 2005 (99.2%).[13] Specific PAH therapies were not included as candidate predictors of survival in this study

Table 2. Variable Coefficients for the Linear Component of the Cox Model

	Additions and Subtractions to Linear Component of Equation		
WHO group I subgroup	FPAH, +0.7737	APAH-PoPH, +1.2801	APAH-CTD, +0.4624
Demographics and comorbidities	Male >60 y of age, +0.7779	Renal insufficiency, +0.6422	
NYHA/WHO FC	FC I, −0.8740	FC III, +0.3454	FC IV, +1.1402
Vital signs	SBP <110 mm Hg, +0.5128	Heart rate >92 bpm, +0.3322	
6MWD test	6MWD ≥440 m, −0.5455	6MWD <165 m, +0.5210	
BNP	BNP <50 pg/mL or N-terminal-proBNP <300 pg/mL, −0.6922	BNP >180 pg/mL or N-terminal-proBNP >1500 pg/mL, +0.6791	
Echocardiogram	Any pericardial effusion, +0.3014		
Pulmonary function test	% Predicted D_{LCO} ≥80%, −0.5317	% Predicted D_{LCO} ≤32%, +0.3756	
Right heart catheterization (mm Hg, Wood units)	mRAP >20 mm Hg within 1 year, +0.5816	PVR >32 Wood units, +1.4062	

APAH indicates associated PAH; FC, functional class; FPAH, familial PAH; mRAP, mean right atrial pressure; PoPH, portopulmonary PAH hypertension; PVR, pulmonary vascular resistance; and SBP, systolic BP.

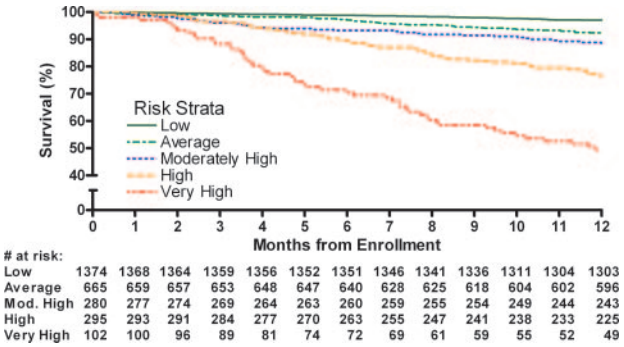

Figure 4. Observed 1-year survival from time of enrollment according to predicted risk strata.

for 2 reasons. First, we believe that these determinations are best left to head-to-head randomized controlled trials. Second, and more important, prognosis is more related to a change of the specific therapy in a modifiable risk factor (ie, 6MWD, BNP, or hemodynamic parameter) than to an individual class of therapy per se. Thus, the relative importance of a particular drug in changing prognosis is diluted by the change in a patient's functional capacity.

This study assimilates previously noted and newly confirmed PAH prognostic findings into a cohesive predictive formula that weighs each one and resolves the relevance of each factor. Importantly, the risk assessment is derived from a multivariable model and thus weighs each risk factor within the context of the other variables. Therefore, some subgroups such as CTD-scleroderma have lower HRs than might have been expected because of other associated risk factors that also contribute to the prognostic equation. This illustrates the importance of a quantitative model rather than a qualitative assessment of the risk factors for each patient. The multivariable model provides considerably better risk stratification than any single variable used alone. Functional class, 6MWD, and BNP variables each had better prognostic value than the NIH equation but had less discriminatory capacity than the full prognostic equations.

Our analyses confirmed increased mortality risk in patients with PAH associated with portal hypertension[14] or scleroderma[15] (and found increased risk among patients with PAH associated with any CTD). Increased mortality risk was also confirmed in patients with renal insufficiency[16] or any pericardial effusion on echocardiogram.[17] Previous investigators have demonstrated low systolic BP at peak exercise to be associated with poor outcome[18]; we found that resting systolic BP <110 mm Hg and resting heart rate >92 bpm were associated with worse survival. Prior studies have demonstrated the utility of 6MWD in predicting outcome,[19] but a recent meta-analysis has raised doubts about this association.[20] We found that 6MWD thresholds of ≥ 440 m are associated with longer survival and <165 m with increased mortality. We have extended the utility of low percent predicted DLCO as a prognosticator, demonstrating that it is also an important discriminator at high levels even after the exclusion of patients with anemia and despite differing methodologies used at multiple sites.

The NIH registry identified mean right atrial pressure, cardiac index, and mean pulmonary artery pressure as important predictors of survival.[1] Our analyses confirmed the importance of hemodynamic parameters obtained by right heart catheterization. However, in contrast to the NIH registry

Table 3. Sample Patients From 5 Risk Strata

	Risk Strata According to Shrinkage-Corrected Predicted 1-y Survival				
	Low Risk (>95%)	Average Risk (90%-<95%)	Moderately High Risk (85%-<90%)	High Risk (70%-<85%)	Very High Risk (<70%)
WHO group I subgroup	IPAH	APAH-CHD	FPAH	PoPH	Scleroderma
Demographics and comorbidities	35-y-old Female w/o renal insufficiency	45-y-old Female w/o renal insufficiency	55-y-old Male w/o renal insufficiency	55-y-old Male w/o renal insufficiency	55-y-old Female with renal insufficiency
NYHA/WHO functional class	III	II	III	III	IV
Vital signs					
SBP, mm Hg	115	108	113	100	110
Heart rate, bpm	85	80	85	95	90
6MWD test, m	360	325	150	340	200
BNP, pg/mL	100	150	100	175	500
Echocardiogram	No pericardial effusion	Pericardial effusion	No pericardial effusion	No pericardial effusion	Pericardial effusion
Pulmonary function test, predicted DLCO, %	90	55	50	70	NA
Right heart catheterization					
mRAP,* mm Hg	8	10	10	11	22
PVR, Wood units	10	11	12	15	20

APAH indicates associated PAH; FPAH, familial PAH; PoPH, portopulmonary hypertension; SBP, systolic BP; mRAP, mean right atrial pressure; and PVR, pulmonary vascular resistance.

*Performed within 1 year of enrollment.

Table 4. Assessment of the Effectiveness of Risk Stratification

Patient Subgroup	n	c Index*		
		NIH Survival Equation†	Model Estimate Without Correction	Model Estimate Corrected for Optimism
All patients	2716	0.588	0.772	0.744
Currently treated with intravenous prostacyclin analogs	687	0.569	0.779	0.752
Currently treated with PAH combination therapy‡	1087	0.590	0.797	0.771
Risk factors and protective factors assessed, n§				
All 19	657	0.572	0.794	0.767
14–18	1672	0.586	0.774	0.745
≤13	387	0.633	0.722	0.694
Newly diagnosed with PAH	367	0.566	0.716	0.683
Pulmonary capillary wedge pressure <12 mm Hg	1797	0.598	0.774	0.744
PAH diagnosis subgroup				
IPAH/familial PAH	1341	0.603	0.770	0.742
Other	1375	0.585	0.767	0.738

*The c index is the probability that a randomly chosen survivor has a lower risk estimate than a randomly chosen death at the time of the death. The c index must be >0.5 to be an improvement over random chance.

†The NIH survival equation is derived from D'Alonzo et al.[1]

‡Combination therapy includes ≥2 PAH therapies, oral, parenteral, or inhaled.

§Patients with missing data are included in the reference category for that particular risk factor rather than excluding the case or imputing data, neither of which would be practical in the clinic setting.

and consistent with contemporary hypotheses, mean pulmonary artery pressure was not an important predictor of survival. When adjusted for all other risk factors making up the final multivariable model, only an elevated mean right atrial pressure within the year preceding study enrollment and a markedly increased pulmonary vascular resistance were independent risk predictors.

Despite its reported importance in predicting outcome, particularly in IPAH,[8,21,22] acute vasoreactivity did not result in an overall survival advantage at 1 year when weighed against other evaluable factors in the multivariable analysis. The 155 vasoreactive patients were more often in the lowest predicted risk category (59% versus 51% overall), with the greatest differences seen among 83 vasoreactive patients with IPAH, suggesting that the advantages of being acutely vasoreactive are captured by other variables. Conceivably, the relatively low importance of acute vasoreactivity may also be due to the inclusion in our analysis of all patients with WHO group I PAH. This may have minimized the overall survival effect of this particular factor because the degree of vasoreactivity important in predicting outcome is seen in only a small proportion of patients with IPAH.[22] We do not believe, however, that this finding should question the usefulness of vasoreactive testing or suggest that testing and treating vasoreactive patients should be abandoned.

Certain findings in our analysis constitute new associations. We noted a survival disadvantage for those with a family history of PAH. Prior studies reported no significant difference in survival when patients with IPAH and familial PAH with and without BMPR2 mutations were compared, despite earlier onset and more severe disease in BMPR2 mutation–positive cases.[23] Because BMPR2 mutations are detected in only ≈70% of familial cases, it is possible that family history identifies increased mortality risk better than BMRP2 mutation detection because alternative, yet unidentified, mutations also may be more closely linked to survival.

Congenital heart disease (CHD), interestingly, was not associated with a survival advantage, regardless of the type of defect or repair status. We were also unable to detect a difference between patients with repaired and unrepaired CHD. The reason for this is unclear but may simply reflect the lesser importance of demographic factors when compared against factors that depict the clinical status of the patient or the reduced power to detect differences in small subgroups with relatively few events. Previous reports of better survival in patients with PAH associated with CHD (APAH-CHD) versus patients with IPAH/familial PAH or PAH associated with CTD were predominantly natural history data derived from unoperated Eisenmenger patients and do not include patients with PAH associated with CHD that has been repaired or patients with small, clinically insignificant congenital systemic to pulmonary shunts, whether or not they are on PAH therapies. Current PAH treatment regimens (including surgical repair now performed more often in patients with increased pulmonary vascular resistance than in the past) suggest that either patients with PAH associated with CHD are being treated less aggressively than other patients with PAH or their response to therapy may be smaller.

Although PAH is predominantly a female disorder, we demonstrated that men >60 years of age have poorer survival compared with men ≤60 years of age at the time of assessment and compared with female patients regardless of age. Despite the subjective nature of functional class assessment, we identified the full 4-category range of functional class as having discriminatory power. Others have identified elevated BNP as a marker for poor survival, but we found that lower-than-average BNPs (<50 pg/mL) are a marker for better survival.

There are several limitations to this study. Unlike randomized clinical trials, all relevant measurements were not collected at mandated study visits; only 24.2% of patients had data available for all 19 of the possible risk factors and protective factors, and the average patient had data available for 16 of the 19. However, our use of a missing data indicator allowed us to include all of these patients, making the model broadly generalizable to clinical practice. Inclusion of 131 patients ≤18 years of age expands the target cohort for the proposed prognostic equation, even though a model developed exclusively for pediatric patients might have led to different cut points for some components of the model. Among all patients, there are some hypothesized predictors that were not captured in our database such as tricuspid annular plane systolic excursion, serum sodium levels, and quantitative measures of renal and hepatic function; these should be examined in future studies.

Although the study of a predominantly prevalent patient population may be perceived as incurring a potential survival bias, recent diagnosis was not an independent prognostic variable in our analysis. Three important predictors (BNP, percent DLCO, and 6MWD) were available exclusively or predominantly at the time of enrollment and not at the time of diagnosis and were missing more often among newly diagnosed compared with previously diagnosed patients. Because each of these 3 variables was associated with both increased and decreased risk, the absence of these tests for individual patients does not bias the predictions upward or downward. Separate validation of the newly diagnosed cohort (Table 4) suggested nearly identical discriminatory ability compared with the total cohort, and sensitivity analyses using left truncation methodology from the time of diagnosis yielded similar results for the prognostic factors available at both time points (see the Appendix in the online-only Data Supplement). Although predicting survival from the time of diagnosis may be valuable, assessing survival risk at any point of disease progression may be even more useful. Suggesting that the prognostic equation may be used at any time is not equivalent to suggesting that changes in the calculated risk, observed through serial measurements, have independent prognostic value. Serial assessment was not evaluated in our analysis. The present analysis does tell us what to expect on the basis of the most recent data at any point in the patient's clinical course, but we have not tested the implications of an upward or downward clinical trajectory.

External validation of the model, preferably including serial assessment, may be considered an important step before widespread application of the prognostic equation. However, the bootstrap cross-validation technique is a statistically rigorous approach that is comparable to external validation in that the patient data used to develop the model are not used in the assessment of the discriminatory power of the model. This protects against overfitting and producing spurious findings and provides the most important diagnostic evaluation of model validity.

Conclusions

We identified key predictors of survival for patients with WHO group I PAH and present them in a weighted prognostic equation. We envision that this equation may be used at diagnosis or at any time during a patient's course. Its potential use as a serial measure may allow regular reassessment of risk and differentiation of patients with stable chronic disease from those with actively progressive disease. By obtaining an evidence-based, global assessment of the patient, clinicians may be better able to individualize and optimize therapeutic strategies to improve survival. Using this equation in future clinical trials will test these hypotheses and guide initial and stepwise therapies. Further investigation with longer follow-up is warranted.

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Disclosures

Dr Benza has received honoraria from Actelion, United Therapeutics, and Gilead and has received or is pending receipt of grants from Actelion, United Therapeutics, Gilead, and Lung Rx. Dr Benza has received honoraria for his service on the REVEAL Steering Committee, which is supported by Actelion. D.P. Miller and A.J. Foreman are employed by ICON Clinical Research, a company that receives research support from Actelion and other pharmaceutical companies. Dr Gomberg-Maitland has received research grant support from Actelion, Gilead, Eli Lilly and Co/ICOS, Novartis, Pfizer, and United Therapeutics and has served as a consultant and/or on advisory boards for Biomarin, Gilead, Medtronic, Millenium, and Pfizer. She has a patent filed for the use of sorafenib in pulmonary hypertension entitled "Compositions and Methods for Treating Pulmonary Hypertension," WO/2007/087575. Dr Frantz has served on advisory boards for Actelion, Gilead, Lung Rx, United Therapeutics, Pfizer, and Medtronic and has served as an investigator for multicenter trials sponsored by these companies. Honoraria for advisory board activities have gone into a Mayo Clinic research account in compliance with Mayo Clinic guidelines for consulting activities when the consultant is an investigator on research studies funded by the company. Dr Frost serves as a consultant for Gilead and Actelion. Dr Frost has received honoraria from Gilead, Actelion, and Pfizer and has provided expert testimony on diet pill litigation. She has also received grants from Gilead and Actelion and grants to Baylor for Institutional Review Board–approved research. Dr Frost has received honoraria for her service on the REVEAL Steering Committee, which is supported by Actelion. Dr Barst serves as a consultant for and has received honoraria from Actelion, Bayer, GeneraMedix, Gilead, Eli Lilly and Co, MondoBIOTECH, and Pfizer. Dr Barst has provided expert testimony on diet pill litigation for the plaintiffs and has also received grants from Actelion, GeneraMedix, Gilead, Eli Lilly and Co, NIH/NHLBI, Novartis, Pfizer, and United Therapeutics. Dr Barst has received honoraria for her service on the REVEAL Steering Committee, which is supported by Actelion. Dr Badesch has received honoraria for service on steering committees and/or advisory boards for Actelion/CoTherix, Gilead/Myogen, Encysive Pharmaceuticals, Pfizer, GlaxoSmith-Kline, Lung Rx, United Therapeutics, Eli Lilly and Co/ICOS, Biogen Idec, and MondoBIOTECH. Dr Badesch has received grants from Actelion/CoTherix, Gilead/Myogen, Encysive Pharmaceuticals, Pfizer, United Therapeutics, Lung Rx, and Eli Lilly & Co/ICOS, and NIH/NHLBI. Dr Badesch has received honoraria for his service on

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CLINICAL PERSPECTIVE

The Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL Registry) was designed to assess longitudinal clinical course and disease management in the largest cohort of patients with pulmonary arterial hypertension ever monitored. Pulmonary arterial hypertension remains a morbid disease unless well-timed clinical intervention is implemented. Therefore, factors that determine survival in pulmonary arterial hypertension can significantly drive and focus clinical management. We analyzed data from 2716 patients with pulmonary arterial hypertension to derive a multivariable, weighted risk formula that could be used by the practicing clinician at any time in the course of a patient's disease progression to predict survival. Nineteen independent factors were identified as having an impact on patient survival. A multivariable risk formula comprising all 19 factors provided a more accurate assessment of clinical outcome than each independent variable. These results emphasize the importance of using the full spectrum of clinical data commonly available to the practicing clinician for the assessment of patients with pulmonary arterial hypertension. We believe that the risk stratification provided by this predictive equation will facilitate counseling of patients about their disease and prognosis and will provide a benchmark for prospective evaluation of new therapies.

SUPPLEMENTAL MATERIAL

This supplement has been provided by the authors to give readers additional information about their work.

Supplement to: Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting Survival in Pulmonary Arterial Hypertension: Insights From the REVEAL Registry

Supplemental Methods

The model-building process for the prognostic equation involved many steps and sensitivity analyses. This appendix is intended to provide the details for three aspects of the model development: (i) a more complete flow of the model-building process; (ii) sensitivity analyses using models of time from diagnosis; and (iii) bootstrap cross-validation and unbiased estimation.

1. Model Development

A. Identification of Predictor Variables

The first step of the model development process was the identification of candidate predictor variables. Although many parameters were collected for many different tests, a decision was made to restrict the set of candidate predictors to variables that had been previously identified in the literature as having an association or possibly having an association with poor outcomes in pulmonary arterial hypertension (PAH). The variables considered from each of the nine components of the prognostic equation are listed in Supplementary Table 1.

B. Handling of Missing Data

A majority of the variables considered were ordinal or continuous variables, and due to the observational nature of the study, few patients had the results for all variables. Two of the most common approaches to missing data are case-wise deletion and imputation. Case-wise deletion was not performed because approximately 80% of patients would have been excluded from the analysis. The fact that so few patients had data for all tests is not due to incomplete reporting, but because it is not standard in clinical practice that all patients receive every test.

Imputation was not considered because the applicability of the final tool depended on a model that would not necessarily require complete data. Furthermore, it seemed likely that some tests would not be missing at random and that informative missing data could complicate any imputation scheme. Thus, we transformed all variables into binary indicator variables with non-missing data as the reference group for missing value indicators. This allowed missing data to be included in the reference group for indicator variables with lower- or higher-than-average survival, as described below.

C. Univariate Analysis

For each candidate predictor variable, including the missing value indicators, the first step in the modeling process was to fit a univariable Cox proportional hazards model and estimate the 12-month survival as a function of that variable. For n-category variables, this yielded n +1 estimates, one for each category and one for patients missing that variable. Sets of indicator variables were created based on five-percentage point increments for predicted 1-year survival; survival that was: better than average (≥95%), worse than average (<90%), poor (<85%), and extremely poor (<80%). No indicator variables were created for variables with average (90%–95%) 1-year survival estimates, and indicator variables were created without regard for statistical significance. For ordinal and continuous candidate predictor variables, we identified the cut points at which predicted 1-year survival values crossed out of the average range into any of the other ranges. These cut points were then used to create new indicator variables. In addition, an extra step was creation of an indicator variable for missing values if those missing a given test had predicted 1-year survival >95% or <90%. For the hemodynamic candidate predictor variables, based on the right heart catheterization, some of the data obtained varied markedly.

The process of selecting cut points was repeated three times, once without regard for how recently the test was performed, once considering all tests ≥2 years old as being missing, and once considering all tests ≥1 year old as being missing.

We considered evaluating interactions during the model-building process. However, due to the large number of variables under consideration, it would not have been feasible to consider all possible interactions. For that reason, we limited the process to only a few interactions that were deemed to be clinically important. Based on conversations with clinical experts, we considered two-way interactions only between gender with age and gender with World Health Organization (WHO) Group subgroup. Thus, gender-specific indicators were considered for WHO Group and age.

Because of the large number of candidate covariates that warranted consideration, we chose to build the model treating WHO Group subgroups as potential main effects rather than evaluating all possible interactions between WHO Group subgroups and other covariates. To confirm that this did not lead to a model that fit well for one set of patients and not others, we evaluated the c-index for key subgroups including associated PAH and found robust discrimination within every group evaluated. Nonetheless, building separate models for each WHO Group subgroup could have conceivably led to a set of equations with even greater discriminatory ability. To assess this, we repeated the model building and bootstrapping process for each subgroup. We found that the apparent discrimination (the c-index calculated on the same data used to fit the models) was slightly weaker (0.772 vs 0.796) when all WHO Group subgroups were evaluated in a single model versus separate models; however, we found that the bootstrap-estimated optimism (a measure of how badly the model was overfit) was much higher

in the subgroup analysis (0.068 vs 0.029), illustrating the importance of the large sample size that REVEAL provides for fitting a single cohesive model.

D. Multivariable Modeling

The resulting set of significant univariate candidate predictor variables from the univariate analysis were input into a multivariable Cox proportional hazards stepwise model. The model was fit with a 0.05 entry criteria. To avoid potentially inflating type I errors beyond the reported alpha level yielding potentially spurious results, we performed bootstrapping to validate our model. Stepwise modeling provided the best opportunity to repeat the process 1000 times for the purposes of cross-validation and estimation of bootstrap confidence intervals.

Univariable and multivariable hazard ratios are presented in Supplementary Table 2 for all variables that were significant predictors. It is noteworthy that multiple cut points were considered for most continuous variables, and the cut points for the same variable (eg, six-minute walk distance [6MWD] <165 m, 6MWD <225 m, and 6MWD <310 m) are collinear to an extent that the inclusion of any of the cut points reduces the chance for the others to be included. Due to the nature of the model-building process, neither linear terms nor every possible cutoff were evaluated. Thus, the cutoffs in the final model should not be interpreted as evidence for a specific threshold effect. Additionally, many variables that are individually strong predictors of survival, such as right ventricular dysfunction and Cardiac Index, were excluded from the final multivariable model. This does not mean that these variables are not predictors of poor survival. Rather, it means that the survival effects reported by these variables are already included in their entirety within the effects reported by the 19 variables that are part of the final model.

E. Development of the Final Prognostic Equation

Due to the desire to have a fully automated process to effectively perform bootstrap sampling, only minor modifications to the model were allowed in translating the model into the final prognostic equation. If the stepwise model resulted in a final model that included interactions without the associated indicator variables for the main effects, the main effects were forced into the model *post hoc* to confirm significance of the interaction. If confirmed, the nonsignificant main effects were removed. Additionally, if two related variables had nearly identical hazard ratios, the two indicator variables were allowed to be collapsed into a single variable to make the model more parsimonious. Finally, the calibration of the final model was assessed comparing predicted values to observed 12-month Kaplan-Meier estimates. The optimism associated with using the same data for fitting the model and assessing the model was estimated using bootstrap methods, and the calibration was further assessed using optimism-corrected Kaplan-Meier estimates. The linear component of the model was then multiplied by the shrinkage factor that provided optimal calibration after correcting for optimism.

2. Sensitivity Analyses

We created survival models for time of enrollment and also for survival from time of diagnosis with all-cause mortality as the endpoint. Models based on time of enrollment are generalizable to a prevalent patient cohort, whereas models based on time from diagnosis are generalizable to newly diagnosed patients. The investigators decided that with more data available at the time of enrollment, the survival from enrollment model comprised the primary analysis, and the model based on time from diagnosis used for the sensitivity analyses.

Fewer variables were collected at time of diagnosis compared with time of enrollment. Most patients had available hemodynamic data due to the entry criteria for inclusion into the REVEAL Registry, as well as age, sex, and WHO Group I PAH subgroup. The two collected variables that were most frequently missing were the 6MWD and modified New York Heart Association (NYHA)/WHO functional class; because of the potential prognostic importance of these two variables, the models from time of diagnosis included only patients with this data. These models were developed using the indicator variables identified and defined in the primary time-from-enrollment analysis. Further sensitivity analyses were conducted, omitting these two variables in one case and replacing the indicator variables with continuous predictors for patients with non-missing data in another case. Models of survival from time of diagnosis utilized left-truncated data, since patients were only in the risk set starting at the time of enrollment. For example, a patient enrolled 2 years after diagnosis and followed without an event for 1 year is considered to enter the risk set at 24 months with a censoring time of 36 months. Use of modified Kaplan-Meier curves, adjusting the risk sets at each failure time to account for delayed entry, allowed for visual assessment of the proportional hazards assumption.[1]

The results of the two models only differed slightly. Only 598 patients had all data available for these multivariable analyses. Mean age and mean 6MWD were slightly lower, while mean right atrial pressure, mean pulmonary artery pressure, and pulmonary vascular resistance were slightly higher at the time of diagnosis than at enrollment (Supplementary Table 3). The WHO PAH subgroups, mean right atrial pressure, 6MWD, and modified NYHA/WHO functional class at diagnosis were confirmed as independent predictors of survival. Familial PAH and pulmonary vascular resistance >32 Wood units did not predict survival, but this may be due to the small sample size. Replacing other marginally significant variables with continuous variables resulted

in strengthening the model. The 1-, 3-, and 5-year survival rates ± standard error from the time of PAH diagnosis were 87.7% ± 1.6%, 72.1% ± 1.8%, and 60.3% ± 2.0%, respectively.

3. Bootstrap Methods, Cross-Validation, and Unbiased Estimation

Bootstrap methodology aided in sensitivity analyses and aided in validating the model in a set of patients not used in the model construction. The sensitivity analysis involved constructing bootstrap confidence intervals. The first set of bootstrap confidence intervals used "patients" as the sampling unit and was based on the 2.5^{th} and 97.5^{th} quantiles from a set of 1000 bootstrap samples. As expected, given the large sample size, these confidence intervals closely matched the parametric estimates of the confidence intervals. Because hierarchical models are not well developed for time to event analyses, the parametric model did not address site effects. For this reason, a second set of 1000 bootstrap samples using "site" rather than "patient" as the sampling unit was analyzed. This conservative technique is not frequently used with a patient-based-sampling application of bootstrap confidence intervals. The analysis of the parametric and nonparametric confidence intervals was similar. Bootstrap hazard ratios and 95% confidence intervals from the Cox model are shown in Supplementary Table 4.

As in the sensitivity analysis, bootstrap cross-validation involves a set of 1000 bootstrap samples. Each bootstrap sample is created by randomly drawing patients with replacement such that for large samples each original observation has a 63.2% chance of appearing at least once in a given sample. Thus, each original observation also has a 36.8% chance of being left out of any given sample. This allows the predicted values based on each bootstrap sample to be estimated for the patients who were excluded from the sample, and statistics assessing the validity of the model can then be evaluated exclusively in the set of patients that were not utilized to fit the model. This approach leads to estimates that are biased in a conservative direction, and it has

been shown that unbiased estimates may be obtained by applying the estimates from each bootstrap sample to the apparent sample to obtain an estimate of the optimism associated with developing the model and assessing the model using the same data. We analyzed the data using both the conservative and unbiased approach, but present only the latter.

The c-index is computed by identifying all possible pairs of patients, where one member had an event and the other member remained in the risk set at the time of the event. The second member of the pair could be a patient who was censored at a later time or who had the event at a later time. To compute the c-index, the predicted values for the pair are compared. The c-index is the probability that the patient with the earlier event also has a higher predicted risk of having the event. Because the aim was to assess not only the final model, but also the process by which the final model was obtained, the stepwise selection process was repeated for each of the 1000 bootstrap samples using the same set of candidate variables and the same model entry criteria. Without bootstrap optimism correction, the c-index is 0.772. The cross-validated estimate is 0.744. As expected in a prospective validation in a new sample, the optimism corrected c-index is lower. Nonetheless, the model discriminates effectively between patients who will and will not have events over the course of approximately 1 year of follow-up. If two new patients (in a new cohort) each have a predicted value based on the prognostic equation, there is roughly a 3 in 4 chance that the patient with the lower predicted risk will survive longer.

Supplemental Reference

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Supplementary Table 1. Prognostic Equation Candidate Variables

Category	Candidate Variables
WHO Group I Subgroup	Idiopathic PAH, familial PAH, APAH-CHD, APAH-CTD-scleroderma, APAH-CTD-not scleroderma, APAH-portal hypertension, APAH-drugs/toxins, APAH-HIV
Demographics and Comorbidities	Gender, age, pediatric (age ≤18), race (White, Black, Hispanic), median income based on ZIP code, new (vs previous) diagnosis of PAH, renal insufficiency
Functional Class (FC)	Modified NYHA/WHO FC I, II, III, and IV
Vital Signs	Heart rate, systolic blood pressure
Six-Minute Walk Test	Borg Dyspnea scale, six-minute walk distance
Lab Values	Brain natriuretic peptide level, N-terminal brain natriuretic peptide level, high total bilirubin
Echocardiogram	Tei index, pericardial effusion, right ventricular dysfunction
PFT	DLco, percent predicted DLco
RHC	Pulmonary vascular resistance, pulmonary vascular resistance index, pulmonary capillary wedge pressure, cardiac index, mean right atrial pressure, mean pulmonary artery pressure, vasoreactivity

APAH-CHD, associated PAH-congenital heart disease; APAH-CTD, associated PAH-connective tissue disease; DLco, carbon monoxide diffusing capacity; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PFT, pulmonary function test; RHC, right heart catheterization; WHO, World Health Organization.

Supplementary Table 2. Univariable and Multivariable Hazard Ratios (HRs) for all Variables That Were Significant Predictors

Candidate Variables	Univariable		Multivariable	
WHO Group I PAH Subgroups	HR (95% CI)	*P* value	HR (95% CI)	*P* value
APAH-CTD: Scleroderma*	2.04 (1.58, 2.62)	<0.001	1.59 (1.24, 2.03)	<0.001
APAH-CTD: Non-Scleroderma	1.51 (1.12, 2.04)	0.008		
APAH-PoPH	1.79 (1.22, 2.64)	0.003	3.60 (2.39, 5.43)	<0.001
FPAH	1.19 (0.67, 2.12)	0.55	2.17 (1.19, 3.95)	0.012
Demographics and Comorbidities				
Renal Insufficiency	3.30 (2.33, 4.66)	<0.001	1.90 (1.33, 2.72)	<0.001
Males	1.31 (1.03, 1.67)	0.027	N/S	N/S
Age >60 years	1.90 (1.53, 2.36)	<0.001	N/S	N/S
Age ≥80 years	1.93 (1.11, 3.36)	0.020	N/S	N/S
Males Age >60 years	2.78 (2.03, 3.81)	<0.001	2.18 (1.57, 3.02)	<0.001
NYHA/WHO FC				
NYHA FC I	0.20 (0.09, 0.45)	<0.001	0.42 (0.18, 0.96)	0.039
NYHA FC III	1.46 (1.18, 1.81)	<0.001	1.41 (1.10, 1.82)	0.008
NYHA FC IV	4.51 (3.38, 6.02)	<0.001	3.13 (2.20, 4.45)	<0.001
Vitals				
Heart Rate >92 bpm	1.56 (1.24, 1.97)	<0.001	1.39 (1.10, 1.76)	0.005
Systolic BP <110 mm Hg	1.85 (1.49, 2.29)	<0.001	1.67 (1.34, 2.08)	<0.001
6MWD				
6MWD ≥ 440 m	0.30 (0.21, 0.44)	<0.001	0.58 (0.39, 0.85)	0.006
6MWD <310 m	2.63 (2.12, 3.27)	<0.001	N/S	N/S
6MWD <225 m	2.91 (2.26, 3.74)	<0.001	N/S	N/S
6MWD <165 m	3.67 (2.75, 4.90)	<0.001	1.68 (1.24, 2.29)	<0.001
Borg Dyspnea Scale ≥5	1.63 (1.25, 2.14)	<0.001	N/S	N/S
Borg Dyspnea Scale ≥8	2.41 (1.45, 4.01)	<0.001	N/S	N/S
BNP				
BNP† <50 pg/mL	0.26 (0.17, 0.41)	<0.001	0.50 (0.32, 0.79)	0.003
BNP† >180 pg/mL	3.15 (2.54, 3.91)	<0.001	1.97 (1.57, 2.49)	<0.001
High Total Bilirubin	1.86 (1.42, 2.42)	<0.001	N/S	N/S
ECHO				
Pericardial Effusion: Any	2.02 (1.61, 2.54)	<0.001	1.35 (1.06, 1.72)	0.014
Pericardial Effusion: Moderate to Severe	2.87 (1.91, 4.29)	<0.001	N/S	N/S
Pericardial Effusion: Moderate-Severe or Severe	3.42 (1.42, 8.28)	0.006	N/S	N/S

Candidate Variables	Univariable		Multivariable	
RV Dysfunction: Moderate-Severe or Severe	2.01 (1.58, 2.55)	<.001	N/S	N/S
RV Dysfunction: Severe	1.94 (1.50, 2.51)	<0.001	N/S	N/S
DLCO				
DLco ≤6	2.41 (1.67, 3.47)	<0.001	N/S	N/S
DLco <12	1.91 (1.52, 2.41)	<0.001	N/S	N/S
DLco >21	0.60 (0.39, 0.92)	0.019	N/S	N/S
% Predicted DLco ≥80	0.43 (0.27, 0.69)	<0.001	0.59 (0.36, 0.95)	0.031
% Predicted DLco ≤50	2.08 (1.66, 2.60)	<0.001	N/S	N/S
% Predicted DLco ≤32	2.61 (1.95, 3.49)	<0.001	1.46 (1.07, 1.99)	0.018
% Predicted DLco <20	2.90 (1.59, 5.29)	<0.001	N/S	N/S
RHC				
Restricted to tests within last year				
mRAP >6 mm Hg	1.69 (1.36, 2.10)	<0.001	N/S	N/S
mRAP ≥15 mm Hg	1.93 (1.39, 2.68)	<0.001	N/S	N/S
mRAP >20 mm Hg	2.98 (1.71, 5.19)	<0.001	1.79 (1.02, 3.14)	0.043
mPAP >19 mm Hg	1.30 (1.05, 1.60)	0.018	N/S	N/S
PVR >7 Wood units	1.50 (1.21, 1.86)	<0.001	N/S	N/S
PVR >24 Wood units	2.17 (1.19, 3.95)	0.012	N/S	N/S
Cardiac Index <2.8	1.43 (1.14, 1.79)	0.002	N/S	N/S
Restricted to tests within last 2 years				
mRAP >7 mm Hg	1.58 (1.27, 1.96)	<0.001	N/S	N/S
mRAP ≥17 mm Hg	1.88 (1.30, 2.70)	<0.001	N/S	N/S
mRAP ≥24 mm Hg	3.19 (1.58, 6.43)	0.001	N/S	N/S
mPAP >45 mm Hg	1.44 (1.16, 1.78)	<0.001	N/S	N/S
PVR >10 Wood units	1.52 (1.22, 1.89)	<0.001	N/S	N/S
PVRI >18 Wood units * m^2	1.40 (1.11, 1.76)	0.005	N/S	N/S
PCWP <13 mm Hg	1.28 (1.03, 1.58)	0.027	N/S	N/S
Cardiac Index ≤2.4	1.39 (1.11, 1.74)	0.004	N/S	N/S
Most recent without time restriction				
mRAP >10 mm Hg	1.71 (1.37, 2.13)	<0.001	N/S	N/S
mRAP ≥20 mm Hg	2.11 (1.40, 3.18)	<0.001	N/S	N/S
PVR >32 Wood units	2.76 (1.37, 5.56)	0.005	4.08 (2.00, 8.34)	<0.001
Cardiac Index ≤1.9	1.39 (1.08, 1.78)	0.011	N/S	N/S

*Terms for APAH-CTD subgroups were collapsed into one indicator variable in the final model;

†If n-terminal BNP is available and BNP is not, listed cut points are replaced with <300 pg/mL and >1500 pg/mL.

6MWD, six-minute walk distance; APAH-CTD, associated PAH-connective tissue disease; APAH-PoPH, associated PAH-portal hypertension; BNP, brain natriuretic peptide; BP, blood pressure; bpm, beats per minute; CI, confidence interval; DLco, carbon monoxide diffusing capacity; FC, functional class; FPAH, familial PAH; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; N/S, not significant; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; PVRI, PVR index; RHC, right heart catheterization; RV, right ventricular; WHO, World Health Organization.

Supplementary Table 3. Hazard Ratios (HRs) and 95% Confidence Intervals (CIs) From Cox Models Using Time of Enrollment or Time of Diagnosis as the Baseline

	Time of Enrollment		Time of Diagnosis	
WHO Group I PAH Subgroups	HR (95% CI)	*P* value	HR (95% CI)	*P* value
APAH-CTD	1.59 (1.24, 2.03)	<0.001	2.49 (1.51, 4.09)	<0.001
APAH-PoPH	3.60 (2.39, 5.43)	<0.001	2.32 (0.95, 5.67)	0.066
FPAH	2.17 (1.19, 3.95)	0.012	NS	NS
Demographics and Comorbidities				
Renal Insufficiency	1.90 (1.33, 2.72)	<0.001	N/A	N/A
Males Age >60 years	2.18 (1.57, 3.02)	<0.001	2.04 (0.97, 4.29)	0.060
NYHA/WHO FC				
I	0.42 (0.18, 0.96)	0.039	NS	NS
III	1.41 (1.10, 1.82)	0.008	NS	NS
IV	3.13 (2.20, 4.45)	<0.001	2.32 (1.21, 4.43)	0.011
Vitals				
Heart Rate >92 bpm	1.39 (1.10, 1.76)	0.005	N/A	N/A
Systolic BP <110 mm Hg	1.67 (1.34, 2.08)	<0.001	N/A	N/A
6MWD				
≥440 m	0.58 (0.39, 0.85)	0.006	0.38 (0.14, 1.07)	0.066
<165 m	1.68 (1.24, 2.29)	<0.001	NS	NS
BNP				
<50* pg/mL	0.50 (0.32, 0.79)	0.003	N/A	N/A
>180* pg/mL	1.97 (1.57, 2.49)	<0.001	N/A	N/A
ECHO				
Pericardial Effusion: Any	1.35 (1.06, 1.72)	0.014	N/A	N/A
DLco				
% Predicted DLco ≥80	0.59 (0.36, 0.95)	0.031	N/A	N/A
% Predicted DLco ≤32	1.46 (1.07, 1.99)	0.018	N/A	N/A
RHC				
mRAP†>20 mm Hg	1.79 (1.02, 3.14)	0.043	2.76 (1.23, 6.20)	0.014
PVR >32 Wood Units	4.08 (2.00, 8.34)	<0.001	NS	NS

*If n-terminal BNP is available and BNP is not, listed cut points are replaced with <300 pg/mL and >1500 pg/mL; †Restricted to tests performed within 1 year of enrollment, otherwise indicator is set to 0. 6MWD, six-minute walk distance; APAH-CTD, associated PAH-connective tissue disease; APAH-PoPH, associated PAH-portal hypertension; BNP, brain natriuretic peptide; BP, blood pressure; bpm, beats per minute; CI, confidence interval; DLco, carbon monoxide diffusing capacity; FC, functional class; FPAH, familial PAH; HR, hazard ratio; mRAP, mean right atrial pressure; N/A, not available; NS, not significant; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterization; WHO, World Health Organization.

Supplementary Table 4. Bootstrap Hazard Ratios (HRs) and 95% Confidence Intervals (CIs) From Cox model – Using Patients and Sites as Unit of Analysis

	Parametric Estimates	Patient-Level Bootstrap	Site-Level Bootstrap
WHO Group I PAH Subgroups	HR (95% CI)	HR (95% CI)	HR (95% CI)
APAH-CTD	1.59 (1.24, 2.03)	1.61 (1.25, 2.10)	1.59 (1.18, 2.13)
APAH-PoPH	3.60 (2.39, 5.43)	3.68 (2.41, 5.52)	3.59 (2.21, 5.90)
FPAH	2.17 (1.19, 3.95)	2.21 (1.08, 3.80)	2.19 (1.22, 3.71)
Demographics and Comorbidities			
Renal Insufficiency	1.90 (1.33, 2.72)	1.92 (1.27, 2.77)	1.94 (1.37, 2.66)
Males Age >60 years	2.18 (1.57, 3.02)	2.16 (1.50, 3.02)	2.10 (1.54, 2.97)
NYHA/WHO FC			
I	0.42 (0.18, 0.96)	0.40 (0.11, 0.82)	0.41 (0.12, 0.78)
III	1.41 (1.10, 1.82)	1.40 (1.10, 1.79)	1.44 (1.07, 1.97)
IV	3.13 (2.20, 4.45)	3.18 (2.19, 4.52)	3.22 (1.92, 5.48)
Vitals			
Heart Rate >92 bpm	1.39 (1.10, 1.76)	1.38 (1.09, 1.78)	1.39 (1.06, 1.86)
Systolic BP <110 mm Hg	1.67 (1.34, 2.08)	1.67 (1.34, 2.11)	1.68 (1.42, 2.02)
6MWD			
≥440 m	0.58 (0.39, 0.85)	0.58 (0.39, 0.82)	0.59 (0.36, 0.90)
<165 m	1.68 (1.24, 2.29)	1.71 (1.22, 2.35)	1.70 (1.28, 2.24)
BNP			
<50* pg/mL	0.50 (0.32, 0.79)	0.50 (0.30, 0.74)	0.50 (0.31, 0.76)
>180* pg/mL	1.97 (1.57, 2.49)	2.00 (1.57, 2.51)	1.97 (1.56, 2.54)
ECHO			
Pericardial Effusion: Any	1.35 (1.06, 1.72)	1.36 (1.05, 1.73)	1.37 (1.05, 1.68)
DLco			
% Predicted DLco ≥80	0.59 (0.36, 0.95)	0.58 (0.33, 0.88)	0.59 (0.35, 0.88)
% Predicted DLco ≤32	1.46 (1.07, 1.99)	1.48 (1.07, 2.10)	1.48 (1.06, 2.11)
RHC			
mRAP† >20 mm Hg	1.79 (1.02, 3.14)	1.78 (0.90, 3.06)	1.74 (0.80, 3.02)
PVR >32 Wood Units	4.08 (2.00, 8.34)	4.04 (1.88, 7.65)	4.15 (1.88, 7.61)

* If n-terminal BNP is available and BNP is not, listed cut points are replaced with <300 pg/mL and >1500 pg/mL; †Restricted to tests performed within 1 year of enrollment, otherwise indicator is set to 0.

6MWD, six-minute walk distance; APAH-CTD, associated PAH-connective tissue disease; APAH-PoPH, associated PAH-portal hypertension; BNP, brain natriuretic peptide; BP, blood pressure; bpm, beats per minute; DLco, carbon monoxide diffusing capacity; FC, functional class; FPAH, familial PAH; mRAP, mean right atrial pressure; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterization; WHO, World Health Organization.

Predicting Survival in Pulmonary Arterial Hypertension: Insights From the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL)

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