

**Contemporary Survival in Patients with Pulmonary Arterial Hypertension:
A Reappraisal of the National Institutes of Health Risk Stratification Equation**

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Running head: Contemporary Survival in PAH

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ABSTRACT

We sought to determine contemporary survival in pulmonary arterial hypertension (PAH) and to investigate whether the National Institutes of Health (NIH) equation still remains an accurate predictor of survival.

In 576 patients with PAH referred to us from 1991 to 2007, we described observed survival using the Kaplan-Meier method. In patients with idiopathic, familial, and anorexigen-associated PAH (N=247), we compared observed versus NIH equation predicted survival. We developed a new survival prediction equation using exponential regression analysis.

The observed 1-, 3-, and 5-year survival in the total cohort were 86%, 69%, and 61%, respectively. In patients with idiopathic, familial, and anorexigen-associated PAH, the observed 1-, 3-, and 5-year survival (92%, 75%, and 66% respectively) were significantly higher than the predicted survival (65%, 43%, and 32% respectively). Our new equation [$P(t) = e^{-A(x, y, z) \cdot t}$], $A(x, y, z) = e^{(-1.270 - 0.0148x + 0.0402y - 0.361z)}$; t: time interval in years; x: mean pulmonary artery pressure; y: mean right atrial pressure, and z: cardiac index] performed well when applied to published contemporary studies of survival in PAH.

Contemporary survival in our PAH cohort was better compared to that predicted by the NIH registry equation. The NIH equation underestimated survival in idiopathic, familial, and anorexigen-associated PAH. Once prospectively validated, our new equation may be used to determine prognosis.

INTRODUCTION

Pulmonary arterial hypertension (PAH), a debilitating disease characterized by progressive obstruction and obliteration of the pulmonary arteries, eventually leads to right ventricular failure and death [1]. PAH can be idiopathic, familial, or associated with other conditions including connective tissue disease, congenital heart disease, portal hypertension, human immunodeficiency virus (HIV), and anorexigen drug exposure[1]. A landmark National Institutes of Health (NIH) registry study, published in 1987, described the clinical characteristics and natural history of patients with primary pulmonary hypertension (PPH), which included idiopathic, familial, and anorexigen-associated PAH [2]. The NIH registry proposed an empirically derived equation, based on baseline hemodynamics, to estimate survival in patients with PPH [3]. Subsequently many clinical trials in PAH have used the NIH equation to suggest improvement in survival by comparing observed survival rates on a study drug vs. survival rates predicted by the NIH equation [4-9].

The NIH registry was initiated during a time when there were no U.S. Food and Drug Administration (FDA) approved therapies for PAH. Patients in the NIH registry were treated only with conventional therapy, which included diuretics, digoxin, supplemental nasal oxygen and, in a minority of cases, anticoagulation with warfarin and/or vasodilators such as calcium channel blockers and hydralazine [2-3]. Over the past two decades, however, the management and therapies of PAH have changed significantly [10].

We aimed to (1) characterize contemporary survival in patients with World Health Organization (WHO) category I PAH, and (2) determine whether the NIH equation is still an accurate predictor of survival in patients with idiopathic, familial, and anorexigen-associated PAH (previously classified as PPH).

METHODS

Study Subjects

We studied patients in the Pulmonary Hypertension Connection (PHC) registry, which we initiated in March 2004. This database has been described in detail previously [11]. Briefly, the PHC registry was created as a customized patient database to longitudinally collect specific variables on every patient treated in our practice. The practice has been sequentially based at three university medical centers in Chicago since 1982. We entered patients in to the database retrospectively from 1982 to February 2004 and prospectively from March 2004 onwards. The recruitment period for the current analysis ended in August 2007. All new patients gave informed consent for participation in the registry during the initial evaluation. Patients who were already being treated at our center prior to the initiation of the registry gave informed consent during a routine office visit. Each local Institutional Review Board approved the registry.

From the PHC registry, we identified all adult patients (≥ 18 years of age at time of referral) with PAH (N = 654). In brief, the diagnosis of PAH required the following: (1) mean pulmonary artery pressure (mPAP) > 25 mm Hg at rest with a pulmonary capillary wedge pressure (PCWP) < 15 mm Hg; and (2) the exclusion of other WHO categories of pulmonary hypertension by clinical evaluation and objective tests [12]. To make our study cohort more comparable to the NIH registry, we excluded 52 patients who were on approved PAH therapy at the time of referral (17 were on prostacyclins, 27 were on bosentan, and 8 were on sildenafil). In addition, we excluded 26 patients diagnosed with PAH before 1991 in order to avoid entering patients who may have been in the NIH registry cohort (recruitment 1981-1985 with follow-up through 1988 and published in 1991). The remaining 576 patients formed our study group, 100 (17%) of whom were studied prospectively (enrolled after initiation of the registry in March

2004). Of the 576 patients in the study group, 282 (49%) patients with idiopathic, familial, and anorexigen-associated PAH formed a subgroup which matched the NIH registry. We included patients with anorexigen-associated PAH in the subgroup since the NIH registry included patients exposed to anorexigens, and based on the recent study by Souza et al demonstrating no significant survival difference between anorexigen-associated PAH and idiopathic and familial PAH patients [13]. Figure I illustrates the study flow chart.

Variables

We analyzed the following baseline variables at the time of referral for characterization of clinical phenotype: demographic data including age and sex, co-morbidities, WHO functional class, medications, and exercise treadmill testing (ETT) using the Naughton-Balke protocol as a measure of exercise capacity [14]. We have previously shown that the ETT is comparable to the six minute walk test and a predictor of mortality in patients with pulmonary hypertension[15-16].

Five hundred twenty one of the 576 patients in the study group (91%) and 270 of the 282 patients with idiopathic, familial, and anorexigen-associated PAH (96%) underwent baseline hemodynamic testing by right heart catheterization. More than 95% of catheterizations were performed at our institution by pulmonary hypertension specialists. Hemodynamic testing included measurement of mean right atrial pressure (mRAP), mPAP, PCWP, cardiac index (CI), and pulmonary vascular resistance (PVR). An acute vasodilator challenge with adenosine was performed during right heart catheterization as described previously [17].

Long-Term Management

All patients who “responded” to acute vasodilator challenge were treated with calcium channel blockers. Initially, we defined positive response as a 20% decrease in mPAP with an increase in CI, but after 2005, we used the following definition: a decrease in mPAP of >10 mm Hg, and to a level below 40 mm Hg, with unchanged or increased CI [18]. Patients who did not respond to the acute vasodilator challenge received either monotherapy or combination therapy with endothelin antagonists, phosphodiesterase inhibitors, or prostacyclins, based on the severity of symptoms. All patients in our cohort without contraindications were offered anticoagulation with warfarin to achieve a target INR of 2 to 3. Patients with arterial oxygen saturation less than 90%, either at rest or during exercise, were prescribed supplemental nasal oxygen. In addition, patients received diuretics and digoxin as needed to treat symptoms of right heart failure. Patients were followed closely every 6-12 months on an outpatient basis and more frequently if medically necessary.

Mortality

We obtained vital statistics for all patients by chart review and Social Security Death Index (SSDI). For each death, we collected the date of death. In all patients who were not identified as deceased by the SSDI, we were able to establish vital status by chart review.

Statistical Analysis

Baseline categorical variables are expressed as frequencies and proportions whereas continuous variables are expressed as mean \pm standard deviation. We calculated survival rates using Kaplan-Meier method and standard life table analyses. The date of baseline right heart catheterization was used as the date of entry into the study as was done in the NIH registry [3].

For patients who survived during follow-up, the date of data cut-off (10 August 2007) was used as the censoring date. For patients who did not undergo initial right heart catheterization, we used the date of referral to our practice as the enrollment date. We compared survival before and after 2002 because bosentan, the first oral therapy for PAH, was approved for use in the United States in 2002. Prior to 2002, treatment consisted of conventional therapy and epoprostenol. For idiopathic, familial, and anorexigen-associated PAH patients with available baseline hemodynamics, we calculated expected survival for each patient based on the NIH equation:

$$P(t) = [H(t)]^{A(x, y, z)}$$

$$\text{Where } H(t) = [0.88 - 0.14(t) + 0.01(t^2)]$$

t is time interval in years

$$A(x, y, z) = e^{(0.007325x + 0.0526y - 0.3235z)}$$

x is mPAP, y is mRAP, and z is CI.

The probabilities of survival at 1, 3, and 5 years are as follows: $P(1) = 0.75^A$, $P(3) = 0.55^A$, and $P(5) = 0.43^A$.

We compared the proportion of observed survival at each time-period with expected survival using chi-squared tests. We performed univariate and multivariate Cox proportional hazards analyses to determine the independent predictors of survival in the total study cohort as well as in the subgroup of patients with idiopathic, familial, and anorexigen-associated PAH. The proportional hazards assumption was tested in all models. We performed univariate analysis with the all baseline characteristics variables. For our final multivariate analyses, we retained any variables with $P < 0.1$ on univariate analysis. In our analysis of the total PAH cohort, we used IPAH/FPAH/anorexigen as the referent group to which we compared all other etiologies of PAH. Only connective tissue disease was statistically significant and retained in final multivariable

models. Functional class and treadmill exercise capacity were significantly correlated (correlation coefficient = 0.73, $p < 0.0001$), so only functional class was retained in the final models to avoid multicollinearity. In addition, separate models were created for each hemodynamic variable to avoid multicollinearity.

In the subgroup of patients with idiopathic, familial, and anorexigen associated PAH, we developed a new survival prediction equation using first a Weibull model followed by an exponential regression model for ease of use [19]. We predetermined *a priori* that the three hemodynamic predictors (mPAP, mRAP, and CI) from the NIH model were clinically relevant to include in the model. We then added the variables that were statistically significant in univariate analysis to these 3 hemodynamic variables to complete the model. Variables were then removed from the model one at a time, using backward elimination. Similar to the NIH equation, only mPAP, mRAP, and CI were retained in our final model, and all three were statistically significant.

In addition, to address concerns about including patients who were calcium channel blocker responders (N=11; all had positive response to vasodilator study during invasive hemodynamic study), we developed a separate equation for responders. We also analyzed our data to see if exclusion of calcium channel blocker responders significantly altered overall survival of the cohort.

To validate our new survival equation, we applied it to three published idiopathic and familial PAH patient cohorts and compared the published observed survival with that predicted by our new survival equation based on the baseline mean hemodynamic data (mPAP, mRAP, and CI) of these study cohorts [8, 20]. All statistical analyses were performed using Stata version 9 (StataCorp LP, College Station, TX).

RESULTS

All Patients with PAH

Baseline characteristics

The mean age upon entry into our registry was 48 ± 14 years and 77% were female (Table I). The majority of subjects (80%) had WHO functional class III or IV symptoms, and poor baseline exercise capacity, achieving a maximum workload of only 3.6 ± 2 metabolic equivalents (METs) on Naughton-Balke protocol ETT. At the time of referral, subjects were on conventional therapy and had severe hemodynamics (Table I).

Survival

Median follow-up time was 3.9 years (interquartile range 1.7 – 7.8 years; maximum follow up time 16.6 years). Of the 576 study patients, 307 (53%) died during follow-up. Vital status was available on all patients but survival time was missing on 30 patients and 1 patient died on the same date of enrollment; therefore, these patients were excluded, leaving 545 patients for final survival analyses. The observed 1-, 3-, and 5-year survival rates for the total PAH cohort were 86%, 69%, and 61%, respectively. The 1-, 3-, and 5-year survival rates were not affected by excluding patients who had a positive vasodilator response to adenosine acutely during invasive hemodynamic testing (Supplemental Figure I).

Multivariable analysis

On univariate analysis in the total cohort (N=576), age, connective tissue disease etiology, worse functional class, decreased exercise capacity, increased mRAP, increased PVR, and decreased CI were all associated with an increased risk of death (Table III). On multivariable

analysis, age, connective tissue disease etiology, functional class, mRAP, and CI all remained independent predictors of death (Table IV).

Subgroup (Idiopathic, familial, and anorexigen-associated PAH)

Baseline Characteristics

The mean age upon entry into our registry was 46 ± 14 years (approximately 10 years older than the NIH registry subjects). The baseline demographic, clinical, and hemodynamic characteristics of the idiopathic, familial, and anorexigen-associated PAH subgroup was comparable to those of patients in the NIH registry (Table II).

Survival

Median follow up time in the subgroup of patients with idiopathic, familial, and anorexigen-associated PAH was 4.9 years (interquartile range 2.3 – 8.7 years; maximum follow up time 16.6 years), and during follow-up, 149/282 (53%) died. Survival time was missing on 16 patients, leaving 266 patients for survival analyses. The observed 1-, 3-, and 5-year survival rates were 91%, 75%, and 65% respectively, and were better compared to patients with PAH associated with connective tissue disease, congenital heart disease, portal hypertension, and HIV (Figure II). Patients diagnosed with idiopathic, familial, and anorexigen-associated PAH after 2002 had a better survival compared to those diagnosed before 2002 (Supplemental Figure II). Of the 282 subgroup patients with idiopathic, familial, and anorexigen-associated PAH, all three baseline hemodynamic data (mRAP, mPAP, and CI) required to calculate survival using the NIH equation were available in 247 patients: mPAP 55 ± 12 mmHg, mRAP 11 ± 6 mmHg, and CI 2.0 ± 0.6 L/min/m². The observed 1-, 3-, and 5-year survival for these patients with available

hemodynamic data were 92%, 75%, and 66%, respectively, which did not differ significantly from those without hemodynamic data. In contrast, the predicted 1-, 3-, and 5-year survival rates, calculated using the NIH equation, were 65%, 43%, and 32%, respectively. The observed survival was significantly greater than the predicted survival at 1, 3, and 5 years ($p < 0.0001$ for all comparisons).

Multivariable analysis

On univariate analysis in the subgroup (N=282), age, worse functional class, decreased exercise capacity, increased mRAP, and decreased CI were all associated with an increased risk of death (Table III). On multivariable analysis, age, functional class, mRAP, and CI remained as independent predictors of death (Table V).

Development of a new survival equation: The Pulmonary Hypertension Connection (PHC) equations

In the subgroup of patients with idiopathic, familial, and anorexigen-associated PAH, we derived the following equation to predict an individual patient's chances of survival based on an exponential regression analysis:

$$P(t) = e^{-A(x, y, z) \cdot t}$$

PHC non-responders: $A(x, y, z) = e^{(-1.270 - 0.0148x + 0.0402y - 0.361z)}$ for non-responders to calcium channel blockers

PHC responders: $A(x, y, z) = e^{(-3.012 - 0.0148x + 0.0402y - 0.361z)}$ for responders to calcium channel blockers

Where:

$P(t)$ = probability of survival

t = number of years after diagnosis

x = mPAP

y = mRAP

z = CI

Example 1: A patient with mPAP of 40 mm Hg, mRAP of 3 mm Hg, CI of 3.5 L/min/m², and who did not respond to an acute vasodilatory challenge would have 1-, 2-, and 3- year survival estimates as follows:

$$A(x, y, z) = e^{(-1.270 - 0.0148(40) + 0.0402(3) - 0.361(3.5))} = 0.049544$$

$$1\text{-year survival} = P(1) = e^{-(0.049544)(1)} = 0.952 = 95\%$$

$$2\text{-year survival} = P(2) = e^{-(0.049544)(2)} = 0.905 = 90.5\%$$

$$3\text{-year survival} = P(3) = e^{-(0.049544)(3)} = 0.861 = 86\%$$

Example 2: A patient with the exact same hemodynamics to the patient in the first example (mPAP 40 mm Hg, mRAP 3 mm Hg, CI 3.5 L/min/m²) but who has a positive response to an acute vasodilatory challenge would have 1-, 2-, and 3- year survival estimates as follows:

$$A(x, y, z) = e^{(-3.012 - 0.0148(40) + 0.0402(3) - 0.361(3.5))} = 0.008679$$

$$1\text{-year survival} = P(1) = e^{-(0.008679)(1)} = 0.991 = 99\%$$

$$2\text{-year survival} = P(2) = e^{-(0.008679)(2)} = 0.983 = 98\%$$

$$3\text{-year survival} = P(3) = e^{-(0.008679)(3)} = 0.974 = 97\%$$

Sensitivity analyses demonstrated that the Cox proportional hazard estimates of the effects of the predictor variables were virtually identical to those from the Weibull or exponential models of the equation. Figure III displays the actual vs. predicted survival (using both our new equation and the NIH equation) in the subgroup patients with idiopathic, familial, and anorexigen-associated PAH. When we applied our new equation to other published PAH patient cohorts, the predicted survival calculated using our new equation was comparable to the actual observed survival (Figure IV).

DISCUSSION

We have shown that survival rates in patients with WHO Category I PAH have improved considerably when compared to the NIH registry cohort. The observed 1-, 3-, and 5-year survival rates for the total PAH cohort were 86%, 69%, and 61%, respectively. This is the first evaluation of survival of WHO Category I PAH patients. In patients with idiopathic, familial, and anorexigen associated PAH, the observed survival rates at 1, 3, and 5 years were significantly higher than the predicted survival calculated using the NIH equation, and patients diagnosed after 2002 appeared to have a better survival than those diagnosed before 2002. From our cohort, we developed a new regression equation to estimate survival, based on baseline hemodynamics, in patients with idiopathic, familial, and anorexigen associated PAH. Survival calculated using this new equation performed well when applied to other published patient cohorts [8, 20].

The NIH registry, which prospectively collected data on 187 patients with PPH from 32 centers in the United States between July 1981 and September 1985, described the clinical

characteristics of PPH and its natural history over a seven-year period in an era when there were no approved PAH-specific therapies. In the NIH registry, patients had a median survival time of 2.8 years. The 1-, 3-, and 5-year survival rates were only 68%, 48% and 34% respectively [3]. Mortality correlated with baseline mRAP, mPAP, and CI. The NIH registry proposed an equation to predict survival, which was subsequently validated by Sandoval et al in a small Mexican cohort of 61 patients with PPH [21]. In this study, the predicted survival and the actual observed survival were closer in the patients who received no long-term oral vasodilatory therapy, but the predicted survival underestimated the actual survival in the group as a whole.

The improved survival in our patients with WHO Category I PAH, and our subgroup analysis compared to the NIH registry cohort may be due to a multitude of synergistic factors. The number of PAH patients referred to tertiary care centers has increased when compared to the NIH registry time period, and physicians are much more familiar with treating right heart failure. However, since most patients were still referred late (functional class III and IV), it may be that the natural history of the disease itself changed. Etiology had a small impact on survival. This may be due to the interaction with the other variables in the multivariable model lessening its effect and the other factors may be stronger predictors. Another factor for improved survival may be the greater use of anticoagulation with warfarin. PAH treatment guidelines recommend warfarin for patients with idiopathic, familial, and anorexigen associated PAH [10] based on two small retrospective clinical trials showing improved survival in PAH patients treated with long-term warfarin therapy[22-23], but it has not been validated in a prospective, randomized clinical trial. Early detection with echocardiography and heightened awareness of PAH may have increased the number of patients evaluated and treated earlier in the course of the disease, explaining their presentation to a referral center a decade later than the NIH registry. Although

earlier intervention may translate into improved survival, we cannot exclude the possibility that lead-time bias is also a factor. However, patients in our cohort were older than those studied in the NIH registry and had similar severity of functional class and hemodynamic abnormalities at the time of initial presentation, arguing against lead-time bias due to earlier diagnosis. This also argues against the possibility of a selected population of less severe disease patients surviving, a “cohort effect” as an explanation for the improved survival.

Our analyses included patients with a positive vasodilatory response, an independent predictor of survival. [7, 18, 23-24] However, the number of responders was significantly lower in our total study cohort (13/576; 2.3%) as well as in the subgroup of patients with idiopathic, familial, and anorexigen-associated PAH (11/ 282; 3.9%). In addition, the number of responders across eras in our database was consistent and low (3.7%, 4.2%, 5.8%; $p=NS$) [11]. Excluding responders did not affect the survival rates significantly, which is likely due to the small numbers of patients who had a positive vasodilatory response acutely during invasive hemodynamic testing. (Supplemental Figure I). We therefore do not believe that positive vasodilatory response acutely has played a significant role in improved survival. However, given the much better survival in patients who have a positive acute vasodilatory response, we derived a separate, new equation for responders.

Finally, improved survival may be due to the availability of approved PAH medications, which include prostacyclin and its analogues, endothelial antagonists, and phosphodiesterase inhibitors.[10] . Figure 3 illustrates that with the availability of oral agents and prostacyclins, it appears that survival has improved. It remains unknown whether the current PAH-specific therapies actually improve long-term survival, as there are no long-term randomized treatment trials with any therapy for PAH. This study is an observational study and thus the true effect of

new therapies on survival can not be evaluated. A recent meta-analysis by Galie et al suggested an improvement of survival in patients treated with PAH-specific therapies (relative risk of all-cause mortality: 0.57; 95% CI 0.35-0.92; $P = 0.023$) [25]. In contrast, in a meta-analysis by Macchia et al, none of the currently available PAH-specific therapies were associated with long-term survival benefit [26]. Thus, to ascertain whether there are any long-term survival benefits with the currently available newer PAH-specific therapies, prospective, randomized placebo-controlled trials, which evaluate clinical outcomes, including true surrogates of death if not death itself, stratified to specific etiologies of PAH will be required [26]. A new formula gives us a new baseline to compare with once it has been validated in independent cohorts.

We decided to revise the NIH formula only when we found a better than predicted survival, understanding that this was only a registry. Our equation included anorexigen-associated PAH since the NIH registry included patients exposed to anorexigens, and based on the recent Souza et al study demonstrating no significant survival difference between anorexigen-PAH and idiopathic and familial PAH patients [13]. If prospectively validated in another idiopathic, familial, and anorexigen-associated PAH cohort, our new equation could be used to estimate contemporary survival in this patient population. In addition, our new survival equations could potentially be used in the clinical and research settings to determine response to therapy and changes in prognosis that occur with changes in invasive hemodynamic profile. Survival in WHO category I PAH patients as a whole should not be evaluated using these equations since congenital heart disease-associated PAH carries a better prognosis, and connective-tissue disease-associated PAH carries a worse prognosis than other forms of PAH [27-28].

Limitations

Our data collection started in 2004 and thus most patients were entered retrospectively. All patients in our cohort were cared for by a single tertiary referral practice; therefore, our results may not be generalizable. The cohort consisted of both incident and prevalent cases which may have contributed to a survival bias. We did not collect subsequent treatment data for each individual patients, hence, the proportion of patients treated with different PAH specific therapies is not available. Thus, our study does not address the key issue whether or not the current PAH-specific therapies affect survival. Nine percent of the study cohort did not have baseline invasive hemodynamics; however, the majority of these patients had follow-up right heart catheterization, which confirmed the diagnosis of PAH. Finally, our new equation was developed based on a heterogeneous patient collection on variety of PAH-specific therapies. Thus, it may not be useful for demonstrating improved survival with a new drug in clinical trials, but may be helpful for clinical prognostication if prospectively validated.

CONCLUSIONS

Contemporary survival in patients with PAH is significantly better than the NIH registry cohort. The NIH equation underestimates survival in patients with idiopathic, familial, and anorexigen associated PAH in our PHC registry. If prospectively validated, our new regression survival equations (PHC equations) should assist in determining prognosis in patients with idiopathic, familial, and anorexigen associated PAH.

ACKNOWLEDGEMENT

We thank Ronald A. Thisted, Ph.D., Chairman of Department of Health Studies at the University of Chicago for his expert statistical review of the survival analysis. This study was supported by Grant Number UL1RR024999 from the National Center For Research Resources. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center For Research Resources or the National Institutes of Health.

FINANCIAL SUPPORT

Dr. Shah was supported by a Heart Failure Society of America Research Fellowship Award, Actelion Entelligence Young Investigator Award, and an American Heart Association Scientist Development Grant. Dr. Rich previously served as a part-time salaried employee at United Therapeutics, which concluded in January 2007. Dr. Archer's research is supported by the Canadian Institutes for Health Research and by NIH grant HL071115. Dr. Gomberg-Maitland has received research grant support from Actelion, Gilead, Lilly/Icos, Pfizer, and United Therapeutics and has served as a consultant and/or on advisory boards for Biomarin, Gilead, Medtronic, Millenium, Pfizer, and United Therapeutics. She has a patent filed entitled, "Compositions and Methods for Treating Pulmonary Hypertension" for the use of sorafenib in pulmonary hypertension.

The funding sources had no role in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

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TABLES

Table I: Baseline Characteristics of All Patients with PAH

Characteristics	All PAH (N = 576)
Age, years (SD)	48 (14)
Female, n (%)	445 (77)
WHO functional class III and IV, n (%): N = 559	449 (80)
Medications [†] , n (%)	
• Calcium channel blockers	177 (31)
• Warfarin	154 (27)
• Digoxin	94 (16)
• Diuretics	275 (48)
Exercise capacity, METs (SD): N = 335	3.6 (2)
Etiology, n (%)	
• Idiopathic	239 (42)
• Familial	23 (4)
• Anorexigen	20 (3)
• Connective tissue disease	173 (30)
• Congenital heart disease	64 (11)
• Portal hypertension	48 (8)
• Human immunodeficiency virus	9 (2)
Hemodynamics (SD): N = 521	
• Right atrial pressure, mm Hg	11 (6)

• Mean pulmonary artery pressure, mm Hg	52 (14)
• Pulmonary capillary wedge pressure, mm Hg	10 (4)
• Cardiac index, l/min/m ²	2.2 (0.9)
• Pulmonary vascular resistance, Woods unit	12.4 (7.3)
• Acute vasodilatory response [‡]	13 (2.3)

PAH = pulmonary arterial hypertension; WHO = World Health Organization; SD = standard deviation; METs = metabolic equivalents; Data complete for all characteristic except as listed. [†] = therapy that patients were taking upon referral to our center. [‡] = positive vasodilator response was defined as a fall in mean pulmonary artery pressure of >10 mm Hg, and to a level below 40 mm Hg, with unchanged or increased cardiac output.

Table II: Baseline Characteristics of Patients with Idiopathic, Familial, and Anorexigen-Associated PAH

Characteristics	Subgroup*	NIH Registry [†]
	(N = 282)	(N = 187)
Age, years (SD)	46 (14)	36 (15)
Female, n (%)	214 (76)	118 (63)
WHO functional class III and IV, n (%)	225 (82)	133 (71)
Medications, n (%)		
• Calcium channel blockers	82 (29)	NA
• Warfarin	91 (32)	NA
• Digoxin	43 (15)	NA
• Diuretics	130 (46)	NA
Exercise capacity, METs (SD): N = 180	3.8 (2)	NA
Hemodynamics (SD): N = 270		
• Right atrial pressure, mm Hg	11(6)	9 (6)
• Mean pulmonary artery pressure, mm Hg	55 (12)	60 (18)
• Pulmonary capillary wedge pressure, mm Hg	10 (4)	9 (4)
• Cardiac index, l/min/m ²	2.0 (0.6)	2.3 (0.9)
• Pulmonary vascular resistance, Woods unit	13.9 (6.7)	NA
• Acute vasodilatory response [‡]	11(3.9)	NA

PAH= pulmonary arterial hypertension, WHO = World Health Organization; NIH = National institutes of Health; METs = metabolic equivalents; NA = not available; Subgroup * =

idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension; † = The NIH registry data listed for comparison and not included in any analysis; SD = standard deviation; ‡ = positive vasodilator response was defined as a fall in mean pulmonary artery pressure of >10 mm Hg, and to a level below 40 mm Hg, with unchanged or increased cardiac output.

Data complete for all characteristic except as listed.

Table III: Univariate Predictors of Death on Cox Proportional Hazards Analysis

Predictor	All PAH			Subgroup*		
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age at diagnosis (per decade increase)	1.26 (1.12-1.40)	<0.0001	1.18 (1.04-1.35)			0.009
Functional class (referent group = I)						
• II	4.51 (1.37-14.84)	0.013	2.87 (0.82-10.12)			0.100
• III	7.94 (2.53-24.97)	<0.0001	3.96 (1.24-12.60)			0.020
• IV	11.6 (3.68-36.63)	<0.0001	5.16 (1.60-16.66)			0.006
Exercise capacity (per 1-MET increase)	0.78 (0.70-0.87)	<0.0001	0.86 (0.76-0.98)			0.026
Etiology (referent group = idiopathic and familial PAH)						
• Anorexigens	1.75 (0.98-3.11)	0.055				
• Connective tissue disease	1.75 (1.34-2.29)	<0.0001				
Hemodynamics						
• Right atrial pressure (per 5 mm Hg increase)	1.29 (1.18-1.41)	<0.0001	1.37 (1.21-1.55)			<0.0001
• Cardiac index (per 1 L/min/m ² increase)	0.73 (0.61-0.88)	0.001	0.56 (0.41-0.77)			<0.0001
• Pulmonary vascular resistance (per 5 Wood unit increase)	1.11 (1.03-1.21)	0.009	1.06 (0.94-1.20)			NS

HR = hazard ratio; CI = confidence intervals; MET = metabolic equivalents; PAH = pulmonary arterial hypertension, and NS = not significant (P-value <0.1 was considered significant). Subgroup * = idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension.

Table IV: Multivariate Predictors of Death on Cox Proportional Hazards Analysis in All Patients with PAH

Variable	Hazard Ratio (95% CI)		
	Regression 1*	Regression 2 [†]	Regression 3 [‡]
Age at diagnosis (per decade increase)	1.22 (1.11-1.35)	1.19 (1.08-1.31)	1.18 (1.07-1.30)
Connective tissue disease etiology	1.70 (1.29-2.24)	1.66 (1.25-2.20)	1.64 (1.23-2.18)
Functional class (per 1-unit increase)	1.43 (1.20-1.72)	1.60 (1.34-1.92)	1.42 (1.17-1.71)
Right atrial pressure (per 5 mmHg increase)	1.30 (1.18-1.44)	—	—
Mean pulmonary artery pressure (per 5 mmHg increase)	—	1.02 (0.97-1.08)	—
Cardiac index (per 1-unit increase)	—	—	0.79 (0.65-0.96)

* Regression 1 independent variables: age at diagnosis, connective tissue disease etiology of PAH, functional class, and right atrial pressure; [†] Regression 2 independent variables: age at diagnosis, connective tissue disease etiology of PAH, functional class, and mean PA pressure; [‡] Regression 3 independent variables: age at diagnosis, connective tissue disease etiology of PAH, functional class, and cardiac index; CI: confidence intervals; and PAH: pulmonary arterial hypertension.

Likelihood ratio analysis:

Regression 1 vs. model with age, connective tissue disease etiology, and functional class alone: p<0.0001

Regression 2 vs. model with age, connective tissue disease etiology, and functional class alone: p=0.35

Regression 3 vs. model with age, connective tissue disease etiology, and functional class alone: p=0.013

Model with age, connective tissue disease etiology, functional class, and right atrial pressure is the best model. Adding cardiac index doesn't help discriminate further (LR test for model 1 with CI vs. model 1 without CI: p = 0.47).

Table V: Multivariate Predictors of Death on Cox Proportional Hazards Analysis in Idiopathic, Familial, and Anorexigen-

Associated PAH

Variable	Hazard Ratio (95% CI)		
	Regression 1*	Regression 2 [†]	Regression 3 [‡]
Age at diagnosis (per decade increase)	1.21 (1.04-1.39)	1.17 (1.01-1.34)	1.21 (1.05-1.39)
Functional class (per 1-unit increase)	1.17 (0.92-1.51)	1.41 (1.10-1.80)	1.12 (0.86-1.45)
Right atrial pressure (per 5 mmHg increase)	1.42 (1.23-1.65)	—	—
Mean pulmonary artery pressure (per 5 mmHg increase)	—	1.01 (0.94-1.08)	—
Cardiac index (per 1-unit increase)	—	—	0.54 (0.38-0.77)

* Regression 1 independent variables: age at diagnosis, functional class, and right atrial pressure; [†] Regression 2 independent variables: age at diagnosis, functional class, and mean PA pressure; [‡] Regression 3 independent variables: age at diagnosis, functional class, and cardiac index; CI: confidence intervals; and PAH: pulmonary arterial hypertension.

Likelihood ratio analysis:

Regression 1 model vs. age and functional class alone: p<0.0001

Regression 2 model vs. age and functional class alone: p=0.78

Regression 3 model vs. age and functional class alone: p=0.0004

Model with age, functional class, and right atrial pressure is the best model. LR test for model 1 with CI vs. model 1 without CI: p = 0.063. Therefore, in the PPH subgroup, adding cardiac index is marginally additive.

FIGURE LEGENDS

Figure I:

Title: Study Flow Diagram

Caption: PAH = pulmonary arterial hypertension, mRAP = mean right atrial pressure, mPAP = mean pulmonary arterial pressure, CI = cardiac index, and NIH = National institutes of Health

Figure II:

Title: Survival in Idiopathic, Familial, and Anorexigen-Associated PAH vs. APAH.

Caption: PAH = pulmonary arterial hypertension, APAH = PAH associated with connective tissue disease, congenital heart disease, portal hypertension, and human immunodeficiency virus (n = 294); IPAH, FPAH, and Anorexigen = idiopathic, familial, and Anorexigen-associated PAH, respectively (n = 282).

Figure III:

Title: Observed vs. Predicted Survival using the PHC Equation and the NIH Equation in Patients with Idiopathic, Familial, and Anorexigen-Associated PAH

Caption: PHC = pulmonary hypertension connections, PAH = pulmonary arterial hypertension, NIH = National Institutes of Health.

Figure IV:

Title: Actual vs. Predicted Survival using the New Equations in Published PAH Cohorts.

Caption:

A: Survival with first-line bosentan in patients with primary pulmonary hypertension [8]

B and C: Survival in patients with class III idiopathic PAH treated with first line oral bosentan compared with an historical cohort of patients started on intravenous epoprostenol [20](B = bosentan group, C = IV epoprostenol group).

PAH = pulmonary arterial hypertension.

Figure I: Study Flow Diagram

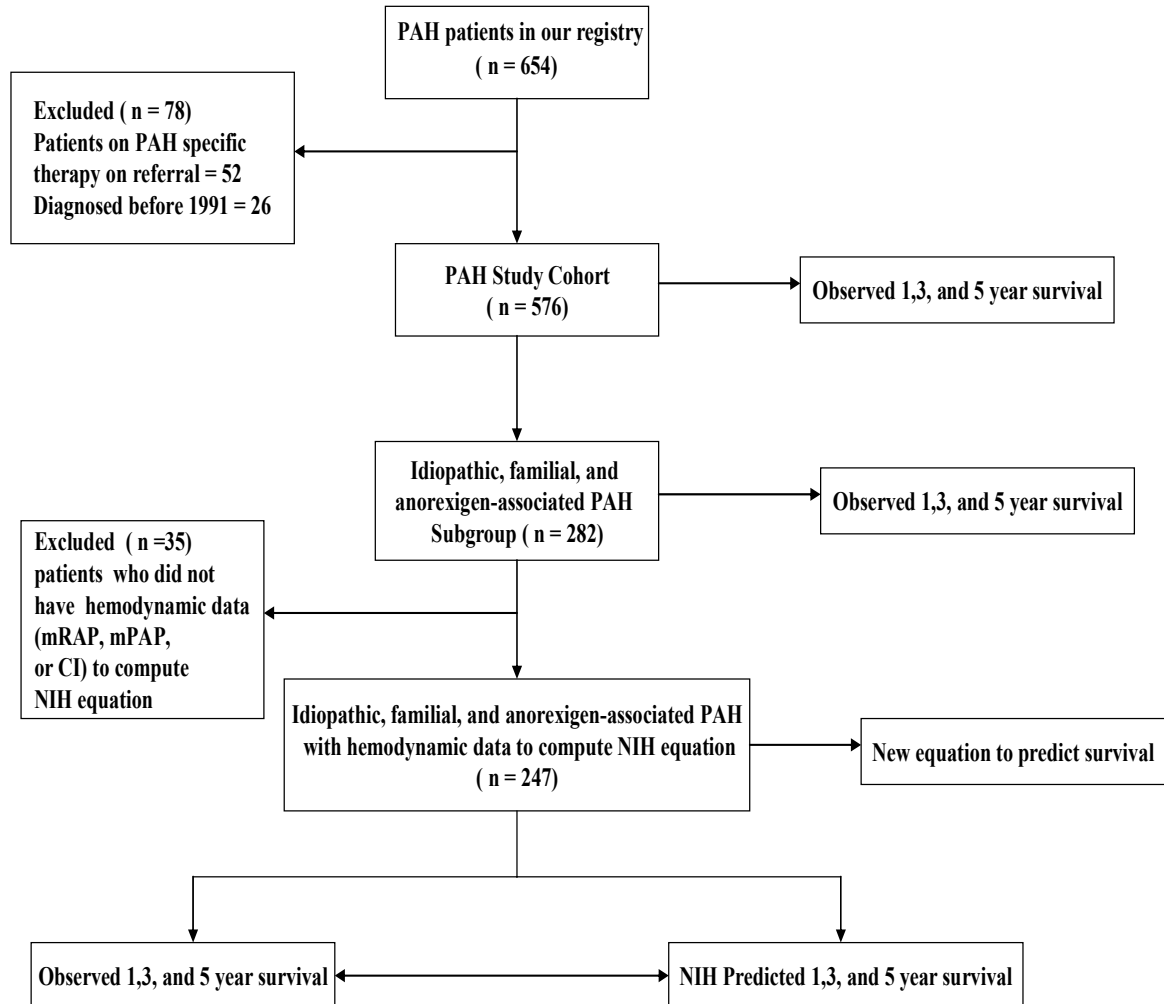


Figure II: Survival in Idiopathic, Familial, and Anorexigen-Associated PAH vs. APAH

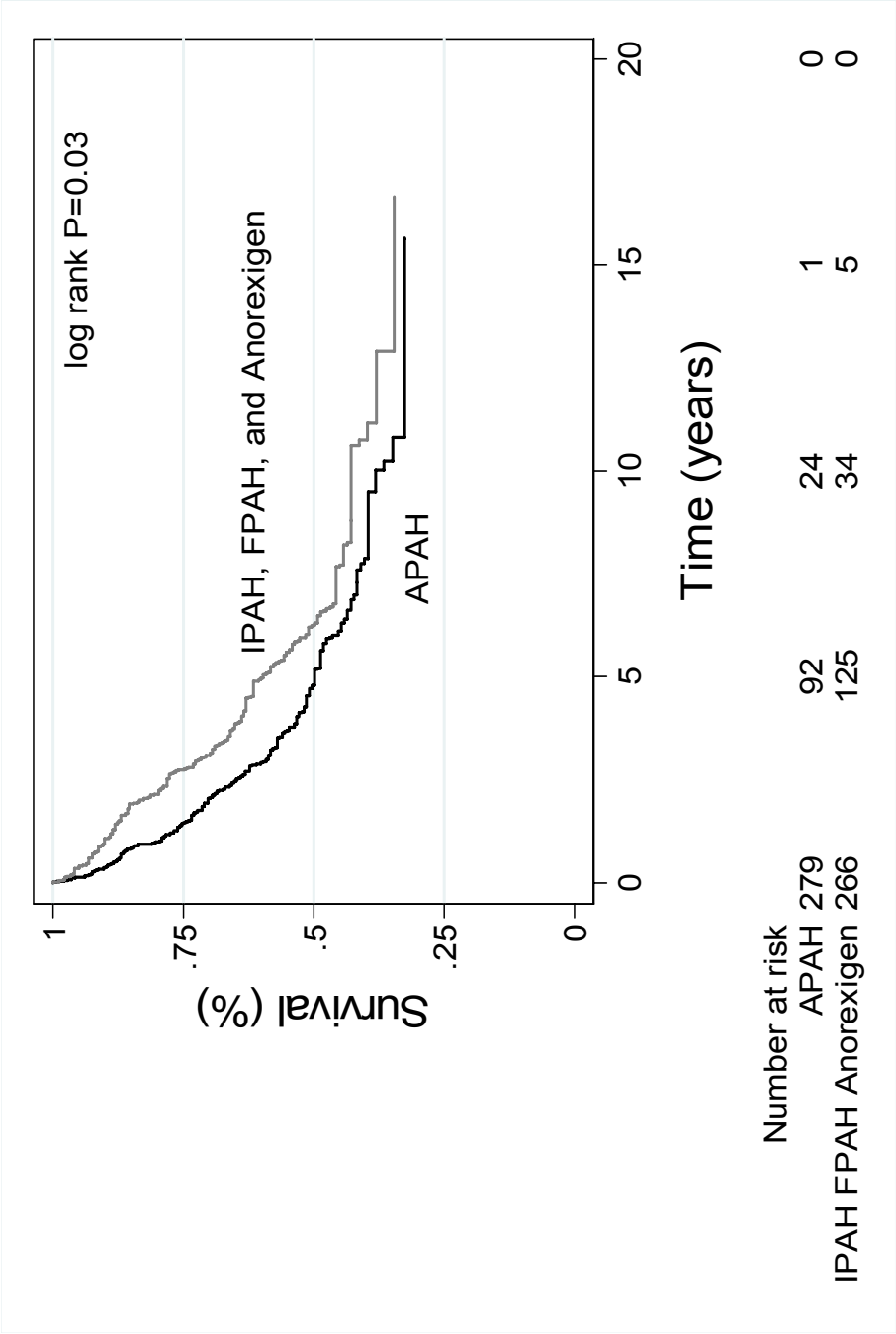


Figure III: Observed vs. Predicted Survival using the PHC Equation and the NIH Equation in Patients with Idiopathic, Familial, and Anorexigen-Associated PAH

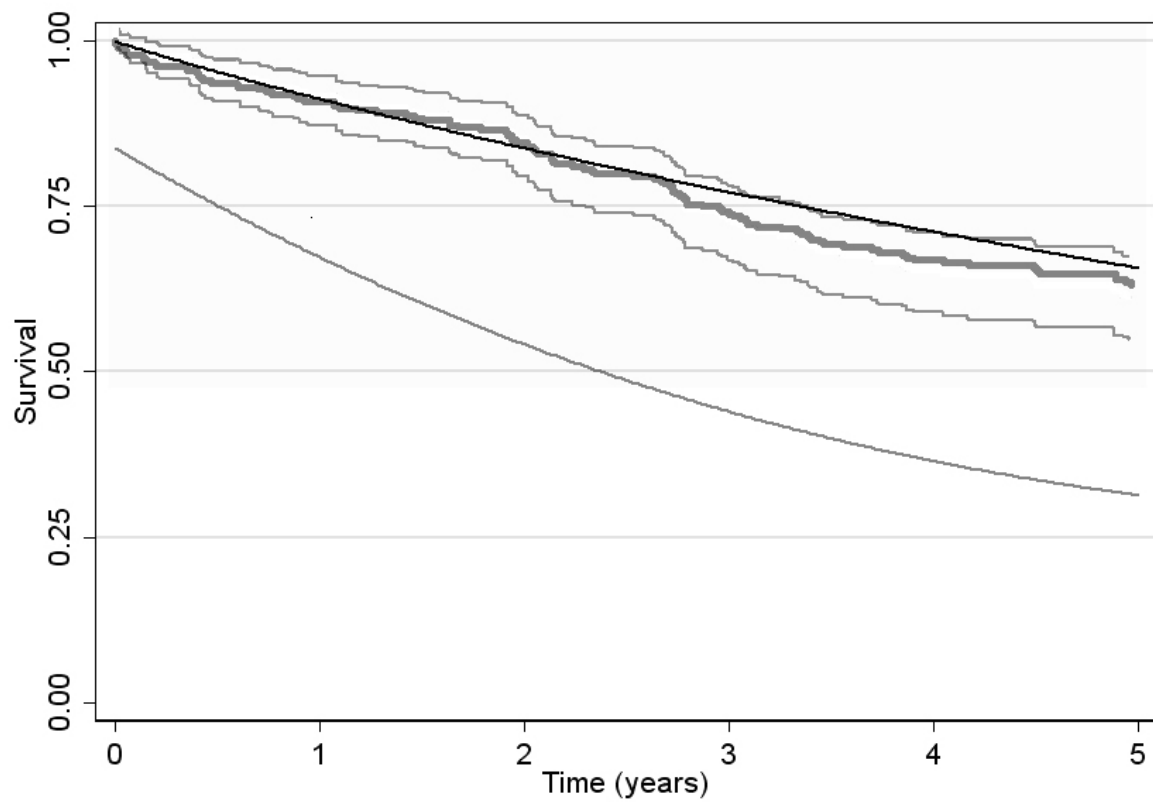
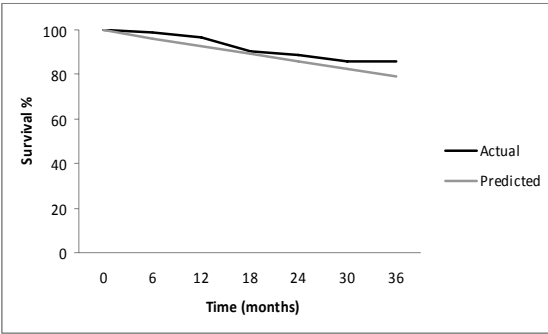
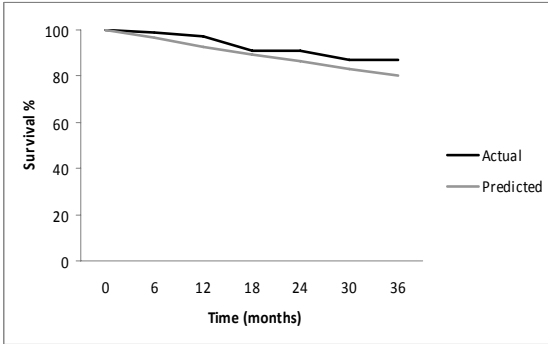


Figure IV: Observed vs. Predicted Survival using the New Equation in Published PAH Cohorts

A



B



C

