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Survival in pulmonary arterial hypertension: a reappraisal of the NIH risk stratification equation

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Abstract

The aim of the present study was to determine contemporary survival in pulmonary arterial hypertension (PAH), and to investigate whether or not the National Institutes of Health (NIH) equation remains an accurate predictor of survival.

In 576 patients with PAH referred during 1991–2007, observed survival was described using the Kaplan–Meier method. In patients with idiopathic, familial and anorexigen-associated PAH (n=247), observed *versus* NIH equation predicted survival was compared. A new survival prediction equation was developed using exponential regression analysis.

The observed 1-, 3- and 5-yr 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-yr survival (92, 75 and 66%, respectively) were significantly higher than the predicted survival (65, 43 and 32%, respectively). The new equation ($P(t)=e^{-A(x,y,z)t}$, *where P(t) is probability of survival,* t *the time interval in years,* $A(x,y,z)=e^{(-1.270-0.0148x+0.0402y-0.361z)}$, *x* the mean pulmonary artery pressure, *y* the mean right atrial pressure and *z* the cardiac index) performed well when applied to published contemporary studies of survival in PAH.

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

Keywords

National Institutes of Health equation; prognosis; pulmonary arterial hypertension; survival

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STATEMENT OF INTEREST

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Pulmonary arterial hypertension (PAH), a debilitating disease characterised 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, HIV and anorexigen 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 haemodynamics, for the estimation of survival in patients with PPH [3]. Subsequently, many clinical trials in PAH have used the NIH equation to suggest improvements in survival by comparing the observed survival rates on a study drug *versus* the survival rates predicted by the NIH equation [4–9].

The NIH registry was initiated during a time when there were no US Food and Drug Administration-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]. Since the mid-1980s, however, the management and therapies of PAH have changed significantly [10].

The aim of the present study was to: 1) characterise contemporary survival in patients with World Health Organization (WHO) category I PAH; and 2) determine whether or not the NIH equation remains an accurate predictor of survival in patients with idiopathic, familial and anorexigen-associated PAH (previously classified as PPH).

METHODS

Study subjects

Patients in the Pulmonary Hypertension Connection (PHC) registry, which we initiated in March 2004, were studied. This database has been described in detail previously [11]. Briefly, the PHC registry was created as a customised patient database in order to longitudinally collect specific variables on every patient treated in the authors' practice. The practice has been sequentially based at three university medical centres in Chicago since 1982. Patients were entered into 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 the practice 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, all adult patients (aged ⩾18 yrs at the time of referral) with PAH (n=654) were identified. In brief, the diagnosis of PAH required the following: 1) a mean pulmonary artery pressure $(\bar{P}_{pa})$ of >25 mmHg at rest, with a pulmonary capillary wedge pressure of <15 mmHg; and 2) the exclusion of other WHO categories of pulmonary hypertension by clinical evaluation and objective tests [12]. In order to make the study cohort more comparable to the NIH registry, 52 patients who were on approved PAH therapy

at the time of referral (17 on prostacyclins, 27 on bosentan and eight on sildenafil) were excluded. In addition, 26 patients diagnosed with PAH before 1991 were excluded in order to avoid entering patients who may have been in the NIH registry cohort (recruitment 1981–1985, with follow-up to 1988 and publication in 1991). The remaining 576 patients formed the 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%) with idiopathic, familial and anorexigen-associated PAH formed a subgroup that matched the NIH registry. Patients with anorexigen-associated PAH were included in the subgroup since the NIH registry included patients exposed to anorexigens, and based on the recent study of SOUZA *et al.* [13] demonstrating no significant survival difference between anorexigen-associated PAH and idiopathic and familial PAH patients. Figure 1 illustrates the study flow chart.

Variables

The following baseline variables were analysed at the time of referral for characterisation of clinical phenotype: demographic data, including age and sex; comorbid conditions; WHO functional class; medications; and exercise treadmill testing (ETT) using the Naughton–Balke protocol as a measure of exercise capacity [14]. It has previously been shown that the ETT is comparable to the 6-min walking test and a predictor of mortality in patients with pulmonary hypertension [15, 16].

Among the patients, 521 (91%) of the 576 in the study group, and 270 (96%) of the 282 with idiopathic, familial and anorexigen-associated PAH underwent baseline haemodynamic testing by means of right heart catheterisation. More than 95% of catheterisations were performed at the University of Chicago Medical Center (Chicago, IL, USA) by pulmonary hypertension specialists. Haemodynamic testing included measurement of mean right atrial pressure $(\bar{P}_{RA})$, $\bar{P}_{pa}$, pulmonary capillary wedge pressure, cardiac index (CI) and pulmonary vascular resistance (PVR). An acute vasodilator challenge with adenosine was performed during right heart catheterisation, as described previously [17].

Long-term management

All patients who responded to acute vasodilator challenge were treated with calcium-channel blockers. Initially, a positive response was defined as a 20% decrease in $\bar{P}_{pa}$ with an increase in CI, but, after 2005, the following definition was used: a decrease in $\bar{P}_{pa}$ of >10 mmHg, and to <40 mmHg, 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 the present cohort without contraindications were offered anticoagulation with warfarin in order to achieve a target international normalised ratio of 2–3. Patients with an arterial oxygen saturation of <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

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

Statistical analysis

Baseline categorical variables are expressed as frequencies and proportions, whereas continuous variables are presented as mean±SD. Survival rates were calculated using the Kaplan–Meier method and standard life table analyses. The date of baseline right heart catheterisation was used as the date of entry into the study, as for the NIH registry [3]. For patients who survived during follow-up, the date of data cut-off (August, 10 2007) was used as the censoring date. For patients who did not undergo initial right heart catheterisation, the date of referral to the practice was used as the enrolment date. Survival before and after 2002 were compared because bosentan, the first oral therapy for PAH, was approved for use in the USA in 2002. Prior to 2002, treatment consisted of conventional therapy and epoprostenol. For idiopathic, familial and anorexigen-associated PAH patients with available baseline haemodynamic data, expected survival was calculated for each patient based on the NIH equation:

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

where $P(t)$ is the probability of survival, $H(t)=0.88–0.14t+0.01t^2$, t the time interval in years, $A(x,y,z)=e^{(0.007325x+0.0526y–0.3235z)}$, x the $\bar{P}_{pa}$, y the $\bar{P}_{RA}$ and z the CI. The probabilities of survival at 1, 3 and 5 yrs are as follows: $P(1)=0.75^A$; $P(3)=0.55^A$; and $P(5)=0.43^A$.

The proportion of observed survival for each time period was compared with expected survival using Chi-squared tests. Univariate and multivariate Cox’s proportional hazards analyses were performed in order 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. Univariate analysis was performed with all baseline characteristic variables. For the final multivariate analyses, any variables with a p-value of <0.1 on univariate analysis were retained. In the analysis of the total PAH cohort, the subgroup of patients with idiopathic, familial and anorexigen-associated PAH was used as the referent group, to which all other aetiologies of PAH were compared. Only connective tissue disease was significant and retained in the final multivariable models. Functional class and treadmill exercise capacity were significantly correlated (correlation coefficient=0.73, p<0.0001), and so only functional class was retained in the final models in order to avoid multicollinearity. In addition, separate models were created for each haemodynamic variable to avoid multicollinearity.

In the subgroup of patients with idiopathic, familial and anorexigen-associated PAH, a new survival prediction equation was developed, using first a Weibull model followed by an exponential regression model for ease of use [19]. It was predetermined *a priori* that the

three haemodynamic predictors ($\bar{P}_{pa}$, $\bar{P}_{RA}$ and CI) from the NIH model were clinically relevant for inclusion in the model. The variables that were significant on univariate analysis were then added to these three haemodynamic variables in order to complete the model. Variables were then removed from the model one at a time, using backward elimination. Similar to the NIH equation, only $\bar{P}_{pa}$, $\bar{P}_{RA}$ and CI were retained in the final model, and all three were significant.

In addition, in order to address concerns about inclusion of patients who responded to calcium-channel blocker (n=11; all showed a positive response to the vasodilator study during the invasive haemodynamic study), a separate equation was developed for responders. The data were also analysed to determine whether exclusion of responders to calcium-channel blocker significantly altered the overall survival of the cohort.

In order to validate the new survival equation, it was applied to three published idiopathic and familial PAH patient cohorts, and the published observed survival compared with that predicted by the new survival equation based on the baseline mean haemodynamic data ($\bar{P}_{pa}$, $\bar{P}_{RA}$ and CI) of these study cohorts [8, 20]. All statistical analyses were performed using Stata version 9 (StataCorp, College Station, TX, USA).

RESULTS

All PAH patients

Baseline characteristics—The mean age upon entry into the registry was 48±14 yrs, and 77% of patients were female (table 1). The majority (80%) of subjects showed WHO functional class III or IV symptoms and poor baseline exercise capacity, achieving a maximum workload of only 3.6±2 metabolic equivalents of the task using the Naughton–Balke protocol ETT. At the time of referral, subjects were on conventional therapy and gave severe haemodynamic results (table 1).

Survival—The median follow-up time was 3.9 yrs (interquartile range 1.7–7.8 yrs; maximum follow-up time 16.6 yrs). Of the 576 study patients, 307 (53%) died during follow-up. Vital status was available for all patients, but survival time was missing for 30 and one died on the date of enrolment; therefore, these patients were excluded, leaving 545 patients for the final survival analyses. The observed 1-, 3- and 5-yr survival rates for the total PAH cohort were 86, 69 and 61%, respectively. The 1-, 3- and 5-yr survival rates were not affected by exclusion of patients who exhibited a positive acute vasodilator response to adenosine during invasive haemodynamic testing (Fig. I of online supplementary material).

Multivariable analysis—On univariate analysis in the total cohort (n=576), age, connective tissue disease aetiology, worse functional class, decreased exercise capacity, increased $\bar{P}_{RA}$, increased PVR and decreased CI were all associated with an increased risk of death (table 2). On multivariable analysis, age, connective tissue disease aetiology, functional class, $\bar{P}_{RA}$ and CI all remained independent predictors of death (table 3).

Subgroup (idiopathic, familial and anorexigen-associated PAH)

Baseline characteristics—The mean age upon entry into the registry was 46±14 yrs (~10 yrs older than the NIH registry subjects). The baseline demographic, clinical and haemodynamic characteristics of the idiopathic, familial and anorexigen-associated PAH subgroup were comparable to those of patients in the NIH registry (table 4).

Survival—The median follow-up time in the subgroup of patients with idiopathic, familial and anorexigen-associated PAH was 4.9 yrs (interquartile range 2.3–8.7 yrs; maximum follow-up time 16.6 yrs), and, during follow-up, 149 (53%) out of 282 died. The survival time was missing for 16 patients, leaving 266 patients for survival analyses. The observed 1-, 3- and 5-yr survival rates were 91, 75 and 65%, respectively, and were better than for patients with PAH associated with connective tissue disease, congenital heart disease, portal hypertension and HIV (fig. 2). Patients diagnosed with idiopathic, familial and anorexigen-associated PAH after 2002 exhibited better survival than those diagnosed before 2002 (fig. II of online supplementary material). Of the 282 subgroup patients with idiopathic, familial and anorexigen-associated PAH, all of the three baseline haemodynamic data ($\bar{P}_{RA}$, $\bar{P}_{pa}$ and CI) required to calculate survival using the NIH equation were available for 247 patients ($\bar{P}_{pa}$55±12 mmHg, $\bar{P}_{RA}$11±6 mmHg and CI 2.0±0.6 L·min^{-1}·m^{-2}). The observed 1-, 3- and 5-yr survival of these patients with available haemodynamic data were 92, 75 and 66%, respectively, which did not differ significantly from that of those without haemodynamic data. In contrast, the predicted 1-, 3- and 5-yr survival rates, calculated using the NIH equation, were 65, 43 and 32%, respectively. The observed survival was significantly greater than the predicted survival at 1, 3 and 5 yrs ($p<0.0001$ for all).

Multivariable analysis—On univariate analysis in the subgroup (n=282), age, worse functional class, decreased exercise capacity, increased $\bar{P}_{RA}$ and decreased CI were all associated with an increased risk of death (table 2). On multivariable analysis, age, functional class, $\bar{P}_{RA}$ and CI remained as independent predictors of death (table 5).

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

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

where $A(x,y,z)=e^{(-1.270-0.0148x+0.0402y-0.361z)}$ in nonresponders to calcium-channel blockers and $A(x,y,z)=e^{(-3.012-0.0148x+0.0402y-0.361z)}$ in responders to calcium-channel blockers.

Example 1: A patient with a $\bar{P}_{pa}$ of 40 mmHg, $\bar{P}_{RA}$ of 3 mmHg and CI of 3.5 L·min^{-1}·m^{-2}, and who did not respond to an acute vasodilatory challenge, would have 1-, 2- and 3-yr survival estimates as follows:

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

giving probabilities of survival at 1, 2 and 3 yrs of $P(1)=e^{-0.049544\times1}$ (0.952 or 95%); $P(2)=e^{-0.049544\times2}$ (0.905 or 90.5%); and $P(3)=e^{-0.049544\times3}$ (0.861 or 86%).

Example 2: A patient with exactly the same haemodynamics as the patient in the first example, but who showed a positive response to an acute vasodilatory challenge, would have 1-, 2- and 3-yr survival estimates as follows:

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

giving $P(1)=e^{-0.008679\times1}$ (0.991 or 99%); $P(2)=e^{-0.008679\times2}$ (0.983 or 98%); and $P(3)=e^{-0.008679\times3}$ (0.974 or 97%).

Sensitivity analysis: Sensitivity analyses demonstrated that the Cox's 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 3 displays the observed *versus* predicted survival (using both the new equation and the NIH equation) in the subgroup of patients with idiopathic, familial and anorexigen-associated PAH. When the new equation was applied to data from other published PAH patient cohorts, the predicted survival calculated using the new equation was comparable to the observed survival (fig. 4).

DISCUSSION

It has been shown that survival rates in patients with WHO category I PAH have improved considerably compared to those in the NIH registry cohort. The observed 1-, 3- and 5-yr 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 yrs were significantly higher than the predicted survival calculated using the NIH equation, and patients diagnosed after 2002 appeared to show better survival than those diagnosed before 2002. From the present cohort, a new regression equation was developed to estimate survival, based on baseline haemodynamic data, in patients with idiopathic, familial and anorexigen-associated PAH. The 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 centres in the USA between July 1981 and September 1985, described the clinical characteristics of PPH and its natural history over a 7-yr period in an era when there were no approved PAH-specific therapies. In the NIH registry, patients showed a median survival time of 2.8 yrs. The 1-, 3- and 5-yr survival rates were only 68, 48 and 34%, respectively [3]. Mortality correlated with baseline $\bar{P}_{RA}$, $\bar{P}_{pa}$ and CI. The NIH registry proposed an equation for prediction of survival, which was subsequently validated by SANDOVAL *et al.* [21] in a small Mexican cohort of 61 patients with PPH. In this study, the predicted and observed survival were closer in the patients who received no long-term oral vasodilatory therapy, but the predicted survival underestimated the observed survival in the group as a whole.

The improved survival in the present patients with WHO category I PAH, and the 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 centres has increased 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 or IV), it may be that the natural history of the disease itself has changed. Aetiology 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 randomised 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 centre a decade after the NIH registry. Although earlier intervention may translate into improved survival, the possibility cannot be excluded that lead-time bias is also a factor. However, patients in the present cohort were older than those studied in the NIH registry, and showed a similar severity of functional class and haemodynamic 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 severely diseased patients surviving, a cohort effect as an explanation for the improved survival.

The present 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 the total study cohort (13 (2.3%) out of 576), as well as in the subgroup of patients with idiopathic, familial and anorexigen-associated PAH (11 (3.9%) out of 282). In addition, the number of responders across eras in the present database was consistent and low (3.7, 4.2 and 5.8%; p=NS)) [11]. Excluding responders did not affect survival rates significantly, which is probably due to the small numbers of patients who showed a positive acute vasodilatory response during invasive haemodynamic testing (fig. I of online supplementary material). We, therefore, do not believe that a positive acute vasodilatory response has played a significant role in improved survival. However, given the much better survival in patients who show a positive acute vasodilatory response, a separate new equation was derived for responders.

Finally, the improved survival may be due to the availability of approved PAH medications, which include prostacyclin and its analogues, endothelial antagonists and phosphodiesterase inhibitors [10]. It remains unknown whether or not the current PAH-specific therapies improve long-term survival, as there are no long-term randomised treatment trials with any therapy for PAH. The present study is an observational study, and thus the true effect of new therapies on survival cannot be evaluated. A recent meta-analysis by GALIE *et al.* [25] suggested an improvement in survival in patients treated with PAH-specific therapies (relative risk of all-cause mortality 0.57 (95% confidence interval 0.35–0.92); p=0.023). In contrast, in a meta-analysis by MACCHIA *et al.* [26], none of the currently available PAH-specific therapies were associated with long-term survival benefit [26]. Thus, in order

to ascertain whether or not there are any long-term survival benefits with the currently available newer PAH-specific therapies, prospective randomised placebo-controlled trials, which evaluate clinical outcomes, including true surrogates of death if not death itself, stratified to specific aetiologies of PAH are required [26]. A new formula gives us a new baseline against which to make comparisons once it has been validated in independent cohorts.

It was decided to revise the NIH formula only when better-than-predicted survival was found, understanding that this was only a registry. The equation included anorexigen-associated PAH since the NIH registry included patients exposed to anorexigens, and based on the recent SOUZA *et al.* [13] study demonstrating no significant survival difference between anorexigen-associated PAH and idiopathic and familial PAH patients. If prospectively validated in another idiopathic, familial and anorexigen-associated PAH cohort, the new equation could be used to estimate contemporary survival in this patient population. In addition, the new survival equations could potentially be used in clinical and research settings in order to determine response to therapy and changes in prognosis that occur with changes in invasive haemodynamic 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 a worse prognosis than other forms of PAH [27, 28].

Limitations

Data collection started in 2004, and thus most patients were entered retrospectively. All patients in the cohort were cared for by a single tertiary referral practice; therefore, the results may not be generalisable. The cohort consisted of both incident and prevalent cases, which may have contributed to a survival bias. Subsequent treatment data were not collected for individual patients; hence the proportion of patients treated with different PAH-specific therapies is not available. Thus, the study does not address the key issue of whether or not the current PAH-specific therapies affect survival. A total of 9% of the study cohort did not have baseline invasive haemodynamic data; however, the majority of these patients underwent follow-up right heart catheterisation, which confirmed the diagnosis of PAH. Finally, the new equation was developed based on a heterogeneous patient collection on a 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 that in the NIH registry cohort. The NIH equation underestimates survival in patients with idiopathic, familial and anorexigen-associated PAH in the present PHC registry. If prospectively validated, the new regression survival equations (PHC equations) should assist in determining prognosis in patients with idiopathic, familial and anorexigen-associated PAH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES:

1. Farber HW, Loscalzo J. Pulmonary arterial hypertension. N Engl J Med 2004; 351: 1655–1665. [PubMed: 15483284]
2. Rich S, Dantzker R, Ayres S, et al. Primary pulmonary hypertension: a national prospective study. Ann Intern Med 1987; 107: 216–223. [PubMed: 3605900]
3. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension: results from a national prospective registry. Ann Intern Med 1991; 115: 343–349. [PubMed: 1863023]
4. Barst RJ, Galie N, Naeije R, et al. Long-term outcome in pulmonary arterial hypertension patients treated with treprostinil. Eur Respir J 2006; 28: 1195–1203. [PubMed: 16899485]
5. Kuhn K, Byrne D, Arbogast PG, et al. Outcome in 91 consecutive patients with pulmonary arterial hypertension receiving epoprostenol. Am J Respir Crit Care Med 2003; 167: 580–586. [PubMed: 12446266]
6. McLaughlin VV. Survival in patients with pulmonary arterial hypertension treated with first-line bosentan. Eur J Clin Invest 2006; 36: Suppl. 3, 10–15. [PubMed: 16919005]
7. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. Circulation 2002; 106: 1477–1482. [PubMed: 12234951]
8. McLaughlin VV, Sitbon O, Badesch DB, et al. Survival with first-line bosentan in patients with primary pulmonary hypertension. Eur Respir J 2005; 25: 244–249. [PubMed: 15684287]
9. Provencher S, Sitbon O, Humbert M, et al. Long-term outcome with first-line bosentan therapy in idiopathic pulmonary arterial hypertension. Eur Heart J 2006; 27: 589–595. [PubMed: 16431875]
10. Badesch DB, Abman SH, Simonneau G, et al. Medical therapy for pulmonary arterial hypertension: updated ACCP evidence-based clinical practice guidelines. Chest 2007; 131: 1917–1928. [PubMed: 17565025]
11. Thenappan T, Shah SJ, Rich S, et al. A USA-based registry for pulmonary arterial hypertension: 1982–2006. Eur Respir J 2007; 30: 1103–1110. [PubMed: 17804449]
12. McGoon M, Gutterman D, Steen V, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004; 126: Suppl. 1, 14S–34S. [PubMed: 15249493]
13. Souza R, Humbert M, Sztrymf B, et al. Pulmonary arterial hypertension associated with fenfluramine exposure: report of 109 cases. Eur Respir J 2008; 31: 343–348. [PubMed: 17959632]
14. Patterson JA, Naughton J, Pietras RJ, et al. Treadmill exercise in assessment of the functional capacity of patients with cardiac disease. Am J Cardiol 1972; 30: 757–762. [PubMed: 5084774]

15. Gomberg-Maitland M, Huo D, Benza RL, et al. Creation of a model comparing 6-minute walk test to metabolic equivalent in evaluating treatment effects in pulmonary arterial hypertension. J Heart Lung Transplant 2007; 26: 732–738. [PubMed: 17613405]
16. Shah SJ, Thenappan T, Rich S, et al. Value of exercise treadmill testing in the risk stratification of patients with pulmonary hypertension. Circ Heart Fail 2009; 2: 278–286. [PubMed: 19808350]
17. Nootens M, Schrader B, Kaufman E, et al. Comparative acute effects of adenosine and prostacyclin in primary pulmonary hypertension. Chest 1995; 107: 54–57. [PubMed: 7813311]
18. Sitbon O, Humbert M, Jais X, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation 2005; 111: 3105–3111. [PubMed: 15939821]
19. Carroll KJ. On the use and utility of the Weibull model in the analysis of survival data. Control Clin Trials 2003; 24: 682–701. [PubMed: 14662274]
20. Sitbon O, McLaughlin VV, Badesch DB, et al. Survival in patients with class III idiopathic pulmonary arterial hypertension treated with first line oral bosentan compared with an historical cohort of patients started on intravenous epoprostenol. Thorax 2005; 60: 1025–1030. [PubMed: 16055621]
21. Sandoval J, Bauerle O, Palomar A, et al. Survival in primary pulmonary hypertension. Validation of a prognostic equation. Circulation 1994; 89: 1733–1744. [PubMed: 8149539]
22. Fuster V, Steel P, Edwards W, et al. Primary pulmonary hypertension: natural history and the importance of thrombosis. Circulation 1984; 70: 580–587. [PubMed: 6148159]
23. Rich S, Kaufman E, Levy P. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. N Engl J Med 1992; 327: 76–81. [PubMed: 1603139]
24. Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J Am Coll Cardiol 2002; 40: 780–788. [PubMed: 12204511]
25. Galie N, Manes A, Negro L, et al. A meta-analysis of randomized controlled trials in pulmonary arterial hypertension. Eur Heart J 2009; 30: 394–403. [PubMed: 19155250]
26. Macchia A, Marchioli R, Marfisi R, et al. A meta-analysis of trials of pulmonary hypertension: a clinical condition looking for drugs and research methodology. Am Heart J 2007; 153: 1037–1047. [PubMed: 17540207]
27. Kawut SM, Taichman DB, Archer-Chicko CL, et al. Hemodynamics and survival in patients with pulmonary arterial hypertension related to systemic sclerosis. Chest 2003; 123: 344–350. [PubMed: 12576350]
28. Fisher MR, Mathai SC, Champion HC, et al. Clinical differences between idiopathic and scleroderma-related pulmonary hypertension. Arthritis Rheum 2006; 54: 3043–3050. [PubMed: 16947776]

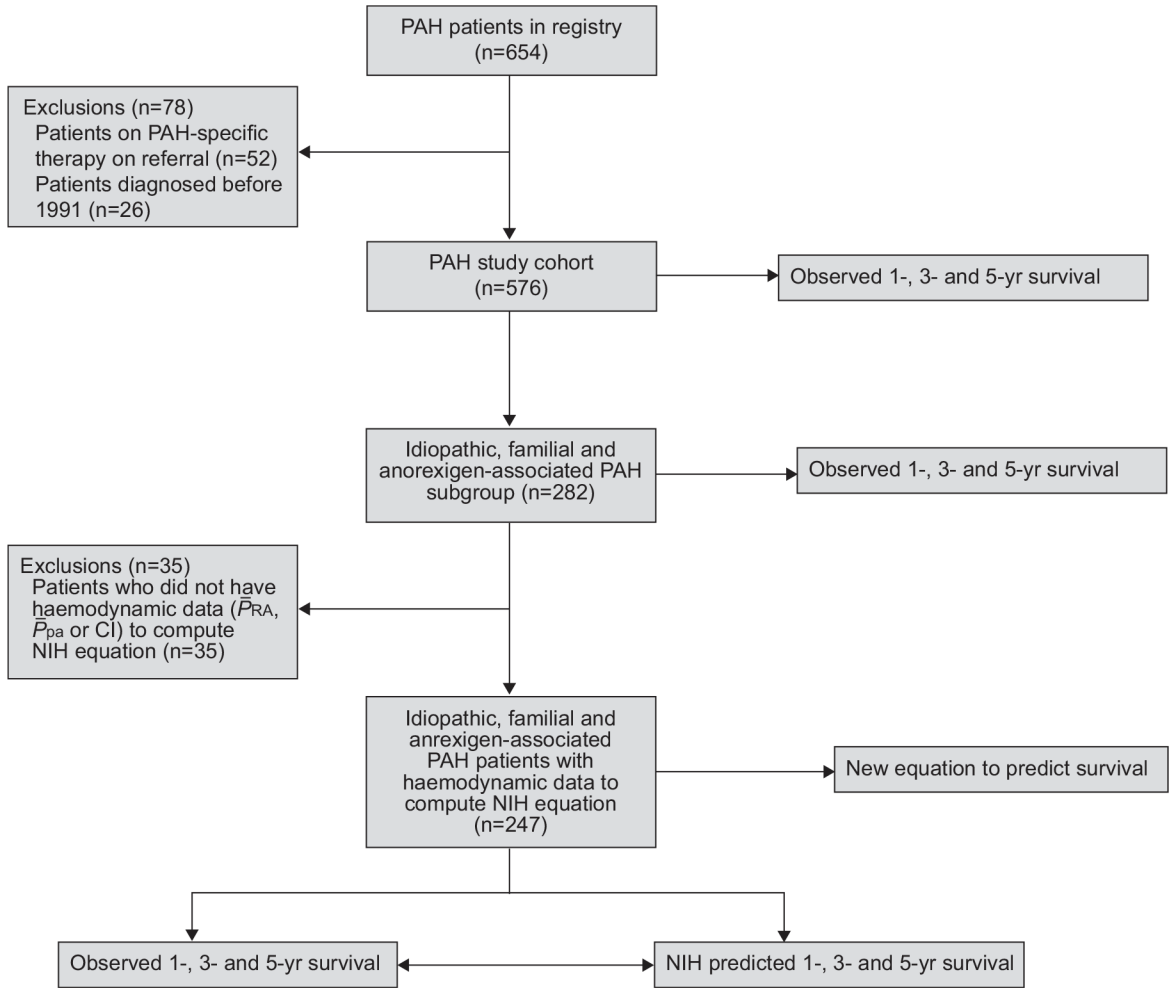

FIGURE 1.

Study flow diagram. PAH: pulmonary arterial hypertension; $\bar{P}_{RA}$: mean right atrial pressure; $\bar{P}_{pa}$: mean pulmonary arterial pressure; CI: cardiac index; NIH: National Institutes of Health.

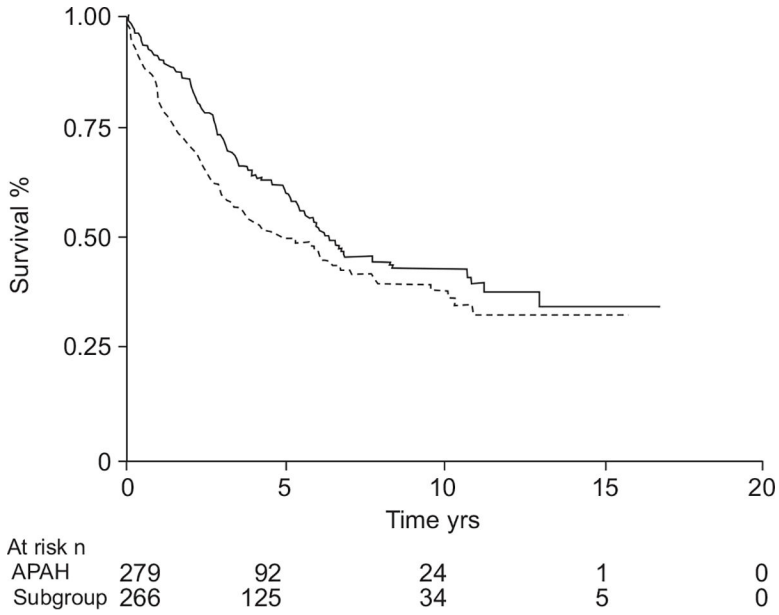

FIGURE 2.

Survival in idiopathic, familial and anorexigen-associated pulmonary arterial hypertension (PAH) subgroup (——; n=282) *versus* PAH associated with connective tissue disease, congenital heart disease, portal hypertension and HIV (APAH; ------; n = 294) (p=0.03 (log-rank test)).

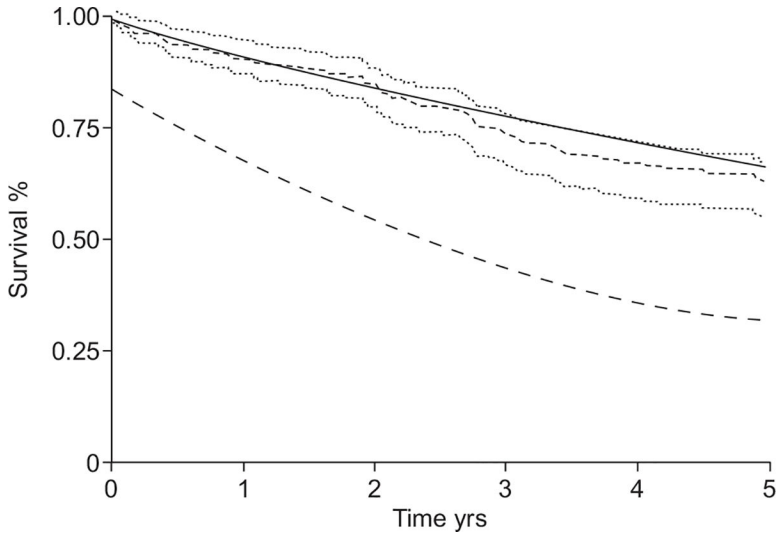

FIGURE 3.

Observed (-------; 95% confidence interval: ·····) *versus* predicted survival using the Pulmonary Hypertension Connection (———) and National Institutes of Health (– – –) equations in patients with idiopathic, familial and anorexigen-associated pulmonary arterial hypertension.

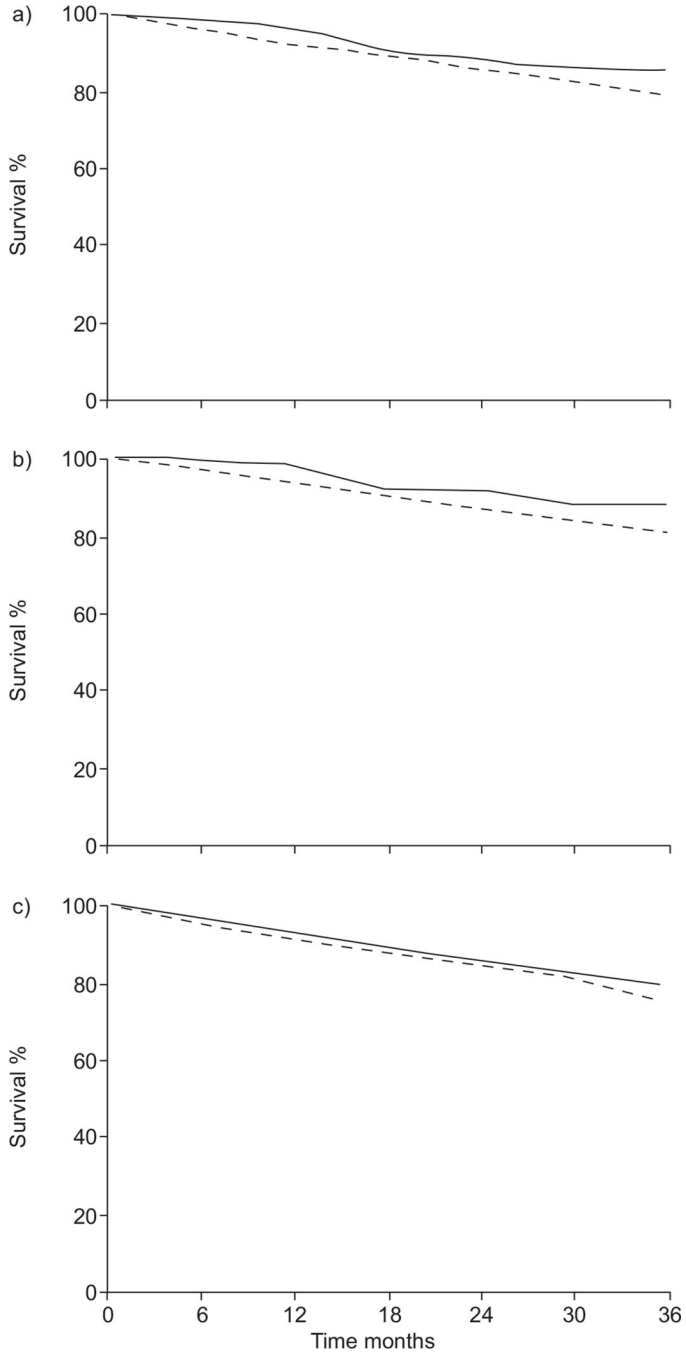

FIGURE 4.

Observed (——) *versus* predicted (------) survival using the new equation with data from published pulmonary arterial hypertension (PAH) cohorts: a) survival with first-line bosentan in patients with primary pulmonary hypertension [8]; and b, c) survival in patients with class III idiopathic PAH treated with first-line oral bosentan (b) compared with a historical cohort of patients started on intravenous epoprostenol (c) [20].

TABLE 1

Baseline characteristics of all pulmonary arterial hypertension patients

Subjects n	576
Age yrs	48±14
Females	445 (77)
WHO functional class III or IV [#]	449 (80)
Medication [¶]	
Calcium-channel blockers	177 (31)
Warfarin	154 (27)
Digoxin	94 (16)
Diuretics	275 (48)
Exercise capacity METs [+]	3.6±2.0
Aetiology	
Idiopathic	239 (42)
Familial	23 (4)
Anorexigen	20 (3)
Connective tissue disease	173 (30)
Congenital heart disease	64 (11)
Portal hypertension	48 (8)
HIV	9 (2)
Haemodynamics [§]	
Right atrial pressure mmHg	11±6
Mean pulmonary arterial pressure mmHg	52± 14
Pulmonary capillary wedge pressure mmHg	10±4
Cardiac index $L \cdot min^{-1} \cdot m^{-2}$	2.2±0.9
Pulmonary vascular resistance Wood units	12.4±7.3
Acute vasodilatory response[f]	13±2.3

Data are presented as mean±SD or n (%), and were complete unless otherwise indicated. WHO: World Health Organization; MET: metabolic equivalent of the task.

[#]: n=559

[¶]: therapy on referral to the centre

[+]: n=335

[§]: n=521

[f]: defined as a fall in mean pulmonary arterial pressure of >10 mmHg, and to <40 mmHg, with unchanged or increased cardiac output.

TABLE 2

Univariate predictors of death on Cox's proportional hazards analysis

	All PAH		Subgroup[#]	
	HR	**p-value**	**HR**	**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				
I	Reference		Reference	
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
Aetiology				
Idiopathic/familial	Reference		Reference	
Anorexigen	1.75 (0.98–3.11)	0.055		
Connective tissue disease	1.75 (1.34–2.29)	<0.0001		
Haemodynamics				
Right atrial pressure per 5-mmHg increase	1.29 (1.18–1.41)	<0.0001	1.37 (1.21–1.55)	<0.0001
Cardiac index per 1-L·min^{-1}·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

Data are presented with 95% confidence intervals in parentheses. A p-value of <0.1 was considered significant. PAH: pulmonary arterial hypertension; HR: hazard ratio; MET: metabolic equivalent of the task; NS: nonsignificant.

[#]: idiopathic, familial and anorexigen-associated PAH.

TABLE 3

Multivariate predictors of death on Cox's proportional hazards analysis in all pulmonary arterial hypertension (PAH) patients

	Hazard ratio		
	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 aetiology	1.70 (1.29–2.24)	1.66 (1.25–2.20)	1.64 (1.23–2.18)
Functional class per 1-class 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 arterial pressure per 5-mmHg increase		1.02 (0.97–1.08)	
Cardiac index per 1-L·min^{-1}·m^{-2} increase			0.79 (0.65–0.96)

Data are presented with 95% confidence intervals in parentheses. Likelihood ratio (LR) analysis was performed *versus* the model with age, connective tissue disease aetiology and functional class alone. The model with age, connective tissue disease aetiology, functional class and right atrial pressure is the best model. Adding cardiac index does not help discriminate further (LR test for model 1 with cardiac index *versus* model 1 without cardiac index: p=0.47).

[#]: independent variables: age at diagnosis, connective tissue disease aetiology of PAH, functional class and right atrial pressure (p<0.0001 on LR analysis)

[¶]: independent variables: age at diagnosis, connective tissue disease aetiology of PAH, functional class and mean pulmonary arterial pressure (p=0.35 on LR analysis)

[+]: independent variables: age at diagnosis, connective tissue disease aetiology of PAH, functional class and cardiac index (p=0.013 on LR analysis).

TABLE 4

Baseline characteristics of idiopathic, familial and anorexigen-associated pulmonary arterial hypertension (PAH) patients

	Subgroup[#]	NIH registry[¶]
Subjects n	282	187
Age yrs	46± 14	36± 15
Females	214 (76)	118 (63)
WHO functional class III or IV	225 (82)	133 (71)
Medication		
Calcium-channel blockers	82 (29)	NA
Warfarin	91 (32)	NA
Digoxin	43 (15)	NA
Diuretics	130 (46)	NA
Exercise capacity METs [+]	3.8±2.0	NA
Haemodynamics [§]		
Right atrial pressure mmHg	11±6	9±6
Mean pulmonary arterial pressure mmHg	55±12	60±18
Pulmonary capillary wedge pressure mmHg	10± 4	9±4
Cardiac index $L \cdot min^{-1} \cdot m^{-2}$	2.0±0.6	2.3±0.9
Pulmonary vascular resistance Wood units	13.9±6.7	NA
Acute vasodilatory response[f]	11 ±3.9	NA

Data are presented as mean±SD or n (%), and were complete unless otherwise indicated. NIH: National institutes of Health; WHO: World Health Organization; MET: metabolic equivalent of the task; NA: not available.

[#]: idiopathic, familial and anorexigen-associated PAH

[¶]: listed for comparison and not included in any analysis

[+]: n=180

[§]: n=270

[f]: defined as a fall in mean pulmonary arterial pressure of >10 mmHg, and to <40 mmHg, with unchanged or increased cardiac output.

TABLE 5

Multivariate predictors of death on Cox's proportional hazards analysis in idiopathic, familial and anorexigen-associated pulmonary arterial hypertension

	Hazard ratio		
	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-class 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 arterial pressure per 5-mmHg increase		1.01 (0.94–1.08)	
Cardiac index per 1-L·min^{-1}·m^{-2} increase			0.54 (0.38–0.77)

Data are presented with 95% confidence intervals in parentheses. Likelihood ratio (LR) analysis was performed *versus* the model with age and functional class alone. The model with age, functional class and right atrial pressure is the best model. Adding cardiac index is marginally additive in this primary pulmonary hypertension subgroup (LR test for model 1 with cardiac index *versus* model 1 without cardiac index: p=0.063).

[#]: independent variables: age at diagnosis, functional class and right atrial pressure (p<0.0001 on LR analysis)

[¶]: independent variables: age at diagnosis, functional class and mean pulmonary arterial pressure (p=0.78 on LR analysis)

[+]: independent variables: age at diagnosis, functional class and cardiac index (p=0.0004 on LR analysis).

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