Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension

Running head: Survival in pulmonary arterial hypertension

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Abstract

Background: Pulmonary arterial hypertension (PAH) is a progressive, fatal disease.

Methods: We studied 674 consecutive adult patients who were prospectively enrolled in the French PAH registry (121 incident and 553 prevalent cases). Two survival analyses were performed. First, the cohort of 674 patients was followed for 3 years after study entry and survival rates described. Then, we focused on the subset with incident idiopathic, familial and anorexigen-associated PAH (n=56) combined with prevalent patients who were diagnosed within 3 years prior to study entry (n=134).

Results: In the cohort of 674 patients, 1-, 2-, and 3-year survival rates were 87% (95% CI, 84-90), 76% (73-80), and 67% (63-71), respectively. In prevalent idiopathic, familial and anorexigen-associated PAH, 1-, 2-, and 3-year survival rates were higher than in incident patients (p=0.037). In the combined cohort of patients with idiopathic, familial and anorexigen-associated PAH, multivariable analysis showed that survival could be estimated by means of a novel risk-prediction equation using gender, 6-minute walk distance, and cardiac output at diagnosis.

Conclusions: This study highlights survivor bias in prevalent cohorts of PAH patients. Survival of idiopathic, familial and anorexigen-associated PAH can be characterized by means of a novel risk-prediction equation using patients’ characteristics at diagnosis.

Key words: exercise; pulmonary arterial hypertension; mortality; risk factors; sex
INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare and severe condition defined as mean pulmonary arterial pressure $\geq 25$ mmHg at rest and pulmonary artery wedge pressure $\leq 15$ mmHg, in the absence of other disorders such as chronic thrombo-embolic disease or chronic respiratory diseases and/or hypoxemia.\textsuperscript{1-5} PAH is characterized by remodeling of the small pulmonary arteries, resulting in a progressive increase in pulmonary vascular resistance leading to right ventricular failure and death.\textsuperscript{1-5} Besides idiopathic and familial cases, PAH can be associated with conditions such as connective tissue disease, or develop as a consequence of drug or toxin exposure (e.g. anorexigens).\textsuperscript{2,5} Patients with idiopathic, familial, or anorexigen-associated PAH exhibit similar clinical, functional, and hemodynamic characteristics, as well as overall survival. Different clinical outcomes have been observed, however, among patients with PAH associated with other underlying diseases.\textsuperscript{5-15}

Data describing the natural history of idiopathic and familial PAH were derived from a 1980s National Institutes of Health (NIH)-supported registry in the United States.\textsuperscript{16} A dismal median survival of 2.8 years following diagnosis was reported for this cohort.\textsuperscript{17} Based on estimates obtained from the proportional hazards models, an equation (‘NIH equation’) was devised to predict a patient’s likelihood of survival according to baseline hemodynamic measurements.\textsuperscript{17} This method has been widely used since as a comparator in survival analyses.\textsuperscript{18-23} However, the management of PAH has advanced significantly since the publication of the NIH-registry. In particular, a more extensive assessment of patients using objective parameters is now routine and novel medical therapies have become available.\textsuperscript{2,23} Whilst survival among patients with idiopathic, familial, and anorexigen-associated PAH has improved in comparison
with historical estimates, recent studies indicate that PAH nonetheless remains a progressive, fatal disease despite these advances.\textsuperscript{22,23}

In the present study, we describe the entire cohort of 674 consecutive adult PAH patients enrolled in 2002/2003 in the French Registry\textsuperscript{24} with an emphasis on incident and prevalent cohorts of patients idiopathic, familial and anorexigen-associated PAH (in order to eliminate survival bias due to comorbidities in subjects with associated conditions). In addition, we show that survival of idiopathic, familial and anorexigen-associated PAH can be characterized by means of a novel risk-prediction equation using patients’ characteristics at diagnosis.
METHODS

The French Network on Pulmonary Hypertension has been previously described.\textsuperscript{23,24} It was opened in 2002 in 17 pulmonary vascular university centers. For the purposes of this study, we evaluated all patients recruited between October 2002 and October 2003. This cohort was then prospectively followed for three years.\textsuperscript{23} The registry is in compliance with requirements of the French Commission Nationale de l’Informatique et des Libertés and all patients provided written informed consent to participate.\textsuperscript{23,24}

PAH was defined as a mean pulmonary arterial pressure $\geq 25$ mmHg at rest and a pulmonary artery wedge pressure $\leq 15$ mmHg, measured during right heart catheterization.\textsuperscript{2,23,24} In order to ensure a homogeneous study population, patients with evidence of severe obstructive or restrictive ventilatory defects (defined as reduction to $<60\%$ in measures of forced vital capacity, total lung capacity, or forced expiratory volume in 1 second) or those with pulmonary hypertension secondary to other known chronic respiratory disease and/or hypoxaemia\textsuperscript{5} were excluded.

PAH was classified as idiopathic, familial, or associated with anorexigen exposure, connective tissue disease, portal hypertension, human immunodeficiency virus (HIV) infection and congenital heart disease.\textsuperscript{2,5} Incident cases were defined as patients diagnosed with PAH by right-heart catheterization during the recruitment phase of the study (October 2002–October 2003).\textsuperscript{23,24} Prevalent cases were defined as patients in whom the diagnosis was made prior to the start of the study.\textsuperscript{23,24} Date of diagnosis was established as the date of confirmatory right heart catheterization.\textsuperscript{23,24}

There was no mandatory specific treatment algorithm employed. Use of targeted therapies, including prostacyclin derivatives, endothelin receptor antagonists, and phosphodiesterase type-5 inhibitors was at the discretion of treating clinicians at each center, according to current guidelines\textsuperscript{23,25,26} and availability (in France,
epoprostenol, bosentan, iloprost, and sildenafil were approved for PAH in March 1998, May 2002, September 2003, and October 2005, respectively).

**Survival analysis**

Patients who underwent lung transplantation were censored at time of operation. Patients lost to follow-up were censored at time of last clinic visit. Since cause of death could not always be confidently ascribed, all-cause mortality was used for analyses. Patients were followed prospectively after inclusion in the study and right-censored at 3 years.

We first described 1-, 2-, and 3-year survival in the general population of 674 PAH patients, with a focus on PAH subtypes, and on incident and prevalent patients with idiopathic, familial, and anorexigen-associated PAH. In a subsequent analysis, data from the incident population with idiopathic, familial, and anorexigen-associated PAH was combined with that from prevalent patients who were diagnosed within 3 years prior to study entry (combined analysis population), as previously described. In order to remove survivor bias which results from the inclusion of prevalent patients, survival estimates and Cox Proportional Hazards model from time to diagnosis were adjusted for the left-truncation arising from the delay between diagnosis and study entry. Patients were only in the risk set from their time of study entry; e.g. a patient recruited 1 year after diagnosis and followed for a further 3 years was considered to enter the risk set at 12 months and was right-censored at 36 months (i.e. 24 months from study entry). Kaplan-Meier analysis was used to estimate survival from time of diagnosis to 3 years post diagnosis. We examined the relationship between potential prognostic variables measured at diagnostic catheterization and mortality in the combined analysis population. All methods have been described elsewhere.
Statistical analyses were performed using SAS software (version 9.1, SAS Institute, North Carolina, United States).23

In order to forecast post-diagnosis survival for an individual patient, a novel risk-prediction equation was developed, similar to the NIH registry model.16 Baseline survival obtained via the multivariate Cox Proportional Hazards model was modeled via a weighted non-linear regression analysis, where baseline survival equals \( H(t) = \exp(a+b\times t); \) a and b are parameters estimated from the multivariate Cox Proportional Hazards model, and t is the time from diagnosis measured in years. The predicted survival of a patient at time t is described by the equation \( P(t;x,y,z) = H(t)A(x,y,z). \)

Here, \( A(x,y,z) \) is a function also obtained from the same Cox Proportional Hazards model, where x is the distance walked (m) at diagnosis, y=1 if female, y=0 if male, and z is the cardiac output (L/min) at diagnosis. The functional form of \( A(x,y,z) = \exp[-(c\times x + d\times y + e\times z)] \) where c, d, and e were parameters obtained from the model.

Thus, given the presentation of a patient with certain demographic and functional characteristics, a clinician may use this model to predict an individual patient's survival from 6 months up to 3 years post-diagnosis.
RESULTS

DESCRIPTIVE ANALYSIS OF SURVIVAL FROM STUDY ENTRY IN A COHORT OF 674 INCIDENT AND PREVALENT PAH PATIENTS

674 consecutive adult patients were prospectively enrolled, corresponding to 121 incident and 553 prevalent cases.\textsuperscript{24} Idiopathic, familial, anorexigen, connective tissue disease, congenital heart disease, portal hypertension and HIV infection-associated PAH accounted for 39.2%, 3.9%, 9.5%, 15.3%, 11.3%, 10.4% and 6.2% of the population, respectively (Figure 1).\textsuperscript{24} Of note 4.3% of patients had two coexisting risk factors. Among patients with connective tissue disease, the majority displayed systemic sclerosis (72%). Baseline characteristics of this population have been previously described.\textsuperscript{24}

In the general population (n=674), 1-, 2-, and 3-year survival rates after study entry were 87% (95% CI, 84-90), 76% (73-80), and 67% (63-71), respectively (Figure 2A). Better survival was observed in females (Figure 3A), as well as in younger patients (age ≤ 51 years) (Figure 3B) and in patients in New York Heart Association (NYHA) functional class I or II (Figure 3C). Survival was also better in the prevalent cohort, as compared to the incident one: in the prevalent cohort, 1-, 2-, and 3-year survival rates were 88% (85-91), 79% (75-82), and 71% (67-74), as compared to 88% (80-93), 65% (56-74), and 51% (42-60) in the incident cohort, respectively (P<0.0001). In addition, survival differed according to co-morbidities. Better 3-year survival rates were observed in patients with congenital heart disease, whilst the cohort with
connective tissue disease had a worse survival, highlighting the influence of associated conditions on PAH outcomes (Figure 2B).

Similar survival rates were observed in patients with idiopathic, or familial or anorexigen-associated PAH, highlighting the relevance of grouping these 3 subcategories together (data not shown). In prevalent idiopathic, familial and anorexigen-associated PAH, 1-, 2-, and 3-year survival rates were 89% (86-93), 77% (73-82), and 69% (63-74) (Figure 4A). This was higher than in incident patients who were characterized by 1-, 2-, and 3-year survival rates of 89% (78-97), 68% (55-81), and 55% (42-68) (P=0.037) (Figure 4A). Interestingly, analysis of survival from study entry according to quartiles of time from diagnosis revealed better survival in prevalent patients with longer duration of disease prior to inclusion in the study (Figure 4B). In summary, PAH prevalent cohorts had significantly better outcomes than incident cohorts (Figure 4A).

**NOVEL EQUATION PREDICTING SURVIVAL FROM DIAGNOSIS IN A COMBINED POPULATION OF 190 PREVALENT AND INCIDENT CASES WITH IDIOPATHIC, FAMILIAL AND ANOREXIGEN-ASSOCIATED PAH**

Because outcomes were markedly influenced by the presence or absence of associated conditions, we next focused our analysis on the incident cohort of patients with idiopathic, familial and anorexigen-associated PAH. As previously discussed, we grouped the 56 incident cases together with those 134 prevalent patients who were diagnosed within 3 years prior to study entry (n=190). Treatments at study inclusion in the combined population of patients with idiopathic, familial, or anorexigen-
associated PAH have been described elsewhere. Briefly, at study entry medical management consisted solely of conventional therapy in 29.5% of patients, corresponding mostly to acute vasodilator responders who benefited from first-line calcium channel blocker therapy, patients in NYHA FC II, or patients who died prematurely before any specific therapy was initiated. Targeted therapies were epoprostenol in 14.7%, other prostacyclin derivatives in 5.2%, endothelin receptor antagonists in 35.3%, type 5 phosphodiesterase inhibitors in 2.1%, and combination of these therapies in 12.6%. Modification or combinations of targeted therapies were proposed over the 3-year period at the discretion of treating clinicians at each center. Survival estimates of this combined cohort have been detailed elsewhere. Briefly, 1-, 2-, and 3-year survival was 83% (72–95), 67% (57–79), and 58% (49–69), and multivariable analysis indicated a significantly improved survival rate among females and those with higher measures of 6MWD and cardiac output.

Applying the post-diagnosis survival prediction method, the baseline survival was estimated as \( H(t) = \exp(-0.02t - 0.28t) \), where \( t \) corresponds to number of years since diagnosis. The multivariate Cox Proportional Hazards model gave parameter estimates such that \( A(x,y,z) = \exp[-(0.004x + 0.98y + 0.28z)] \), where \( x = 6\text{MWD at diagnosis} - 280 \text{ (m)} \), \( y=1 \) if female, \( y=0 \) if male, and \( z = \text{cardiac output at diagnosis} - 4.0 \text{ (L/min)} \). Therefore, the estimated survival of a patient at \( t \) years post-diagnosis is \( P(t; x,y,z) = H(t)A(x,y,z) = \exp(-0.02t - 0.28t) \exp[-(0.004x + 0.98y + 0.28z)] \). For example, in a female who presents with a 6MWD of 200 m and a cardiac output of 3.2 L/min at diagnosis, the equation generates \( A(200,1,3.2) = \exp[-(0.004\times(200–280) + 0.98\times1 + 0.28\times(3.2–4.0))]) = 0.647 \). Baseline survival at year 2 is estimated as \( H(2) = \exp(-0.02 - 0.28\times2) = 0.560 \), therefore, this patient’s estimated survival two years post-diagnosis is \( P(2; 200,1,3.2) = H(2)A(200,1,3.2) = 0.560^{0.647} = 0.69 \text{ (69%)}. \)
Discussion

The present study shows that survival in patients with PAH is influenced by several factors. Although highly relevant baseline clinical characteristics are strong determinants of outcome, estimation of survival is also subject to several biases, including presence of associated conditions and interval from diagnosis to study enrolment. This strongly suggests that analysis of incident cohorts of homogeneous PAH populations should be recommended in future survival studies.

As previously described, associated conditions may dramatically influence survival rates in PAH cohorts.\textsuperscript{5-14} Our results confirm that patients with PAH complicating the course of congenital heart diseases are more likely to be survivors at 3 years compared to patients that develop PAH in the setting of connective tissue diseases such as systemic sclerosis, despite similar management approaches.\textsuperscript{5,9,10} Therefore, we recommend that PAH cases with associated conditions (e.g. connective tissue disease, portal hypertension, HIV infection and congenital heart disease), should not be merged with patients having isolated pulmonary vascular disease (such as idiopathic PAH) in future survival analysis. In accordance with this statement, we focused our present study on patients with idiopathic, familial, and anorexigen-associated PAH, i.e. etiologies with similar outcomes that share clinical and genetic characteristics.\textsuperscript{9-11}

Another survivor bias confirmed in our analyses is the interval between time of diagnosis and study recruitment. We clearly show that survival of incident cohorts is poorer than that of prevalent cohorts, and that better survival is observed in prevalent patients with longer duration of disease prior to inclusion in the study. This information has important consequences as many patients enrolled in randomized
trials of investigational therapies are characterized by stable prevalent disease, suggesting a major survivor bias when long-term survival is described in such clinical trials or their long-term extensions.\textsuperscript{20,21,27} In this regard, the better outcomes of prevalent populations may relate to the enrichment of such studies with patients that have better right ventricular function (i.e. patients with marked and progressive right-heart failure are more likely to die early and thus be underrepresented in late prevalent cohorts) and/or patients with better response to PAH management (i.e. patients with refractory PAH will die or will be transplanted earlier). Further studies are needed to better understand the reasons for the better prognosis observed in prevalent PAH cohorts.

In incident PAH patients with idiopathic, familial or anorexigen-associated PAH, independent predictors of survival included female gender, greater 6MWD, and higher cardiac output.\textsuperscript{23} Whilst this study was not designed to compare treatment strategies with the previous management era described at the time of the NIH registry, we nevertheless observed that despite novel therapeutic strategies, PAH remains a progressive and fatal disease.\textsuperscript{23} In addition, we generated an equation that may be useful in predicting survival in an incident population of idiopathic, familial, and anorexigen-associated PAH treated in the modern management era. However, our proposed new formula needs to be validated in an independent patient population in order to establish its reliability and its generalizability to populations different to that from which it was derived. Since recent pulmonary hypertension guidelines now advocate a more aggressive management approach, including early treatment of mildly symptomatic NYHA functional class II patients and use of sequential combination therapies in those who do not reach predefined treatment goals, it would be interesting to study survival trends in more recent cohorts.\textsuperscript{2}
present manuscript we have studied survival among patients with a rare disease at a national level between 2002 and 2006. Obviously with more data/events we could make more accurate estimates of predicted survival. We consider that our work represents a worthy addition to this scientific field but should be considered hypothesis-generating, not hypothesis-confirming. While survival estimates can be calculated for a given patient as proposed in our manuscript, one must emphasize that our equation simply reflects outcomes in a cohort of patients managed in France between 2002 and 2006 and that the risk-prediction equation has obvious limitations when one attempts to predict outcomes of a given individual.

PAH mortality is most closely associated with male gender, right ventricular hemodynamic function, and exercise limitation. An improved understanding of the influence of gender on PAH development and outcomes is therefore of critical importance. PAH is a disease with an undisputed female predominance, suggesting that hormonal influences promote the development of pulmonary vascular remodelling in predisposed individuals (as strongly suggested by the female PAH predominance even in patients carrying a \textit{BMPR2} mutation). Nevertheless, our study shows that male gender is associated with poorer survival. These gender-related characteristics deserve further attention and it would be timely to support research programs attempting to understand the influence of gender on disease occurrence and outcomes.

Our analysis has several limitations. First, our risk-prediction equation focused on a homogeneous patient population with idiopathic, familial, and anorexigen-associated PAH, and therefore it cannot be readily generalized to patient groups with PAH associated with other diseases. In addition, our study was performed at a time when several currently available therapies were not yet available and in the context of
treatment guidelines that advocated a relatively less aggressive treatment approach.\textsuperscript{23-26} These factors may have negatively affected outcomes in some patients who would be likely to be treated more aggressively in the current management era.\textsuperscript{2} In addition, we analyzed patients treated in selected centers with expertise in pulmonary vascular medicine and may therefore have focused on a subset of patients with severe disease. However, as PAH care in France is performed by a network of selected sites associated with the French National Referral Center,\textsuperscript{23,24} our results presumably represent the prevailing status of PAH management and outcomes at the time of our study (2002-2006). The selection of a robust outcome measure (survival) in a population without co-morbid conditions is a strength of this multicenter nationwide study. It is important to note, however, that the population used to generate the risk-prediction equation in our study is rather small (190 patients with 53 deaths in three years), thereby limiting the identification of potentially strong risk factors. Thus, the prediction equation derived from this sample might over/under-estimate survival in other PAH samples. In an attempt to validate our risk-prediction equation, we are currently testing our proposed new formula in an independent patient population.

In conclusion, our results indicate that PAH remained a severe life-threatening disease at the start of the last decade despite better awareness and improved management. Recent guidelines now recommend more active treatment strategies, including systematic referral to expert centers, early management with specific therapies in symptomatic PAH patients as early as NYHA functional class II and use of sequential combination therapies when ambitious treatment goals are not met.\textsuperscript{2} The impact on patient outcome of this therapeutic paradigm shift is the focus of an ongoing study evaluating a new cohort selected from our national network. In any
case, the current analysis clearly emphasizes the need for additional research and discoveries in the field of PAH in order to improve outcomes for those with this dismal disease.
Annex

The following investigators contributed to the conduct and reporting of this study: Marc Humbert, Olivier Sitbon, Azzedine Yaïci, David Montani, Laurent Savale, Xavier Jaïs, Florence Parent, Bruno Degano, Dermot S. O’Callaghan, Sven Günther, Zhi-Cheng Jing, Rogério Souza, Gérald Simonneau (Clamart), Ari Chaouat, Irina Enache, Emmanuel Weitzenblum (Strasbourg), Michèle Bertocchi, Bénédicte Mastroianni, Vincent Cottin, Jean-François Mornex, Jean-François Cordier (Lyon), Claire Dromer, Joël Constans (Bordeaux), Nahed Beuraud, François Chabot (Nancy), Marcel Laurent, Claude Almange (Rennes), Christophe Pison, Carole Saunier, Hélène Bouvaist, Christelle Saint Raymond (Grenoble), Gilbert Habib, Sébastien Renard, Martine Reynaud-Gaubert (Marseille), Eric Hachulla, Benoît Wallaert (Lille), Alain Haloun (Nantes), Irène Frachon (Brest), Jocelyn Inamo (Fort de France), Roger Escamilla, Bruno Degano (Toulouse), Boris Melloni (Limoges), Loïc Guillemin, Luc Mouthon (Paris, France).

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FIGURE LEGENDS

Figure 1: Flow diagram chart

2002/2003 French PAH cohort
n=674

Idiopathic, familial or associated PAH
n=354

PAH with associated conditions
n=320
- 100 connective tissue diseases
- 76 congenital heart diseases
- 70 portal hypertension
- 42 HIV infection
- 29 with 2 risk factors

Incident cases
n=56

Prevalent cases diagnosed <36 months before inclusion
n=134

Prevalent cases diagnosed >36 months before inclusion
n=184

Combined Population
(n=180)
cohort used for calculation of risk-prediction equation
Figure 2:

A. Three-year survival of the entire cohort of 674 PAH patients

B. Three-year survival in PAH patients with congenital heart disease, idiopathic disease, or connective tissue disease

(PAH: pulmonary arterial hypertension)
Figure 3:

A. Three-year survival of the entire cohort of 674 PAH patients, according to gender

B. Three-year survival of the entire cohort of 674 PAH patients, according to age at study entry

C. Three-year survival of the entire cohort of 674 PAH patients, according to NYHA functional class at study entry

(PAH: pulmonary arterial hypertension; NYHA: New York Heart Association)
Figure 4:

A. Three-year survival from study entry of incident and prevalent patients with idiopathic, familial and anorexigen-associated PAH

B. Survival from study entry according to quartiles of time from diagnosis in the prevalent population