Rev Port Pneumol. 2017;xxx(xx):xxx–xxx

revista portuguesa de PNEUMOLOGIA
portuguese journal of pulmonology
www.revportpneumol.org

ORIGINAL ARTICLE

Real-world, long-term survival of incident patients with pulmonary arterial hypertension

P. Marques-Alves[a], R. Baptista[a,b], A. Marinho da Silva[a], M. Pêgo[a], G. Castro[a,*]

[a] *Pulmonary Vascular Unit, Department of Cardiology A, Centro Hospitalar e Universitário de Coimbra, Praceta Mota Pinto, Coimbra, Portugal*
[b] *CNC.IBILI Research Consortium, University of Coimbra, Coimbra, Portugal*

Received 8 September 2016; accepted 16 January 2017

KEYWORDS
Pulmonary arterial hypertension;
Survival;
Predictors of mortality;
Predictors of heart failure

Abstract
Background: Pulmonary arterial hypertension (PAH) is a progressive, fatal disease. Long-term outcomes data are scarce in Portugal. We aimed to estimate survival of newly diagnosed PAH at a Portuguese referral center in the modern management era.
Methods: Between January 2009 and November 2015 all incident PAH cases were consecutively enrolled in a prospective cohort study. Sixty-five patients were followed up for a median of 3.1 [interquartile range 1.7–5.4] years. Kaplan–Meier survival analysis was used to estimate 1-, 3-, and 5-year survival and to compare it with a historical PAH survival estimated from the NIH cohort.
Results: Mean age was 48 ± 19 years with female preponderance (68%). The most common PAH subgroup was congenital heart disease (PAH-CHD) ($n = 31$; 48%), followed by connective tissue disease (PAH-CTD) ($n = 16$; 25%), idiopathic (IPAH) ($n = 8$; 12%) and hereditary (HPAP) ($n = 1$; 1.5%). BNP values (hazard ratio [HR] 2.07; 95%CI 1.34–3.22; $P = 0.001$) and male gender [HR 4.34 (1.44–13.09); $P = 0.009$] were predictors of death. Survival rates at 1-, 3- and 5-years were 95%, 77% and 71%. Survival was not statistically different between PAH etiologies (Log-rank $P = 0.7$). However, PAH-CHD was associated with a decreased risk of the combined endpoint of all-cause mortality and admission for decompensated heart failure [HR 0.36 (0.15–0.85); $P = 0.02$]. We found a non-significant numerically higher survival of incident IPAH, HPAH and DPAH patients in comparison with the historical NIH cohort.
Conclusions: In this cohort of incident PAH patients, PAH-CHD patients had better overall prognosis. Higher BNP values and male gender were associated with higher mortality.

* Corresponding author.
E-mail address: castro2406@gmail.com (G. Castro).

http://dx.doi.org/10.1016/j.rppnen.2017.01.006

Introduction

Pulmonary arterial hypertension (PAH) is a progressive, symptomatic, and ultimately fatal disorder that involves the lung vasculature.[1] Vascular proliferation and remodeling constitute the hallmark of the disease, leading to a progressive increase in pulmonary vascular resistance, right ventricular afterload and ultimately right heart failure.[2] PAH is clinically divided into several groups: idiopathic (IPAH), hereditable (HPAH), drug-related (DPAH), congenital heart disease-associated (PAH-CHD), connective tissue disease-associated (PAH-CTD), portopulmonary (PoPH) and associated to infections, such as HIV or schistosomiasis.[3] Pulmonary capillary hemangiomatosis (PCH) and pulmonary veno-occlusive disease (PVOD), a spectrum of diseases involving the capillaries and venules, are included in a separate group (1′) within the PAH group.[3] PAH is a very rare disease with an estimated incidence of 1–3 cases per million.[4] The population-based prevalence ranges from 15 to 50 per 1 million.[5,6]

Substantial advances in treatment have been made during the past decade.[4,7,8] In the late 1980s, the National Institutes of Health (NIH) registry was the first to evaluate the epidemiology of IPAH, HPAH and DPAH during an era lacking specific PAH therapies.[9] The survival rates reported at 1-, 3- and 5- years were 68%, 47% and 37%, respectively.[10] In the modern management era, several registry-based studies have reported an improved survival, compared with the historical NIH registry.[11]

In Portugal, PAH care delivery is provided by 4 treatment centers designated by the Ministry of Health. Although retrospective[12] and prospective[13] short-term outcomes studies are available for Portuguese cohorts, long-term outcomes data are scarce, specifically in relation to incident patients, a critical issue to prevent immortal-time bias.[11] Therefore, we aimed to characterize and estimate survival in the modern management, guideline-driven treatment era of newly diagnosed, incident PAH patients[14] in a Portuguese treatment center.

Methods

Between January 2009 and November 2015, all incident patients diagnosed with PAH were consecutively enrolled in our registry at the Pulmonary Vascular Unit of *Centro Hospitalar e Universitário de Coimbra*. Patients from local hospitals from the central region of Portugal, with a referral population of ca. 2.5 million, are referred to our center to undergo diagnostic workup and initiate specific therapy. We followed the Declaration of Helsinki (2008) principles, with local research ethic committee approval.

Study design

We designed a single-center, prospective cohort study based on incident cases of PAH. PAH was defined as *per* guidelines[14]: right heart catheterization (RHC)-confirmed precapillary pulmonary hypertension (PH) in the absence of other etiologies for PH (left heart disease, lung disease, chronic thromboembolic PH). Precapillary PH was defined as a mean pulmonary arterial pressure (mPAP) of $\geq$25 mmHg and a pulmonary arterial occlusion pressure (PAOP) of $\leq$15 mmHg. PAH was classified into six different groups based on etiology, based on the latest guidelines[14]: IPAH, HPAH, DPAH, PAH-CHD, PAH-CTD, PoPH, and PVOD (group 1′). Patients were ineligible if they were aged under 18 years at enrollment.

For purposes of analysis, we divided the groups into two major diagnostic subgroups: PAH-CHD patients (Eisenmenger syndrome in non-corrected systemic to pulmonary shunts and PAH after shunt correction) and non-PAH-CHD patients (IPAH, HPAH, DPAH, PAH-CTD and PoPH). IPAH, HPAP and DPAH were combined into one group to simplify survival analysis. We also stratified the population according to age and gender to perform subgroup survival analysis.

We collected information regarding demographics, clinical and laboratorial parameters at presentation, namely 6-minute walking distance (6MWD), B-type natriuretic peptide (BNP) and hemodynamics from the diagnostic, baseline RHC.

Follow-up, outcomes and exposure variables

All follow-up visits were conducted at our institution and managed by a small group of PH specialists (G.C., R.B. and A.M.S.). Follow-up intervals and initiation of relevant therapy were determined at the physician's discretion. Because of changes in therapy, availability, and recommendations throughout the time period, treatment is registered as the latest administration on last visit.

The primary endpoint of our study was all-cause mortality. The secondary endpoint was a combination of all-cause mortality and admission for decompensated heart failure. Survival time was estimated from the date of the diagnostic RHC. At the end of the study, on November 12, 2015, vital status was obtained by access to the National Health Data Platform (*Plataforma Nacional de Dados de Saúde*). We also registered all hospital admissions for decompensated heart failure after the first hospital admission. No patient was lost to follow-up.

Statistical analysis

Continuous variables were reported as means $\pm$ SD or as medians with interquartile range (IQR) where appropriate. Categorical variables were reported as absolute frequencies and percentages. Survival analysis was performed using Kaplan–Meier curves, with the date of entry into the study defined as the date of the first diagnostic RHC or the first visit to the PH clinic for those patients that did not undergo any initial RHC. Patients that did not die were censored at the end of the study. The log-rank test was used for comparison between groups.

Univariate Cox's proportional hazards analysis was used to assess the relationship between PAH and outcomes. Co-linearity between variables was examined. Significant variables on the univariate analysis along with those variables previously reported to be related with mortality, were included in a forward stepwise multivariate Cox's proportional hazards model in order to identify independent predictors of outcomes in the overall PAH population.

Please cite this article in press as: Marques-Alves P, et al. Rev Port Pneumol. 2017. http://dx.doi.org/10.1016/j.rppnen.2017.01.006