CHAPTER

PREDICTORS OF MORTALITY IN INOPERABLE CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

Nabil Saouti, Frances de Man, Nico Westerhof, Anco Boonstra, Jos Twisk, Pieter E. Postmus, Anton Vonk Noordegraaf

ABSTRACT

Introduction: Recent studies suggest that medically treated patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH) have an improved prognosis. However, only limited data are available concerning predictors of mortality in these patients. The aim of this study was to assess, and to identify predictors of, the long-term outcome of inoperable CTEPH patients.

Methods: We analyzed 84 inoperable CTEPH patients from 1999 till 2008. During follow-up (mean 32 months), 17 patients died and one underwent a lung transplantation. The 1, 3 and 5 year survival rates were 93%, 78 % and 68% respectively. Univariate analysis demonstrated that 6 minute walking distance (6MWD), mean pulmonary artery pressure (mPAP), right atrial pressure (RAP) and pulmonary vascular resistance (PVR) were predictive factors for survival. In the multivariate analysis only 6MWD was independently related to poor survival (hazard ratio 0.995; 95% CI, 0.991-0.998; P = .003). Kaplan-Meier curves showed that patients with a mPAP > 40 mmHg, PVR > 584 dyne·s·cm⁻² and RAP > 12 mmHg had a very poor prognosis.

Conclusions: Hemodynamic parameters and simple clinical variables at baseline are very good predictive factors for mortality of medically treated inoperable CTEPH patients. A subgroup of these patients with good prognostic factors, defined by their hemodynamics and clinical measures, have an improved long-term survival and outcome.
INTRODUCTION

Chronic Thromboembolic Pulmonary Hypertension (CTEPH) is an uncommon, although increasingly diagnosed, disease of the pulmonary artery vasculature characterized by intraluminal thrombus formation and fibrous stenosis or complete obliteration. These obstructions are typically distributed in the central pulmonary arteries. As a result patients develop various degrees of pulmonary hypertension, depending on the extension of the vascular obstructions. Left untreated, this leads to right ventricular failure and death. Predictive factors for survival in patients with inoperable CTEPH treated medically have not been sufficiently elucidated.

In recent years medical treatment with proven efficacy in idiopathic pulmonary arterial hypertension (IPAH) and other forms of PAH, such as prostacyclin, phosphodiesterase-5 inhibitors (PDE-5 inhibitors) and endothelin-receptor antagonists (ERA), has been tried for inoperable CTEPH or as a therapeutic bridge to pulmonary endarterectomy (PEA). Although the effect of treatment on the long-term survival has never been investigated in a randomised trial, recent data from two large PAH centres shows that long-term survival of treated medically CTEPH patients is much better than reported in earlier studies when compared with untreated patients. However, it is unclear which parameters predict long-term survival in this era of PH-specific (oral) medical treatment. Therefore the aim of this study was to identify the determinants of survival in medically treated inoperable CTEPH patients.

MATERIALS AND METHODS

Subjects and study design:

This observational cohort study encompassed 84 inoperable CTEPH patients. All patients were referred to the department of pulmonary diseases at the VU medical center (a specialised referral center for the evaluation and treatment of PH) between May 1999 and February 2008. Cohort entry was defined as the time/date of first right heart catheterization, to establish the diagnosis of pulmonary arterial hypertension. See table 1 for baseline patient characteristics.

Methods:

The diagnosis CTEPH was made using standard diagnostic criteria. All patients were evaluated by a multi disciplinary team of pulmonary physicians, surgeons and radiologists using ventilation/perfusion scintigraphy, CT pulmonary angiography, conventional pulmonary angiography, and right heart catheterization. CTEPH patients were regarded inoperable when either distal, surgically inaccessible vascular occlusions were present or when the severity of the PH was greater than predicted from the degree of vascular obliteration. In addition, all patients
received a complete work-up to exclude left sided heart disease by means of echocardiography, and pulmonary diseases as an underlying cause of the pulmonary hypertension by means of high resolution computed tomography and pulmonary function testing. In the clinical diagnostic workup all patients were classified according to the NYHA functional class and all patients (n=75) had to perform a six-minute walk test (6MWD), according to current guidelines. Blood was taken from a peripheral vein to assess N-terminal pro brain natriuretic peptide (NT pro-BNP) (n=60) analyzed on an ELECSYS 1010 bench top analyzer (Roche Diagnostics Netherlands). Since NT-pro BNP measurement was not available until the end of 2003, this data could not be obtained in 25 patients. In addition to coumadin (adjusted to a target international normalized ratio between 2.0 and 3.0) oxygen and diuretics CTEPH patients also received PH specific medications. The pharmacological treatment varied among patients (see table 2), depending on the clinical condition. The introduction of new drugs during the time course of this study is another source of treatment variability. In the period after 2003 patients in NYHA class III received oral therapy as first line. Choice of oral monotherapy was based on medication availability and clinical data available at that time.

Statistical analyses:
Baseline parameters between survivors and nonsurvivors were compared using independent Students t-test. Categorical data were compared using $\chi^2$ test. Univariate analyses based on the proportional hazard model was used to examine the relations between survival and selected demographic, clinical measures and hemodynamics measured at baseline. Forward stepwise multivariate analysis based on the Cox proportional hazard model was used to examine the independent effect of multiple covariates on survival, controlling for possible confounders. Optimal cut-off values assessed with Receiver Operating Curve (ROC) analysis were used to separate the patients on both sides into two groups. Survival curves were derived by Kaplan-Meier method. Groups were compared by the log-rank test.

Survival was estimated from the date of initial diagnosis until February 5, 2008, the date of death or that of lung transplantation. A p value < 0.05 was considered statistically significant.

Results
The baseline patient characteristics and hemodynamics are summarized in table 1. The mean age was 64 ± 13 years and the majority of patients were female. The NYHA functional class II, III en IV is also given in the table. The averaged exercise capacity expressed in 6MWD was 362 m indicating severe exercise intolerance. The hemodynamic parameters showed that patients had significant pulmonary hypertension with increased RV and RA pressures.
Table 1. Baseline parameters between survivors and nonsurvivors with CTEPH. Values are presented as mean ± SD.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n=84)</th>
<th>Survivors (n=66)</th>
<th>Nonsurvivors (n=18)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>64 ± 13</td>
<td>64 ± 14</td>
<td>63 ± 12</td>
<td>.99</td>
</tr>
<tr>
<td>female/ male ratio (n)</td>
<td>59/ 25</td>
<td>47/19</td>
<td>12/6</td>
<td>0.7</td>
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<tr>
<td>Functional class NYHA (%)</td>
<td>4, 26, 45, 25</td>
<td>100, 91, 90, 43</td>
<td>0, 9, 10, 57</td>
<td>0.0001</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>9.4 ± 6.9</td>
<td>8 ± 6</td>
<td>14 ± 7.9</td>
<td>.004 *</td>
</tr>
<tr>
<td>diast RVP (mmHg)</td>
<td>12 ± 13</td>
<td>11 ± 14.6</td>
<td>15.9 ± 8.4</td>
<td>.04 *</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>45 ± 13</td>
<td>42.9 ± 13.4</td>
<td>53 ± 9.6</td>
<td>.003 *</td>
</tr>
<tr>
<td>PVR (dyne•s•cm⁻⁵)</td>
<td>718 ± 368</td>
<td>631 ± 312</td>
<td>1015 ± 399</td>
<td>.0001 *</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>2.6 ± .9</td>
<td>2.8 ± .9</td>
<td>2.2 ± .9</td>
<td>.03</td>
</tr>
<tr>
<td>SvO₂ (%)</td>
<td>62 ± 11</td>
<td>63 ± 9.6</td>
<td>56 ± 12.8</td>
<td>.01 *</td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>363 ± 135</td>
<td>390 ± 124</td>
<td>264 ± 131</td>
<td>.0001 *</td>
</tr>
<tr>
<td>NT-proBNP (ng/L)</td>
<td>1702 ± 2278</td>
<td>1566 ± 2238</td>
<td>3206 ± 2420</td>
<td>.1</td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association; RAP, right atrial pressure; diastRVP, diastolic right ventricular pressure; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; SvO₂, mixed venous oxygen saturation; 6MWD, six-minute walking distance; NT-pro BNP, N-terminal pro brain natriuretic peptide; ASD, atrial septal defect; CAD, coronary artery disease; AMC, associated medical conditions (i.e. permanent central intravenous lines, splenectomy, inflammatory bowel disease).
P values refer to comparisons between survivors and nonsurvivors.

Table 2 shows the treatment and comorbidities in the inoperable CTEPH patients. The vast majority of survivors were treated with a PDE-5 inhibitor and in clinically deteriorating patients an ERA was added after initial therapy with a PDE-5 inhibitor. In the nonsurvivors a prostacyclin was the most commonly used drug, reflecting the clinical severity of the condition in these patients. Prostacyclin was the most commonly used drug before 2003 in contrast to after 2003 (39% vs. 8% respectively).

Associated medical conditions (AMC) and cancer were the most common comorbidities.

Differences in parameters between survivors and nonsurvivors are also shown in Table 1. The nonsurvivors had a significantly worse hemodynamic status at baseline than survivors (i.e. significantly higher RAP, diastolic RVP, mean PAP, PVR and significant lower SvO₂). The higher pressures in nonsurvivors were reflected in the higher NT-pro BNP values compared to survivors. Moreover this is not significant due to the wide spread of the standard deviation. As expected nonsurvivors had a significantly worse NYHA functional class compared to survivors. The performance in 6MWD was also lower in the nonsurvivors (P < 0.0001).
Survival

During a mean observation time of 32 ± 20 months (range 0 to 87 months) no patients were censored for reasons other than death. From the 84 patients 17 patients (20%) died from right heart failure (n=13), and respiratory failure in the end stage of right heart failure (n=4). At two years one patient had undergone lung transplantation.

The 1, 3 and 5 year survival for the total cohort was 93%, 78% and 68% respectively.

Although survival was significantly better after 2003 compared with the survival before 2003, with 1-, 3- and 5-year survival rates of 97 %, 84% and 79% vs. 71%, 50% and 43% respectively, patients had more severe disease as reflected by their hemodynamics at clinical presentation in the period before 2003 in comparison to after 2003 (mPAP 51 ± 9 vs. 44 ± 14, P = .02; PVR 924 ± 427 vs. 686 ± 353, P = .03).

Univariate analysis

Table 3 shows the results of the univariate Cox proportional hazards regression analysis. Of the hemodynamic variables mPAP, RAP and PVR were associated with poor survival, and of the clinical variables only 6MWD was significantly related to an increased risk of death. The hazard ratio for a 10 m difference in 6MWD was 0.95 (95% CI; 0.92 - 0.99) and for a 50 dynes·s·cm⁻² difference in PVR 1.11 (95%
CI: 1.00 - 1.22). Also related with an increased risk of death was the patients date of diagnosis and treatment after 2003 compared with before 2003.

Mortality was not associated with patient age, NT-pro BNP, mixed venous oxygen saturation, cardiac index, NYHA functional class and associated medical conditions (AMC).

Table 3. Univariate predictors of mortality in CTEPH patients (n=84). Univariate Cox proportional hazard analysis of variables associated with mortality in inoperable CTEPH. NYHA class is dichotomized comparing classes I and II with classes III and IV. Before vs. After 2003 denotes patients diagnosed before or after 2003 respectively.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>0.996</td>
<td>0.963-1.030</td>
<td>.82</td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>0.995</td>
<td>0.991-0.998</td>
<td>.003 *</td>
</tr>
<tr>
<td>NT-proBNP (ng/L)</td>
<td>1.000</td>
<td>1.000-1.000</td>
<td>.22</td>
</tr>
<tr>
<td>NYHA I, II vs III, IV</td>
<td>3.044</td>
<td>0.700-13.226</td>
<td>.14</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>1.038</td>
<td>1.003-1.074</td>
<td>.034 *</td>
</tr>
<tr>
<td>PVR (dyne•s•cm⁻⁵)</td>
<td>1.002</td>
<td>1.001-1.003</td>
<td>.004 *</td>
</tr>
<tr>
<td>SvO₂ (%)</td>
<td>0.974</td>
<td>0.938-1.012</td>
<td>.18</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>0.599</td>
<td>0.322-1.116</td>
<td>.11</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>1.072</td>
<td>1.009-1.140</td>
<td>.025 *</td>
</tr>
<tr>
<td>AMC</td>
<td>2.307</td>
<td>0.740-7.187</td>
<td>.149</td>
</tr>
<tr>
<td>Before vs. After 2003</td>
<td>0.299</td>
<td>0.115-0.779</td>
<td>.01 *</td>
</tr>
</tbody>
</table>

Definition of abbreviations. CI = confidence interval; AMC = associated medical conditions (i.e. splenectomy, permanent central intravenous lines, and inflammatory disorders)

Receiver-Operating Characteristics

To distinguish survivors from nonsurvivors according to baseline parameters, a ROC analysis was performed with the significant predictors from the univariate analysis. Groups were created based on the optimal cut-off values determined by ROC analysis and Kaplan Meier curves were compared for the different groups.

Patients with a 6MWD less than 298 m had a significantly lower survival rate than those with a 6MWD more than 298 m (log rank test, P < 0.009; Figure 1a). Separation of the groups using the median 6MWD of 386 m was significantly less predictive than when using the optimal cut-off value of 298 m determined by the ROC analysis (data not shown). The same Kaplan Meier curves showed that patients with a mPAP > 40 mmHg, RAP > 12 mmHg and, PVR > 584 dyne•s•cm⁻⁵ were significantly at an increased risk of death compared with patients who had a mPAP < 40 mmHg (P < 0.02), RAP < 12 mmHg (P = 0.009), and PVR < 584 dyne•s•cm⁻⁵ (P = 0.002) respectively (Figure 1b, c and d).
Multivariate analysis

In the forward stepwise multivariate analysis, we examined the effect on mortality of each independent baseline variable in the presence of others. Each independent variable found to be significant in the univariate analysis was included. Only 6MWD was independently related to poor survival (hazard ratio 0.995; 95% CI, 0.991-0.998; P = .003). Backward multivariate analysis showed the same outcome.

Figure 1. Kaplan-Meier curves according to the optimal cut-off value derived by ROC analysis for six-minute walking distance (6MWD; panel a), mean pulmonary artery pressure (mPAP; panel b), right atrial pressure (RAP; panel c) and pulmonary vascular resistance (PVR; panel d).
DISCUSSION

In the present study, we provide new insights on prognostic factors in patients with CTEPH who are treated medically, and we show that the long-term outcome and survival are favourable in a subgroup of inoperable CTEPH patients. We found that hemodynamic parameters (ie. mPAP, RAP, PVR) at baseline and simple clinical variables such as 6MWD are strongly related to survival.

**Survival.** Data on long-term survival in inoperable CTEPH patients before modern vasoactive treatment were very poor. The only 2 studies describing the survival in medically untreated CTEPH patients showed that the three year survival rate was as low as 10% in patients with a meanPAP > 30 mmHg \(^1^9\) and the 5 year survival 14 % in patients with a meanPAP > 50 mmHg. \(^3\) In the current study, with modern treatment, the overall 1, 3 and 5 year survival was 93%, 78% and 68% respectively. These survival rates are comparable with recently published studies of Bonderman and Condliffe et al. \(^1^4,1^5\) In the study of Bonderman et al. 1, 3 and 5 year survival was 88%, 65% and 65% respectively, although these were patients without associated medical conditions. With associated medical conditions these inoperable CTEPH patients had a poorer 1, 3 and 5 year survival of 74%, 45% and 15%. Condliffe et al. showed in a multicenter study of medically treated inoperable CTEPH patients from the United Kingdom 1, 3 and 5 year survival of 82%, 70% and 55% respectively. \(^1^5\)

**Prognostic factors.** In IPAH cardiac index, degree of RAP and PAP are associated with survival. \(^2^0\) In CTEPH little data are available about prognostic factors of survival with modern vasoactive therapy. In previous studies of medically untreated CTEPH patients the degree of mPAP was a strong predictor of mortality. \(^3,1^9\) In this study of medically treated inoperable CTEPH patients various hemodynamic variables derived at baseline are well able to predict long-term survival. A low mPAP, PVR and and RAP at baseline (all below the cut-off value determined by ROC analysis) were prognostic beneficial for these patients. Of the clinical variables a relatively high 6MWD (above the cut-off value determined with ROC analysis) was associated with a better long-term survival. Bonderman et al. showed that AMC are related to increased mortality. \(^1^4\) In this study 4 of the 10 patients with AMC patients (40%) died. The reason that AMC was found not to be significant in the univariate analysis is probably due to the low number of deaths in the total cohort of patients. Although univariate analysis showed that survival is worse in the period before 2002 at the time when only prostacycline was available, multivariate analysis showed that this variable was not significant, most probably since the patients diagnosed with CTEPH had more severe disease reflected by their hemodynamics in comparison to the patient group diagnosed after 2002.

We are the first to show that the 6MWD in the multivariate analysis is the only independent factor that predicts the survival. Patients with a 6MWD more than 298 m had a significantly better long-term survival than patients walking less. This finding is in accordance with the study by Myamoto in IPAH showing that
6MWD is a strong independent factor associated with mortality. Miyamoto et al assessed the cut-off value by the median and found that IPAH patients walking more than 332 m had a significantly better survival. Another study showed that with ROC analysis a preoperative distance of ≤ 345 m was able to predict death in patients who had undergone pulmonary endarterectomy with a sensitivity of 100% and specificity of 36%. Using the cut-off value of 298 m in this study, as determined by ROC analysis, provided the best discrimination between survivors and non-survivors.

**CLINICAL IMPLICATION**

We have tried to provide a profile of the survivors and nonsurvivors with both clinical measures and hemodynamics evaluated at baseline. Although it is clear that the treatment of choice is pulmonary endarterectomy (PEA) in patients with CTEPH eligible for surgery, the indications for surgery are not always so clear since the degree of vascular obstruction on angiography is often not correlated to hemodynamic and clinical severity. The findings in this study could be used as a risk stratification in CTEPH patients if surgery is questionable.

The main limitation of this study is its retrospectively observational design. As a result of this we miss some NT-proBNP data. This study concerns only inoperable CTEPH patients and therefore results cannot be applied to patients with operable CTEPH patients. Another limitation is the small number of events, therefore the results of the multivariate analysis should be interpreted with caution. Nonetheless, 6MWD remains a strong independent predictor for mortality. Finally, our patients were very heterogeneously treated, according to new introduced drugs over the years, and the available clinical insights. Since it was not the aim of this study to prove that medical treatment is beneficial in CTEPH, nor to study the differences in efficacy between treatment strategies, no conclusions can be drawn on the optimal treatment schedule.

**Conclusions.** Long-term survival and outcome of medically treated inoperable CTEPH patients is much improved in this therapeutic era compared with untreated patients and is comparable with recently reported survival rates. Severity at baseline, assessed by hemodynamics and clinical measures, predicts the survival of these patients very accurately. Six-MWD above 298 m at baseline is associated with a favourable long-term survival.

**REFERENCE LIST**


