Clinical and Biochemical Predictive Factors of Mortality in Patients with Chronic with thromboembolic pulmonary Hypertension

Peer review status: No

Corresponding Author:
Dr. Jola Klosi,
University Hospital Center "Mother Theresa", Internal Medicine and Arterial Hypertension, Rruga e Dibrës 372, Tirana 1000, 1001 - Albania

Submitting Author:
Dr. Jola Klosi,
University Hospital Center "Mother Theresa", Internal Medicine and Arterial Hypertension, Rruga e Dibrës 372, Tirana 1000, 1001 - Albania

Other Authors:
Dr. Aneida Vevecka,
Regiomedkliniken, Cardiology clinic, Coburg - Germany
Dr. Elizana Petrela,
University Hospital Center "Mother Theresa", Statistical Department - Albania
Prof. Mihal Tase,
University Hospital Center "Mother Theresa", Internal Medicine and Arterial Hypertension - Albania

Article ID: WMC005110
Article Type: Original Articles
Submitted on: 25-May-2016, 09:11:43 PM GMT  Published on: 27-May-2016, 05:52:02 AM GMT
Article URL: http://www.webmedcentral.com/article_view/5110
Subject Categories: PULMONARY MEDICINE
Keywords: CTEPH, mortality, predictive factors, clinical, biochemical

How to cite the article: Klosi J, Vevecka A, Petrela E, Tase M. Clinical and Biochemical Predictive Factors of Mortality in Patients with Chronic with thromboembolic pulmonary hypertension. WebmedCentral PULMONARY MEDICINE 2016;7(5):WMC005110

Copyright: This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC-BY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Source(s) of Funding:
University Hospital Center "Mother Theresa", Tirana, Albania.

Competing Interests:
None
Clinical and Biochemical Predictive Factors of Mortality in Patients with Chronic with thromboembolic pulmonary Hypertension

**Author(s):** Klosi J, Vevecka A, Petrela E, Tase M

**Abstract**

**Aim:** To evaluate clinical and biochemical predictors of mortality in patients with chronic thromboembolic pulmonary hypertension (CTEPH) who did not performed surgical treatment or specific vasodilator treatment.

**Methods:** This is a prospective study, conducted at Department of Internal Medicine, University Hospital Center “Mother Theresa” in Tirana, Albania. During 2012 – 2015, 43 patients who had survived acute pulmonary embolism (PE) were included in the study and were followed periodically. Mean age of patients was 64.23±10.70 years old (31 females). CTEPH was diagnosed in 12 (28%) of 43 patients (pulmonary artery systolic pressure (PAsP) >45 mmHg, at least 3 months after acute PE and effective anticoagulant treatment). Among them, 5 patients (41%) died during follow-up period. We have determined through a detailed statistical analysis which are the clinical and biochemical parameters predictors of mortality in this category of patients.

**Results:** It was seen a strong correlation between mortality and 6-minute walking distance (6mWD) (129.29±35.63; \( p=0.001 \)). The same correlation is observed between mortality and D-Dimer (6540.47±2800.36; \( p=0.008 \)) and mortality – NT-proBNP (3572.0±1215.87; \( p=0.009 \)). Does not exist correlation between mortality and troponin \( (p=0.098) \), hemoglobin \( (p=0.603) \) and creatinine \( (p=0.331) \).

**Conclusion:** Predictive factors of mortality, in our patients, reflect especially the severity of heart failure (6mWT, NT-proBNP) as well their thrombotic state (D-Dimer). Anemia and renal failure were not statistically significant factors which may affect mortality in this category of patients.

**Introduction**

Chronic pulmonary thromboembolic disease is an important cause of severe pulmonary hypertension (PH), affecting from 0.1 – 9.1% of the survivors of an acute pulmonary embolism\(^1\). Due to the honeymoon period which can last from months to years the true prevalence is not known, thereby is believed that the true prevalence may be even greater \(^2\). The prognosis of this condition is reserved and it reflects mostly the degree of associated right ventricular dysfunction as well as the patient’s morbidity profile, making this disease a significant medical problem throughout the world \(^3, 4\).

CTEPH is the only cause of severe PH which is potentially curable with pulmonary endarterectomy (PEA), without the need to resort to lung transplantation. This procedure requires a high degree of anaesthetic and surgical skill, coupled with assiduous preoperative evaluation of potential patients, conditions which in many economically underdeveloped countries are fulfilled with more difficulties \(^5\).

In this context, we think is very important a definition of the predictive factors of mortality in this category of patients, with the purpose of provision of optimal and rapid treatment to patients with high risk of death. The aim of this article will therefore be to emphasize the role of predictive factors of mortality in these patients, and simultaneously contributing to the expansion of contemporary literature regarding this category of patients.

**Methods**

The prospective study included 43 patients who had survived an acute pulmonary embolism. The study was conducted during the years 2012-2015 at University Hospital Center “Mother Theresa”, Tirana, Albania. During the first year of the study was established the group of patients who meet the study’s inclusion criteria. These patients were diagnosed with acute PE; malignant diseases were excluded as well as other serious diseases which can influence mortality. Mean age in this patient group was 64.23±10.70 years (31 females). Data on location and cause of possible death are taken from family in case that death has occurred outside the hospital. The end-point of this study was death.
We have registered anthropometric data, symptoms and time of first diagnosis. All patients were evaluated with ECG, chest X-Ray, computerized tomography, V/Q scan and transthoracic echocardiography by an accredited cardiologist. All participants underwent 6 minute walking test and the blood tests including D-Dimer, Troponin T and pro-BNP, hemoglobin, creatinine and inflammation parameters. Associated diseases were recorded. All patients were followed up with this protocol every 3, 9, 15 and 24 months.

The diagnosis of CTEPH was made by PAsP >45 mmHg, at least 3 months after acute PE and effective anticoagulant treatment. Right heart catheterization and pulmonary endarterectomy were not performed, due to technical impossibility to be carried out such procedures in our country. The patients did not receive any pulmonary vasodilator therapy. This study meets all the criteria of medical ethics, having a non-invasive nature. Each patient was informed of the nature of the study as well as the necessity to follow up, and signed a written consensus to participate in.

Statistical Analysis

All data were collected in Microsoft Excel and then exported to SPSS (Statistical Package for Social Sciences) 20.0, in which the program was implemented all statistical analyzes.

For all numerical variables, when the data subject to normal distribution, were calculated arithmetic averages ± standard deviations. For non-parametric data (ordinal), was calculated Kendall’s tau, correlation coefficients. Differences between groups for discrete variables were performed by Chi-Square test. Differences between groups for quantitative variables were performed by the Student test and ANOVA analysis (when comparing the differences between more than two groups). Bonferoni procedure (as a post-Hoc analysis) was applied to see which groups attributed the difference. To assess the causal links between the dependent and the independent variables was used binary logistic regression analysis. For each of the variables were estimated odds ratio (Odds) and 95% confidence interval. It was considered significant values of p≤0.05.

Results

Regarding the overall characteristics of the patients included in this study, 12 of 43 patients (28%) were diagnosed with CTEPH. Mortality in this group of patients was 41% in 2 years.

We observed that mortality of CTEPH- patients was statistically correlated to the distance of 6 min walking test 129.29±35.63 meters in the group of patients who did exitus letalis compared with 351.06±91.84 meters in patients who were still alive after 2 years (p=0.001). Also we would like to note that the walking distance of patients who developed CTEP is much smaller than those who did not develop pulmonary hypertension after acute pulmonary thromboembolism (527.04±106.07 meters) (Table 1, Figure 1).

Concerning the markers of the damage of the myocardium, mortality was statistically correlated with NT ProBNP levels, with an average of 3572.0±1215.87 pg/dl in the group of patients who died compared with 1659.62±844.51 pg/dl in patients who survived, achieving a high significant statistical level (p=0.009). We underline the fact that in patients who did not develop pulmonary hypertension as a result of acute pulmonary thromboembolism, pro-BNP is almost in normal limits (586.95±307.06 pg/dl). On the other hand we found not a statistically significant correlation between the level of troponin and mortality in our patients with CTEPH (p=0.098) (Table 1, Figure 2).

Thrombophylic state represented by D-Dimer level has a direct and powerful influence on the mortality of patients with CTEPH. We have noted that mean D-Dimer level was 6540.47±2800.36 mg/dl in patients with CTEPH who died compared with 2703.02±1103.57 mg/dl in patients with CTEPH surviving after 2 years, reaching statistically significant values (p=0.008). Interesting is also the fact that even in patients who did not develop pulmonary hypertension after acute episode of PE, is a Thrombophylic trend observed, having an average level of D-Dimer 1265.75±1006.24 mg/dl (Table 1, Figure 3).

Wishing to know if the presence of anemia and renal failure may be predictive factors of mortality, we found that mortality was not statistical correlated to hemoglobin (p=0.603) and creatinine levels (p=0.331) in our group of patients (Table 1).

Discussion

Chronic thromboembolic pulmonary hypertension is not only a disease with a steadily increasing incidence, but also with a very bad prognosis due to rapid progression to right heart failure and death, if left untreated.

From optimistic points of view it can be said that this form of pulmonary hypertension is in fact the only form
of this disease which can be cured completely through pulmonary endarterectomy without being necessary the lung transplant. In reality, only a small proportion of patients with this disease can be treated optimally, including the implementation of modern surgical methods of treatment. The reasons for this “under treatment” are not only diagnosed in the late stages of the disease, but also the lack of appropriate conditions and specialists to apply this treatment in many hospital centers throughout the world, especially in developing countries.

In this context, we think it is necessary to determine the predictive factors of mortality in this category of patients, having as main Priorities providing of optimal treatment, especially in patients who present the highest risk for death.

Joining the results of other studies, we have once again highlights that in patients with CTEPH, mortality was strongly related to the distance walked during the 6-minute walking test. If walked distance is small then the risk of death in these patients is high. This test represents in fact a measure of functional physical capacity and provides a broader scale of functional NYHA class of heart failure. Laboratory data of our patients support once again the fact that severe heart failure is the cornerstone of the high mortality of this disease. We have noted that the high level of NT-proBNP is strongly related to mortality in patients with CTEPH. NT-proBNP is a marker of pathological conditions that affect the left ventricle, but it is also significantly elevated in acute or chronic right ventricular overload and right heart failure, being nowadays one of the most important markers not only for diagnosis but also for prognosis in patients with heart failure.

It is familiar the fact that there is a prothrombotic state in patients who develop CTEPH after acute pulmonary embolism. Similar studies show the presence of an elevated D-dimer in PAH is quite common, though there are no further studies regarding the follow-up values in CTEPH patients. D-dimer itself is a marker of prothrombotic state in CTEPH. It can help following patients already diagnosed with CTEPH and suspecting of having recurrent thrombosis. In our group of patients we noted that high levels of D-Dimer in blood are statistically directly and strongly associated with the mortality of these patients.

Although it is known that the low level of hemoglobin and the worse renal function lead to increased mortality in patients with pulmonary hypertension, due to chronic hypoxia (which is tolerated very badly by these patients), this fact is not supported by statistical analysis in our study.

Limitations

Our patients did not perform right heart catheterization and data on pulmonary pressures are obtained by transthoracic echocardiography. PSAP measured by this method has been shown in many studies that correlates well with the one measured by right heart catheterization, but on the other hand is not accepted as gold method for diagnosis of pulmonary hypertension. Patients who participated in our study there not surgically or with specific pulmonary vasodilatory agents treated. These modern ways of treatment are not available in the medical system of Albania. These contemporary ways of treatment are not available in the medical system in Albania. This fact may justify the higher mortality of these patients compared with other international published studies.

Conclusion

Patients who develop chronic pulmonary hypertension after acute pulmonary embolism represent a significant medical problem due to their late diagnosis, increased incidence and poor prognosis. Determination of patient’s profile and the predictive factors of mortality are welcome, because it can lead to their optimal treatment including surgical contemporary treatment. Clinical and laboratory parameters which represent the presence and severity of heart failure are together with prothrombotic state predictors of mortality in patients with CTEPH.

New studies in this area are necessary, to frame clinical and hemodynamic profile of patients who suffer from this deadly disease but which can be completely treated without need of lung transplant.

Conflict of interest

None

References

2. Riedel M, Stanek V, Widimsky J. et al Longterm follow-up of patients with pulmonary thromboembolism. Late prognosis and evolution of
hemodynamic and respiratory data. Chest 198281151–158. Pivotal study defining the prognosis of CTEPH according to severity of underlying pulmonary hypertension.


Illustrations

Illustration 1

Correlation between mortality and different parameters in patients with CTPEH (compare of the two groups) and non CTEPH patients.

Table 1. Correlation between mortality and different parameters in patients with CTPEH (compare of the two groups) and non CTEPH patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>CTEPH</th>
<th>non CTEPH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Death (nr=5)</td>
<td>Survival (nr=7)</td>
</tr>
<tr>
<td>6mWD</td>
<td>129.29±35.63</td>
<td>351.06±91.8</td>
</tr>
<tr>
<td>D-Dimer</td>
<td>6540.47±2800.36</td>
<td>2703.02±110</td>
</tr>
<tr>
<td>ProBNP</td>
<td>3572.0±1215.87</td>
<td>1659.62±844</td>
</tr>
<tr>
<td>Troponin</td>
<td>0.52±0.24</td>
<td>0.28±0.20</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>12.01±1.34</td>
<td>11.68±0.81</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.48±0.73</td>
<td>1.19±0.24</td>
</tr>
</tbody>
</table>
Illustration 2

Correlation between mortality and 6 minute walking distance in patients with CTPEH (compare of the two groups) and non CTEPH patients

Figure 1: Correlation between mortality and 6 minute walking distance in patients with CTPEH (compare of the two groups) and non CTEPH patients
Illustration 3

Correlation between mortality and pro-BNP levels in patients with CTPEH (compare of the two groups) and non CTEPH patients

Figure 2: Correlation between mortality and pro-BNP levels in patients with CTPEH (compare of the two groups) and non CTEPH patients
Illustration 4

Correlation between mortality and D-Dimer levels in patients with CTPEH (compare of the two groups) and non CTEPH patients

Figure 3: Correlation between mortality and D-Dimer levels in patients with CTPEH (compare of the two groups) and non CTEPH patients