Biomarker-based risk assessment model in acute pulmonary embolism

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Introduction

It is accepted that patients with massive acute pulmonary embolism (APE), defined by systemic hypotension, constitute a high-risk group and should be treated with thrombolysis or embolectomy.¹,² However, risk stratification of normotensive patients is mainly based on echocardiography. Although normotensive patients with right ventricular (RV) overload have a moderately increased in-hospital mortality rate, up to 5–13%,³–⁶ there is an ongoing debate as to whether this group should be treated by anticoagulation or by more aggressive methods.⁷–¹⁰ Recently, it was suggested that serum levels of cardiac troponins and brain natriuretic peptides can be helpful in risk assessment in APE. Elevated cardiac troponin levels indicate increased mortality.¹¹–¹⁴ Serum NT-proBNP was proved to be a marker of left ventricular (LV) overload and was used for reliable differentiation between cardiac and pulmonary origin of dyspnoea.¹⁵ However, elevated NT-proBNP levels can be found in APE. Interestingly, low levels of brain natriuretic peptide can identify patients with good prognosis.¹⁶–¹⁸ However, there are limited data on the simultaneous application of both cardiac biomarkers. Therefore, we tested the value of biomarker-based risk assessment model in APE and compared it with the current risk stratification strategy incorporating haemodynamic parameters and echocardiographic indices of RV dysfunction.

Methods

Clinical data

Study patients were selected from all consecutive patients, admitted to our department between 1999 and 2004, with APE confirmed by thrombo-emboli visualization in at least segmental arteries by contrast-enhanced spiral computed tomography or by high probability lung scintigraphy. All patients with acute coronary syndrome were excluded. Systemic blood pressure and heart rate were measured and transcutaneous pulsoximetry was recorded on admission. All investigated subjects presented systemic systolic blood pressure (SBP) >90 mmHg.
Therefore, according to ESC guidelines, they met criteria of submassive or non-massive APE. The endpoints of the study were defined as APE-related mortality, all-cause mortality, and serious adverse events (SAE). The APE-related mortality comprised deaths caused by irreversible RV insufficiency or recurrent PE, which the diagnosis was based on the clinical assessment. SAE included at least one of the following in-hospital adverse clinical events: death, cardiopulmonary resuscitation, thrombolysis, or the need for intravenous (i.v.) catecholamines infusion. All events were recorded up to 40 days after the diagnosis of APE in all studied patients.

Echocardiographic data

Transthoracic echocardiography (TTE) for the assessment of the degree of RV overload was performed using a GE System Five. The examinations were performed and recorded within 24 h after admission by an experienced echocardiographer blinded to the results of biochemical assays. Average of three consecutive measurements was used for statistical analysis. The end-diastolic dimensions of the right and left ventricles were measured in the long axis parasternal view and the RV/LV ratio was calculated. Hypokinesis of RV free wall was assessed quantitatively according to the previously described criteria. Tricuspid valve peak systolic gradient (TVPG) was calculated. Acceleration time of pulmonary ejection (AcT) was measured. The dimensions of the inferior vena cava were measured during expiration.

RV overload was diagnosed when echocardiography showed RV/LV > 0.6 with RV hypokinesis and/or elevated TVPG > 30 mmHg with a shortened AcT of pulmonary ejection, <80 ms.

Severity of APE

On the basis of the systemic SBP on admission and the result of echocardiography, the following groups were defined: massive APE with SBP < 90 mmHg; non-massive APE with SBP > 90 mmHg without echocardiographic signs of RV overload; and sub-massive APE when, despite SBP > 90 mmHg, RV overload was found.

Biochemical assays

On admission blood samples were collected for routine assays and for serum NT-proBNP and cardiac troponin T (cTnT) assessment. Samples for biomarker determinations were centrifuged and serum was frozen till quantitative assay (Roche, electrochemiluminescence method—ECLIA). Managing physicians were unaware of NT-proBNP and cTnT results.

The protocol of this study was approved by the Bioethics Committee. All participating patients expressed their prior informed consent.

Statistical analysis

Data characterized by a normal distribution are expressed as mean values followed by standard deviation. Parameters without such a distribution are expressed as a median with range. Student's t-test or Mann-Whitney's test was used for comparing the two groups. The χ² test was used to compare discrete variables. The staged statistical approach was used. Initially, univariable hazard risk ratios were estimated for each prognostic factor. Receiver operating characteristic (ROC) analysis was performed to assess the optimal cut-off values of serum NT-proBNP and cTnT for death and SAE selection. The Kaplan–Meier analyses were used to investigate cumulative 40-day survival rates. Next, by Cox proportional hazards regression, stepwise forward multivariable analyses were constructed from the set of significant univariable predictors. Owing to non-linear character of cTnT, a dichotomized value of cTnT was used in the univariable and multivariable analyses. This value was defined as cut-off point assessed at ROC curve. Two methods were used to assess the proportional hazards: the plot of the log-negative-log of the Kaplan–Meier estimates of survival function vs. the log of time and the Schoenfeld residuals. For all models of multivariable Cox proportional hazards regression, the bootstrap analyses were performed to discover the most stable model. All used tests were two-sided. Data were considered significant at P < 0.05. For statistical calculations, STATISTICA software was used.

Results

Patients' characteristics and clinical course

APE was diagnosed in 110 consecutive patients, 38 males and 72 females, aged 63 ± 18 years. Clinically massive APE was found in 10 patients, whereas the remaining 100 patients were normotensive on admission. Thus, finally investigated group included 100 patients (Table 1). Non-massive APE was found in 38 patients, 60 cases formed a subgroup with sub-massive APE. TTE was not performed on two patients, as they died before echocardiography could be performed. All patients with preserved systemic SBP received i.v. infusions of unfractionated heparins, with the dose APTT-adjusted, or subcutaneous low-molecular-weight heparins in a body mass-adjusted dose. A decrease in SBP to <90 mmHg and progressive tachycardia were considered indications for thrombolysis. Eventually, seven patients with sub-massive APE received thrombolysis with 1.5 million units of streptokinase i.v. over 2 h followed by i.v. heparin.

One or more of the following coexisting diseases—chronic obstructive pulmonary disease, neoplasm, renal failure (serum creatinine level >135 μmol/L), chronic heart failure (CHF), and coronary artery disease (CAD)—were present in 44 studied subjects (44%).

Despite treatment, 15 out of 100 patients died by the 40th day of observation (all-cause mortality 15%). This group included 10 (17%) patients with sub-massive APE and three patients (7.9%) with non-massive APE. The two remaining deaths occurred in normotensive patients shortly after admission, before TTE could be performed. There were eight APE-related deaths (APE mortality 8%). APE-related mortality in sub-massive APE was 13% when compared with 0% in non-massive group. Non-APE deaths resulted from fatal bleeding in four patients with significant comorbidities, whereas generalized neoplasms were the direct cause of death in two others. In addition, there was one fatal ventricular fibrillation in a 70-year-old patient with severe LV failure, without echocardiographic signs of RV overload. Thrombolysis was used with similar frequency in non-survivors and survivors (13 and 6%, P = 0.28, respectively).

SAE occurred in 21 (21%) cases. This group comprised 15 deaths and additional five survivors treated with thrombolysis. One patient required catecholamines infusion in pressor doses.

In group with massive APE, all three (30%) deaths were caused by APE.

Cox's proportional hazard regression analysis

Univariable Cox's proportional hazard regression analysis showed that older age and decreased pulsoximetry indicated fatal outcome (Table 2). Serum cTnT > 0.07 μg/L was the most statistically significant predictor of both all-cause and APE-related mortalities among all investigated
variables, hazard ratio (HR) 9.2 (95% CI: 3.3–26.1, P < 0.0001) and 18.1 (95% CI: 3.6–90.2, P = 0.0004), respectively. Serum NT-proBNP also predicted fatal outcome. Coexisting diseases, previously diagnosed CHF, and renal insufficiency also adversely influenced on survival. No echocardiographic parameter was found to predict deaths in studied patients. However, the presence of RV overload was a significant predictor of APE-related death.

## Serum biomarkers and clinical course

### NT-proBNP

ROC analysis was used to identify the optimal serum NT-proBNP cut-off value for death and SAE prediction during 40-day observation. The area under the ROC curve was 0.769 (95% CI: 0.640–0.898). Two different NT-proBNP cut-off levels were identified. Serum NT-proBNP > 600 ng/L showed high sensitivity and specificity for all-cause deaths [60 and 86%, respectively, HR 6.7 (CI 95%: 2.4–19.0, P < 0.0001)] and APE-related mortality [63 and 83%, respectively, HR 7.3 (CI 95%: 1.7–30.6, P = 0.007)] whereas low levels (NT-proBNP < 600 ng/L) indicated uncomplicated clinical outcome. Importantly, all 15 deaths and 21 SAEs occurred in patients with NT-proBNP > 600 ng/L.

### Cardiac troponin T

On admission serum cTnT > 0.01 ng/L was found in 39 patients (39%). The detectable troponin showed a sensitivity of 60 and 75% and a specificity of 65 and 64% in the prediction of all-cause deaths and APE deaths, respectively. ROC analysis performed in the group with detectable cTnT showed that the optimal cut-off value for death prediction was 0.07 μg/L. The area under the curve was 0.800 (95% CI: 0.665–0.935). Serum cTnT > 0.07 μg/L showed sensitivity of 60 and 75% and specificity of 89 and 87% in the prediction of all-cause deaths [HR 9.2 (95% CI: 3.3–26.1, P < 0.0001)] and APE deaths [HR 18.1 (95% CI: 3.6–90.2, P = 0.0004)], respectively.

The Kaplan–Meier survival analysis using the biomarker levels determined by ROC showed significant survival differences (Figure 1A). There was no death among the 28 (28%) patients with NT-proBNP < 600 ng/L and cTnT < 0.07 μg/L. The 54 (54%) patients with NT-proBNP ≥ 600 ng/L and cTnT < 0.07 μg/L formed an intermediate risk group, whereas the 18 (18%) subjects with elevated levels of both biomarkers were at the highest risk of fatal outcome (P = 0.0004). When only APE-related mortality was considered, the Kaplan–Meier curves also showed significant differences (Figure 1B).

### Multivariable Cox’s proportional hazard regression analysis

Stepwise multivariable Cox’s proportional hazard regression analysis revealed that cTnT > 0.07 μg/L and older age were the independent mortality predictors for all-cause deaths (χ² = 22.9, P < 0.0001, cTnT > 0.07 μg/L: HR 6.5 (95% CI: 2.4–19.0, P = 0.0004).
The bootstrap analysis revealed that all models constructed from the set of significant univariable predictors are of similar value. Eventually, the bootstrap analysis also showed that the most stable models for both, all-cause and APE-related mortalities, are based on cTnT ≥ 0.07 μg/L, age, and renal failure, although the renal failure, as a single predictor, did not reach statistical significance at the stepwise multivariable Cox’s proportional hazard regression.

**NT-proBNP and RV overload**

Echocardiography was performed in 98 of the investigated patients. Only 17 (17%) patients showed no echocardiographic alterations of RV morphology or function. Sixty (60%) patients presented RV dysfunction that met predefined criteria of RV overload. Only slight RV abnormalities were seen in 21 (21%) others. Serum NT-proBNP was higher in RV overload than patients without it [median 4868 ng/L (range: 64–60 958) vs. 509 ng/L (16–33 340), \( P = 0.0001 \)]. Moreover, significant correlations were observed between echocardiographic indices and NT-proBNP levels (Table 3). The area under the ROC curve of serum NT-proBNP for the detection of RV overload was 0.77 (95% CI: 0.67–0.88).

TTE showed LV systolic dysfunction, defined by an ejection fraction <50%, in 17 patients (17%). In the group with LV dysfunction, NT-proBNP was higher than in patients with preserved LV function [median 4650 (range: 188–60 958), vs. 2001 (16–27 752), \( P = 0.046 \)].

**Algorithm of risk assessment**

On the basis of the decision tree analysis, we tried to identify the optimal risk assessment algorithm in APE (Figure 2). The group with SBP < 90 mmHg had a 30% APE-related mortality. Risk stratification of initially normotensive patients was based on serum biomarker levels. APE-related mortality of patients with serum NT-proBNP > 600 ng/L and cTnT > 0.07 μg/L reached 33% (NPV and PPV are indicated in Table 4). Patients with NT-proBNP < 600 ng/L (28% of patients) formed a low-risk group, with no deaths and SAE during follow-up (NPV for death and SAE 100%). Patients with NT-proBNP ≥ 600 ng/L and cTnT < 0.07 μg/L (54% of patients) had an intermediate risk of fatal outcome, with an APE-related mortality of 3.7% and an all-cause mortality of 11%.

### Table 2 Univariable Cox’s proportional hazard regression analysis of normotensive patients \( n = 100 \) for 40-day mortality

<table>
<thead>
<tr>
<th></th>
<th>All-cause mortality</th>
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<th>APE-related mortality</th>
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<td>HR 95% CI P-value</td>
<td>HR 95% CI P-value</td>
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<tr>
<td>Age (years)</td>
<td>1.07 (1.02–1.11) 0.005</td>
<td>1.12 (1.03–1.21) 0.005</td>
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<tr>
<td>Pulsoximetry (%)</td>
<td>0.93 (0.87–0.99) 0.03</td>
<td>0.89 (0.82–0.97) 0.01</td>
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<td>RV overload</td>
<td>2.24 (0.62–8.13) 0.22</td>
<td>5.08 (1.21–21.37) 0.03</td>
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<tr>
<td>NT-proBNP per 1000 ng/L</td>
<td>1.056 (1.028–1.08) &lt;0.0001</td>
<td>1.06 (1.03–1.09) 0.0001</td>
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<tr>
<td>cTnT &gt; 0.07 μg/L</td>
<td>9.2 (3.3–26.1) &lt;0.0001</td>
<td>18.1 (3.6–90.2) 0.0004</td>
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<tr>
<td>Comorbidity</td>
<td>1.74 (1.24–2.45) 0.002</td>
<td>1.85 (1.17–2.92) 0.01</td>
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<tr>
<td>CHF</td>
<td>4.10 (1.42–11.83) 0.01</td>
<td>9.11 (2.17–38.17) 0.003</td>
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<tr>
<td>Renal failure</td>
<td>6.43 (2.22–18.61) 0.002</td>
<td>8.53 (2.13–34.27) 0.003</td>
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Discussion

Elevated serum troponin levels indicated increased mortality risk, even in initially normotensive patients. Low brain natriuretic peptide levels identified APE patients with favourable prognosis. Although troponin assessment was shown to improve the predictive value of echocardiography in APE and the incorporation of biomarkers into the echocardiography-based risk assessment strategy was recently proposed, no decision-making cut-off values for biomarker levels have been identified. Therefore, we developed a biomarker-based risk assessment model, evaluated its predictive value, and compared it with the currently applied risk stratification strategy in 100 consecutive initially haemodynamically stable patients with symptomatic APE. Univariable hazard regression analysis showed
that cTnT and NT-proBNP levels measured on admission predicted all-cause mortality and APE-related deaths in the studied patients, whereas RV overload predicted only APE-related mortality. ROC analysis identified serum cTnT ≥ 0.07 μg/L as the most useful cut-off level for the selection of the high-risk group among normotensive patients. Interestingly, serum NT-proBNP levels >7600 ng/L, as determined by ROC, also significantly predicted fatal outcome. These findings confirm that both biomarkers can stratify short-term prognosis in APE. However, multivariable Cox’s analysis showed that only cTnT ≥ 0.07 μg/L and age were independent mortality predictors. It is worth noting that no echocardiographic parameter was identified in multivariable analysis as an independent prognostic predictor for all-cause mortality or APE-related deaths. Thus, troponin assessment seems to be superior to NT-proBNP measurement and echocardiography in the identification of the high-risk group. However, low serum NT-proBNP < 600 ng/L selected a subgroup with a favourable clinical course.

The Kaplan–Meier analysis with biomarker levels detected at ROC showed significant differences in survival, both in terms of all-cause mortality and APE-related mortality (Figure 1). Patients with elevated concentrations of both biomarkers were at the highest risk of fatal outcome. Importantly, APE-related mortality in this group was similar to the mortality observed in 10 patients with clinically massive embolism, whereas there was no death among patients with NT-proBNP < 600 ng/L. This indicates that the combination of the cut-off values for both biomarkers has a significant impact on the short-term prognosis in APE.

Interestingly, although RV overload in normotensives showed a NPV of 100% for APE-related mortality, its PPV was quite low, at only 13%. In contrast, the PPV of NT-proBNP > 600 ng/L and cTnT > 0.07 μg/L was 33%, importantly without a marked decrease of NPV (97%) (Table 4). Interestingly, we found a close correlation between NT-proBNP and echocardiographic indices of RV overload. These findings correspond with the observations that brain natriuretic peptide levels indicate the degree of RV overload. Therefore, we propose that the incorporation of serum NT-proBNP and cTnT could replace echocardiography in the risk assessment of APE. Importantly, systolic SBP measured on admission was not of significance and was not included in any of the analysed models.

Eventually, on the basis of the decision tree analysis, we developed a risk assessment algorithm for APE patients (Figure 2). Patients with massive APE are at high mortality risk and, according to current guidelines, should be aggressively treated. The subsequent stratification of normotensive patients is based on biomarker levels (Figure 2). Importantly, the 18% of initially normotensive patients with NT-proBNP ≥ 600 ng/L and cTnT ≥ 0.07 μg/L had a comparable APE-related mortality to patients with massive APE. Thus, these biomarker criteria allow to identify, among studied patients, a subgroup with a significantly elevated risk of all-cause mortality and APE-related mortality. In our opinion, they are candidates for thrombolysis. Patients with NT-proBNP < 600 ng/L (28% of the studied group) had excellent prognosis (NPV for death and SAE 100%), Patients with NT-proBNP ≥ 600 ng/L and only moderately elevated cTnT < 0.07 μg/L (54% of patients) had an intermediate risk of fatal outcome.

Clinical implications and study limitations

According to the current guidelines, hypotensive patients with APE should receive aggressive therapy. Echocardiography is currently the principal tool for the risk stratification in normotensive patients. Although it is accepted that RV overload indicates an increased mortality risk among normotensives, which reaches ~10%–6 thrombolysis in sub-massive APE is still controversial.1,7 In addition, echocardiography suffers from several limitations. It is a user-dependent method, not fully reproducible, and it is not always immediately available. Although no formal recommendations can be made, we believe that a biomarker-based strategy can be useful. Patients with low NT-proBNP levels form a group at low risk of complicated clinical course, and they are potential candidates for an abbreviated hospital stay. Patients with elevated cTnT ≥ 0.07 μg/L should be closely monitored in an ICU and should be considered for thrombolysis. However, the proposed risk assessment algorithm was developed by post hoc analysis of a single centre’s data. Therefore, in order to validate the clinical value of this model, a prospective trial is necessary.

Conclusion

Simultaneous measurement of serum cTnT and NT-proBNP levels upon admission allows for precise prognosis in initially haemodynamically stable patients with APE.

Acknowledgement

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References


