COMPARATIVE PROGNOSTIC VALUE OF CARDIAC BIOMARKERS IN NORMOTENSIVE PATIENTS WITH ACUTE PULMONARY EMBOLISM

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Abstract: *In non-high risk, normotensive patients with acute pulmonary embolism, elevated cardiac biomarkers can predict an increased early mortality risk. The aim of the study was to assess the prognostic value of blood biomarkers determined at initial presentation for death or serious adverse events. We studied 75 consecutive normotensive patients with confirmed acute pulmonary thrombembolism and analysed correlations between biomarker levels and the occurrence of death or a complicated clinical course. Elevated N-terminal pro-brain natriuretic peptide levels showed a strong predictive power and a cutoff value of 5300 ng/mL could be used to separate low and high-risk patients for adverse outcomes. Other biomarkers were not associated with an increased risk. Elevated blood N-terminal pro-brain natriuretic peptide levels at presentation are associated with an increased increase risk of 30-day mortality or complicated in-hospital course in normotensive, non-high risk patients with acute pulmonary embolism.*

INTRODUCTION

Early mortality risk stratification in patients presenting with acute pulmonary thrombembolism (APE) has become an essential part of management and treatment, according to current guidelines recommendations.(1) However, controversies still exist on the predictive power of some parameters. As a result, over 50 studies published in the last ten years have contributed to this field of research(2) and have investigated variable prognostic markers form clinical measurements, to imagistic evaluations and laboratory tests.

It is widely accepted that patients presenting with arterial hypotension or signs of shock are at high early mortality risk, greater than 15%,(1) and benefit from more aggressive therapies, including primary reperfusion with thrombolythics. Normotensive, hemodinamically stable patients are considered at non-high risk and have an estimated 30-day mortality between 1 and 15%. In these patients, further risk stratification could determine management strategies and the need for increased care. The most widely used risk prediction calculators are the pulmonary embolism severity index (PESI) and its simplified version (sPESI) (3,4), which are based entirely on clinical parameters.

Predictors of APE complications in normotensive patients include myocardial injury, cardiac dysfunction, hypotension and tachycardia.(5) Blood biomarkers such as cardiac troponins, D-dimers, N-terminal pro-brain natriuretic peptide (NT-proBNP), creatinine and glucose, are involved in pathophysiological mechanisms of cardiac dysfunction and have the advantage of being a potential estimate of their presence and importance. Also they can be early signs of dysfunction, before it is clinically overt, which makes them ideal targets for prognostic marker research.

PURPOSE

The aim of this study was to assess the prognostic values of cardiac and non-cardiac biomarkers in normotensive, non-high risk patients with APE. The objectives were to evaluate blood levels of D-dimers, troponin I, NT-proBNP, creatinine and glucose at admission and identify correlations with 30-day mortality or a complicated clinical course.

MATERIALS AND METHODS

The study carried out was a prospective, observational one, on consecutive patients with APE admitted in the 1st Adult Cardiology Clinic of the Emergency Institute for Cardiovascular Diseases and Transplant Tîrgu-Mureș. The diagnosis was confirmed by contrast medium enhanced computer tomography, considered the current imaging gold-standard, performed after initial diagnostic evaluation. A probable diagnostic of APE was set using history taking, clinical examination, probability scores, D-dimer levels and echocardiography, according to current diagnostic guidelines recommendations. Patients with signs of shock, hypoperfusion or arterial hypotension of less than 90 mmHg or a 40 mmHg drop in blood pressure for at least 15 minutes were considered at high-risk and were excluded from the study. Patients were included if they had a normal or high blood pressure and were considered non-high risk, were over 18 years old and signed informed consent was obtained. Local ethics committee approval was obtained for this study.

As part of the initial patient evaluation, peripheral venous blood samples were drawn for biochemistry and cardiac biomarker analysis. Plasma troponin I, D-dimers and NT-proBNP were evaluated using a table-top chemilluminesence immunoassay analyzer (Pathfast, LSI Medience Corporation, Tokyo, Japan). Calibration values ranged from 0 to 50 ng/mL for troponin I, 0 to 5.00 ng/mL for D-dimers and 0 to 20 000 pg/mL for NT-proBNP. Serum creatinine and glucose levels were evaluated using a spectrophotometric Immunoassay Analyzer (Architect i1000SR, Abbott Diagnostics, Lake Forest, IL, USA). Calibration values ranged from 50 to 2000 mg/dL for glucose and 0 to 200 mg/dL for creatinine.

Patients were followed after admission for 30 days

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and composite endpoint events were recorded. These consisted of APE-related death or a complicated in-hospital course, consisting of pulmonary embolism recurrence or hemodynamic instability, measured by the need for circulatory support through inotropic drugs administration.

All numerical data collected were analysed for normal-Gaussian distribution using the Kolmogorov-Smirnov test. If data distribution was normal, the student t test was used for comparing means and if the distribution was non-Gaussian, the Mann-Whitney U test was used. The $\chi 2$ test was used to compare discrete variables. Receiver operator characteristic (ROC) analysis was performed to determine the area under the curve (AUC) of baseline biomarker concentrations in predicting the composite endpoint. Cut-off values for optimal sensitivity and specificity were determined using the Youden index. We performed univariable and multivariate logistic regression to evaluate independent associations between baseline biomarker levels and the composite endpoint, with the results presented as odds ratio (OR) and corresponding 95% confidence intervals (CI). A two-tailed p value of <0.05 was considered significant. The statistical software used for analysis were SPSS v20 (IBM, Armonk, NY, USA) and Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA).

RESULTS

The study enrolled 75 normotensive, non-high risk patients with APE, all confirmed by contrast-enhanced computer tomography. Due to causes independent of the study, not all patients had full laboratory examinations performed, as written in the study protocol. Troponin I evaluation was performed on 45 patients, NT-proBNP on 43 patients, D-dimer on 53 patients, and biochemical analysis for serum creatinine and glucose was performed on 74 patients. The baseline clinical characteristics of the patients and biomarker evaluations are presented in table no. 1.

Table no. 1. Patient characteristics

Characteristic, unit	Value
Age, years	69 ± 13
Sex	
Male, pts.	35 (47%)
Female, pts.	40 (53%)
Systolic Blood Pressure, mmHg	133 ± 23
PESI score	
Class I	6 (8%)
Class II	25 (33%)
Class III	25 (33%)
Class IV	11 (15%)
Class V	8 (10%)
D-dimer, ng/mL	5.00 (4.91 – 5.00)
Troponin I, ng/mL	0.079 (0.019 – 0.200)
NT-proBNP, pg/mL	4859 ± 4843
Creatinine, mg/dL	1.00 (0.74 – 1.20)
Glucose, mg/dL	126 (110 – 164)

Values are expressed as number of patients (percent), mean ± SD for normal distribution or median (25^{th}-75^{th}percentile) for non-normal distribution, PESI pulmonary embolism severity index

Patient treatment was conducted according to current management guideline recommendations. No patient required thrombolytic therapy and all were given initial parenteral anticoagulation with unfractionated heparin or low molecular weight heparin, followed by long-term oral anticoagulation with an INR adjusted anti-vitamin K or a novel non-vitamin K anticoagulant. Other medications were prescribed according to the attending physicians' indication.

The composite endpoint of 30-day APE-related death and complicated clinical in-hospital course occurred in 7 patients. Four patients died, of which three in the first three days and one after three weeks, and three patients required inotropic drug administration in vasopressor doses for hemodynamic instability, all within the first three days after admission. The patients that experienced serious adverse events, in the composite endpoint group, were significantly older (p=0.023) and more likely to be female, but not significantly (p=0.438), compared to the non-endpoint group. The correlations of mean biomarker levels and the composite endpoint are summarized in table no. 2.

Table no. 2. Correlations with the composite endpoint

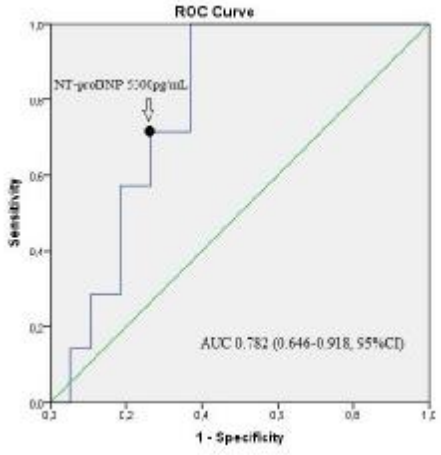
Characteristic, unit	Non-endpoint patients (n = 68)	Endpoint patients (n = 7)	p value
Male/Female, pts.	33/35	2/5	0.438
Age, years	68 ± 13	74 ± 5	0.023
D-dimer, ng/mL	5.00 (4.86 – 5.00)	5.00 (3.83 – 5.00)	0.840
Troponin I, ng/mL	0.052 (0.011-0.197)	0.112 (0.040-0.280)	0.351
NT-proBNP, pg/mL	4258 ± 4811	8124 ± 3807	0.051
Creatinine, mg/dL	1.00 (0.74 – 1.11)	1.31 (0.74 – 1.53)	0.141
Glucose, mg/dL	125 (110 – 164)	128 (66 – 210)	0.825

Values are expressed as number of patients (percent), mean ± SD for normal distribution or median (25^{th}-75^{th}percentile) for non-normal distribution

In the composite endpoint group, biomarker analysis showed an increase in mean troponin I, NT-proBNP, creatinine and glucose levels, but none reached statistical significance level. There was no difference in the mean D-dimer levels between the two groups.

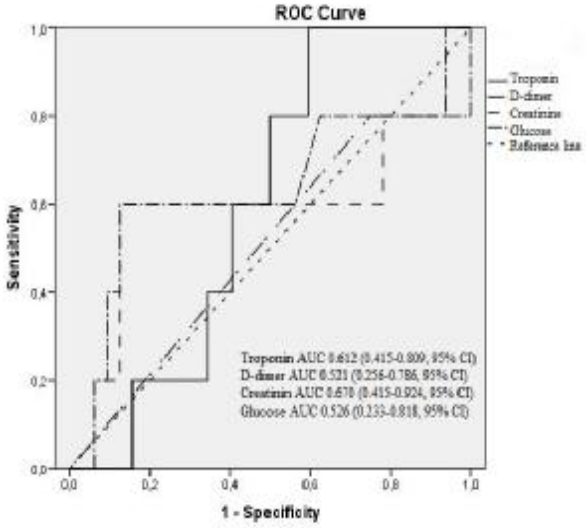
ROC analysis showed an AUC for NT-proBNP in predicting the composite endpoint of 0.782 (0.646-0.918, 95%CI), with a statistical significant p value (p=0.019). Using the Youden index, an optimal cutoff value of 5300 pg/mL was determined for NT-proBNP, which was associated with a prognostic sensitivity of 71% and a specificity of 74%. Of the 15 patients with a NT-proBNP level of above 5300 pg/mL, 5 (33%) experienced a composite endpoint event. And out of the other 43 patients with NT-proBNP levels <5300 pg/mL, only 2 (4.65%) experienced a composite endpoint event (figure no. 1).

Figure no. 1. ROC curve for NT-proBNP showing prognostic specificity and sensitivity for the composite endpoint.



The AUC of the ROC analysis for the other biomarkers was lower and with no statistical significance, for troponin I 0.612 (0.415-0.809, 95% CI, p=0.351), for D-dimers 0.521 (0.256-0.786, 95% CI, p=0.879), for creatinine 0.670 (0.415-0.924, 95% CI, p=0.142) and for glucose 0.526 (0.233-0.818, 95% CI, p=0.825) (figure no. 2).

Figure no. 2. ROC curves for troponin, D-dimer, creatinine and glucose showing prognostic specificity and sensitivity for the composite endpoint.



In the logistic regression univariable analysis, increased serum levels of troponin I (OR 1.59) and creatinine (OR 1.51) predicted the composite endpoint, but with no statistical significance (p>0.05).D-dimer (OR 0.87), NT-proBNP (OR 1.00) and glucose (OR 1.00) levels did not show predictive value, also without statistical significance (table no. 3).

Table no. 3. Univariable logistic regression analysis of biomarkers and composite endpoint association

Biomarker	Unadjusted OR	95% CI	p value
D-dimer	0.87	0.324-2.385	0.799
Troponin I	1.59	0.019-134.718	0.837
NT-proBNP	1.00	1.000-1.000	0.065
Creatinine	1.51	0.504-4.540	0.461
Glucose	1.00	0.990-1.014	0.735

The multivariate logistic regression analysis model found troponin I (Adjusted OR 2.85) to be a strong predictor of the composite endpoint, but with no statistical significance (p >0.05). The other biomarkers in the model did not show any predictive power (Adjusted OR 0.48-1.00), all without statistical significance (table no. 4).

Table no. 4. Multivariate logistic regression analysis of biomarkers and composite endpoint association

Biomarker	Adjusted OR	95% CI	p value
D-dimer	0.48	0.129-1.788	0.274
Troponin I	2.85	0.014-580.169	0.698
NT-proBNP	1.00	1.000-1.000	0.306
Creatinine	0.87	0.181-4.270	0.873
Glucose	1.00	0.990-1.013	0.816

DISCUSSIONS

Risk stratification plays an important part in early management of patients with APE. High-risk patients presenting with arterial hypotension or shock warrant aggressive reperfusion therapy, performed usually with thrombolysis.(1) Normotensive APE patients are considered non-high risk and have an estimated 30-day mortality between 1 and 15%.(1) Nevertheless, the absolute majority of deaths from APE come from this patient group that are initially stable at presentation, and are caused by late decompensation of the right ventricle due to prolonged, excessive overload or by recurrent pulmonary embolisms. Recent studies have focused on identifying prognostic markers of this unapparent circulatory instability. Another incentive in this regard are the results of the recent multicentre, randomised controlled trial PEITHO (6) that assessed the benefits of thrombolysis in normotensive patients with APE at intermediate-high mortality risk. The trial showed a benefit of reducing the incidence of secondary hemodynamic decompensation at an increased risk of major and life-threatening bleeding. Although it did not show overall survival benefit, it did suggest the existence of a group of patients within the intermediate risk class that could profit from the more aggressive thrombolytic therapy and the need for further risk stratification of these normotensive APE patients.

While mortality risk prediction models based on clinical variables, like the PESI (3) and sPESI (4) have been proven to accurately identify low-risk patients who can be safely treated out of hospital, there is yet no validated prediction score that can differentiate the higher risk normotensive APE patients from the lower risk ones.

The pathophysiological mechanisms of right ventricular failure of myocardial injury and volume overload have directed the search of prognostic markers in the direction of right ventricular imaging and myocardial stress biomarkers. Right ventricular dysfunction, identified by echocardiography, has been proven as a predictor of 30-day mortality in normotensive APE patients.(7)

Several cardiac and non-cardiac biomarkers have been investigated as predictors of early mortality in non-high risk patients. The present study assessed the prognostic value of serum troponin I, NT-proBNP, D-dimer, creatinine and glucose for the occurrence of 30-day mortality or a complicated in-hospital course, alone and in comparison, in normotensive APE patients.

D-dimers are produced by the degradation of fibrin and serum level assessment has an important role in the diagnosis of APE. In a study by Keller et al.(8), elevated levels were associated with sub massive pulmonary embolism and an increased shock index, but a prognostic value for mortality has not yet been proven. In our study, no analysis demonstrated an association between increased D-dimer levels and the composite endpoint. The probable cause is the type of D-dimer evaluation method used, that had an upper calibration level of 5.00 ng/mL that was reached by 75% of evaluations and made statistical analysis difficult.

Troponins are the most frequently used markers of myocardial injury. Their prognostic value in normotensive APE patients has been identified in numerous studies and is used in current management guidelines risk stratification.(1) Lankeit et al.(9) identified a high-sensitive troponin level greater than 14 pg/mL of having a 5-fold increase in early and long-term mortality risk in haemodinamically stable patients with APE. In a large cohort randomized controlled trial, Jiménez et al. (10) identified in a multivariate logistic regression analysis an elevated Troponin I as having an adjusted OR of 1.96 in predicting 30-day complicated clinical course in normotensive APE patients. In our model, troponin I had an even higher adjusted OR (2.85), but with no statistical significance. While more studies also identified an elevated troponin as a prognostic

factor for increased early mortality in APE patients (11-15), no uniform predictive cutoff value has been identified for these assays.

NT-proBNP is a marker of cardiac pressure and volume overload, with great importance in heart failure. In the setting of APE, elevated levels have been significantly associated with increased 30-day mortality in both high and non-high risk patients. In our study, the ROC analysis showed an AUC of 0.782 for the prediction of the composite endpoint with a statistical significance. This value demonstrates a good prognostic power of increased NT-proBNP levels in predicting early mortality or complicated in-hospital course for normotensive APE patients. Our results are almost identical to the ones from the study by Kaczyñska et al.(16) on a cohort of 77 APE patients, which calculated an AUC of NT-proBNP for predicting 30-day APE-related death of 0.785. Other studies on normotensive APE patients have showed a lower value AUC for the ROC analysis of 0.639 (17) or 0.670 (18) for adverse 30-day outcomes. From the ROC analysis we calculated a cut-off value for NT-proBNP of 5300 pg/mL that provided the evaluation with an optimal combined sensitivity and specificity level (71% and 74%) and divided the study population into groups with a high risk rate (33%) and a low risk rate (4.65%). Our cut-off value is close to the one identified by Kostrubiec et al. (11) of 7600 pg/mL that had a sensitivity and specificity for all-cause death of 60% and 86%.

Chronic renal failure has been identified as a predictor of 30-day adverse events in patients with APE.(19) Also, acute renal failure, measured by a decreased glomerular filtration rate, has been associated with adverse 30-day outcomes in non-high risk APE patients.(9) In the study by Aujesky et al.(3) that developed the PESI, the prognostic score model was calculated using 11 clinical variables. In that study, an elevated blood urea nitrogen level was identified as an independent predictor of increased 30-day mortality and was included in another 17 variable model that had a higher discriminatory power than the 11 variable model, but with similar mortality rates, and so was considered to add insufficient benefit to the simpler one and was not used. Although elevated creatinine levels per se have been significantly associated with sub massive pulmonary embolism (8), in our study we did not find any significant association between elevated serum creatinine and the composite endpoint.

Blood glucose levels have many determinants, and increased levels have been associated with pulmonary embolism severity.(12) However, in our analysis there were no significant differences between glucose levels in the two endpoint and non-endpoint patient groups.

Recent studies have focused attention on other novel cardiac biomarkers that are currently not generally available such as plasma heart-type fatty acid binding protein, and have shown a strong prognostic significance of early mortality and adverse effects.(18,20-22) Other studies have shown significantly greater prognostic power in combinations of biomarkers and right ventricular dysfunction (13,23,24), biomarkers and clinical variables (25) or biomarkers, right ventricular dysfunction and clinical variables.(5,26)

CONCLUSIONS

Elevated blood NT-proBNP levels at presentation are associated with an increased risk of 30-day mortality or complicated in-hospital course in normotensive, non-high risk APE patients. A cutoff value of 5300 ng/mL can be used to separate low and high-risk patients for adverse outcomes.

Our study did not show any predictive value for the other investigated biomarkers. Serum biomarker levels should be used in addition to clinical scores and echocardiography in early mortality risk stratification of normotensive patients with APE.

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