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# Heart-type fatty acid-binding protein and myocardial creatine kinase enable rapid risk stratification in normotensive patients with pulmonary embolism

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ABSTRACT

*Background:* Risk assessments of hemodynamically stable patients with pulmonary embolisms (PE) remain challenging. In this context heart-type fatty acid–binding protein (H-FABP), creatine kinase isoenzyme MB (CK-MB), and troponin I (TnI) may hold prognostic utility for patients with pulmonary embolism.
*Methods:* We included 161 consecutive normotensive (systolic blood pressure above 90 mm Hg) patients with confirmed PE to study the combined utility of echocardiographic signs of right ventricular dysfunction and several biomarkers (TnI, CK-MB, H-FABP). The primary endpoint was defined as death within 30 days after admission to the hospital.
*Results:* Elevated biomarkers were measured in 26 patients (16.1%) for HFABP, in 66 (41%) for TnI and in 41 (25.5%) for CK-MB. Echocardiography revealed right ventricular dysfunction (RVD) in 99 (61.5%) patients. Overall, 16 patients (9.9%) died within the study period. In the H-FABP positive group 15 (57.7%) patients died compared to 13 (19.7%) patients in the TnI positive group and 15 (37.5%) patients in the CK-MB positive group (H-FABP positive vs TnI positive patients, $P< .001$; H-FABP positive vs CK-MB positive patients $P= .13$; CK-MB positive vs TnI positive patients $P= .07$). All elevated biomarkers correlated with the primary endpoint with H-FABP being strongly, CK-MB intermediately and TnI weakly associated with short term death (H-FABP $r= 0.701$, $P< .001$; CK-MB $r= 0.486$, $P< .001$; TnI $r= 0.272$, $P= .001$). In multivariate logistic regression analysis, a positive H-FABP test (OR 27.1, 95% CI 2.1-352.3, $P= .001$), elevated CK-MB levels (OR 5.3, 95% CI 1.3-23.3, $P= .002$) and a low systolic blood pressure on admission (OR 0.8, 95% CI 0.8-0.9, $P< .001$) emerged as independent predictors of 30-day mortality.
*Conclusions:* Both H-FABP and CK-MB are associated with short term mortality in normotensive PE patients and could be advantageous for risk stratification in this intermediate risk group.


## 1. Introduction

Acute pulmonary embolism (PE) is a frequent and dangerous manifestation of deep venous thrombosis (DVT) [1] and its incidence of about 0.7 per 1000 per year in normal population markedly increases with age [2,3]. Despite recent advances in diagnosis and treatment, assessment of risk and appropriate management of patients with PE remains difficult due to the variability of clinical presentation and the degree of hemodynamic instability. Mortality rates differ dramatically among patients, depending on their hemodynamic situation and right heart function. The “high risk” group comprises hemodynamically unstable patients with evidence of right ventricular dysfunction (RVD). In this group mortality can exceed 50% [4] necessitating prompt thrombolytic or surgical intervention [5,6]. On the other hand, the absence of hypotension and of RVD (ie, “low-risk” group) shows more favorable outcomes with a mortality of less than 1% [5] and the possibility of outpatient treatment [7]. Hemodynamically stable patients with a preserved systolic blood pressure above 90 mmHg but with evidence of serological myocardial injury and impaired right ventricular function are referred to as the “intermediate-high risk” and either one positive are referred to as the “intermediate-low risk” group [5,8]. Short-term mortality can be high in this group and is reported to range between 5% [9] to over 11% [10–13]. However, the recommended treatment option (only anticoagulation, thrombolysis) remains a matter of intense debate and reliable data are scarce.

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Current guidelines do not recommend routine administration of thrombolytic agents in intermediate risk patients despite potentially beneficial effects [5,14]. However, to date the optimal treatment remains controversial especially following the important results from the recent PEITHO trial providing evidence that a fibrinolytic therapy in patients with intermediate-risk PE prevents hemodynamic decompensation but increases the risk of major bleeding [15]. Albeit therapeutic uncertainty in patients with intermediate risk PE remains, consensus exists on the importance of rapid risk stratification in patients presenting with PE [16,17]. Current strategies involve biomarker testing as well as right ventricular imaging to detect RVD either by echocardiography or computed tomography scan [17–21]. At present, cardiac troponins (cTnT, cTnI) represent a crucial component during risk stratification in patients presenting with PE. Their prognostic value was confirmed in a meta-analysis [22]. However, there is contradictory evidence regarding the prognostic performance of cTnT and cTnI in patients with intermediate risk PE [23,24]. Clinicians frequently notice that elevated cTnT/cTnI levels are not uncommon and often "false positive", thus limiting their prognostic value in this risk group. Lately, several studies reported that heart-type fatty acid–binding protein (H-FABP), a low molecular weight cytosolic protein facilitating fatty acid transport within cardiomyocytes, enables more rapid and more accurate diagnosis and risk assessment in patients with acute coronary syndromes as compared to other biomarkers [25,26]. In this context attention was drawn to the diagnostic utility of H-FABP in patients with PE. Recently, it was demonstrated in patients with normotensive PE that elevated H-FABP levels measured on hospital admission may identify patients with an adverse clinical course [9,27].

Even though available for a long time and being part of every lab routine in patients presenting with chest pain, Creatine Kinase Isoenzyme MB (CK-MB) has not been studied in detail for risk assessment in PE. Stein and colleagues were the first to investigate the potential prognostic value of CK-MB, cTnT and right ventricular dilatation in normotensive patients with PE. Although their findings were statistically not significant, CK-MB tended to be a stronger predictor of death than cTnT and the combination of CK-MB, cTnT and echocardiography seemed particularly indicative [28].

Given the ambiguous role of CK-MB for risk stratification in patients with intermediate risk PE, our objective was to further assess its potential role of in view of both new (H-FABP) and established (cTnT/I, RVD) risk markers.

## 2. Methods

### 2.1. Study design, patient population and selection criteria

We prospectively studied consecutive normotensive patients suspicious of acute PE presenting to the cardiology department of the local university hospital from 2008–2011. Typical clinical presentation, elevated D-dimers and the presence DVT suggested the presence of PE, which was subsequently confirmed in all cases by ventilation-perfusion lung scan or spiral CT-scan. Eighteen patients were excluded from further investigation based on one of the predefined exclusion criteria: (1) refusal or inability to give consent; (2) presence of hemodynamic instability on admission i.e. blood pressure <90 mm Hg, shock, administration of inotropic substances and pre-hospital or ongoing resuscitation; (3) concomitant cardiopulmonary disease: acute myocardial infarction, left ventricular decompensation, exacerbated chronic obstructive pulmonary disease. Consequentially, the total study population comprises 161 patients. Of these, 101 patients partially overlap with a previous study (similar design and in-/exclusion criteria) investigating the association between h-FABP levels and echocardiographic signs of RVD [27]. All included patients gave informed consent on admission and blood samples for the H-FABP test and the lab routine were collected. Additionally, basic clinical data (blood pressure, heart rate and oxygen saturation) were obtained. Transthoracic echocardiography was performed within 2 hours after admission by experienced senior doctors. Echocardiographers as well as treating clinicians were blinded to the H-FABP test results and the findings were not used to guide diagnostic or therapeutic decisions at any time.

The primary endpoint was defined as PE-related mortality at 30 days. The secondary end-point was specified as a complicated clinical course and included any of the following: need for (1) administration of vasoactive substances and; (2) thrombolysis or mechanical thrombus removal, and (3) cardiopulmonary resuscitation or (4) late death from PE (>30 days). The study design was observational and was approved by the local ethics committee.

### 2.2. Echocardiographic criteria

On admission, experienced echocardiographers performed transthoracic echocardiography using the Hewlett Packard SONOS 5500 system. During the procedure, patients were awake and in left lateral decubitus position. Right ventricular dysfunction (RVD) was diagnosed in the presence of any of the following criteria: (1) RV end-diastolic diameter greater than 30 mm, (2) RV/LV-ratio greater than 1.0; (3) Paradoxical septal movement; (4) Hypokinesia of the free RV wall or akinesia of the free mid-wall and abnormal wall motion of the base segment, also known as the McConnell sign; (5) visually moderate to severe impairment or RV ejection fraction <45%. The latter was estimated using the modified Simpson's method. Additionally, measurement of the tricuspid annular plane systolic excursion (TAPSE) was performed.

### 2.3. Laboratory investigations and biomarker testing

On admission, blood samples were obtained prior to initiation of treatment in all patients with suspected PE. Plasma concentrations of Troponin I, CK, and CK-MB were measured quantitatively. H-FABP measurement was done only once at the point of admission with routine blood samples. For Troponin I, a quantitative chemiluminescence assay (Ortho-Clinical Diagnosis) was performed with a cut-off value of 0.08 ng/mL. For creatine kinase (CK), a kinetic UV-Test, and for CK-MB isoenzyme, an enzymatic immunological inhibition-test (both on Olympus-Analyzer) were performed. Cut-off value for CK was <2.85μkat/L, and for CK-MB <0.4 μkat/L. H-FABP was measured qualitatively using a sandwich ELISA purchased from Rennesens GmbH, Berlin. The clinical cut-off value for H-FABP was 7 ng/mL. Glomerular filtration rate was estimated by the Modification of Diet in Renal Disease formula. Neither the treating clinician nor the echocardiographers were aware of the patients' H-FABP levels on admission. Our study did not influence diagnostic or therapeutic decisions.

### 2.4. Statistical analysis

Categorical variables are given as absolute numbers and percentages and were compared by Pearson $\chi^2$ or Fisher's exact test as appropriate. The correlation of nominal variables was measured using the φ coefficient. Continuous variables were tested for normal distribution using Lilliefors corrected Kolmogorov-Smirnov test. Normally distributed variables are expressed as means ± SD and means were compared using Student *t* test. Variables not following the Gaussian distribution are shown as medians with 25th and 75th percentiles (interquartile range, IQR) and Mann-Whitney *U* test was used for comparison of two groups. Receiver operating characteristic curve (ROC) analyses were applied to selected clinical, laboratory and echocardiographic parameters and both areas under the curve (AUC) and cut-off values were computed.

Predictors of 30-day mortality were identified by logistic regression analysis (uni- and multivariate models) and are expressed as odds ratios with corresponding 95% CI and *P* values. Cumulative survival was assessed by Kaplan-Meier analysis and statistics were calculated using log-rank test.