Elevated Heart-type Fatty Acid-Binding Protein Levels on Admission Predict an Adverse Outcome in Normotensive Patients With Acute Pulmonary Embolism

Brief title: H-FABP in Normotensive PE

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Abstract

Objectives: We assessed the predictive value of heart-type fatty acid-binding protein (H-FABP) in normotensive patients with acute pulmonary embolism (PE).

Background: Risk stratification of initially normotensive patients with PE based on right ventricular dysfunction or injury remains controversial. Previous studies investigating biomarkers or imaging modalities included unselected patients, some of whom presented with cardiogenic shock.

Methods: We included 126 consecutive normotensive patients with confirmed PE. Complicated 30-day outcome was defined as death, resuscitation, intubation, or use of catecholamines. Long-term survival was assessed by follow-up clinical examination.

Results: During the first 30 days, 9 (7%) patients suffered complications. These patients had higher baseline H-FABP-values (median, 11.2 ng/ml; IQR, 8.0-36.8 ng/ml) compared to patients with an uncomplicated course (3.4 [2.1-4.9] ng/ml; $p<0.001$). H-FABP values were above the calculated (by ROC analysis) cutoff value of 6 ng/ml in 29 patients. Eight (28%) of them suffered complications versus 1 of 97 patients with low H-FABP (negative predictive value, 99%; $p<0.001$). By logistic regression, elevated ($\geq$6 ng/ml) H-FABP was associated with a 36.6-fold increase in the death or complication risk. The combination of H-FABP with tachycardia was a particularly useful prognostic indicator. H-FABP also predicted long-term mortality over 499 (IQR, 204-1166) days (HR, 3.6; 95% CI, 1.6-8.2; $p=0.003$).

Conclusion: H-FABP may be a useful biomarker for risk stratification of normotensive patients with acute PE.

Key words: pulmonary embolism, risk stratification, prognosis, heart-type fatty acid-binding protein

Abbreviation list:

AUC = area under the curve

CI = confidence interval

cTnT = cardiac troponin T

DVT = deep venous thrombosis

GFR = glomerular filtration rate

H-FABP = heart-type fatty acid binding protein

HR = hazards ratio

IQR = interquartile range

NPV = negative predictive value

OR = odds ratio

PE = pulmonary embolism

PPV = positive predictive value

ROC = receiver operating characteristic curve

RV = right ventricle

Introduction

Acute pulmonary embolism (PE) is a relatively frequent cardiovascular emergency (1-3) and a major cause of morbidity and mortality in the population (4). At an average case fatality rate of 11% (1), venous thromboembolism is responsible for up to 15% of all in-hospital deaths (5). However, early or in-hospital death rates may vary widely, mostly depending on the clinical severity of PE at presentation (1,6). Accordingly, recent guidelines have proposed to immediately classify patients presenting with acute PE into a high-risk and a non-high-risk group (7). Patients belonging to the "high-risk" group are those presenting with hemodynamic instability, i.e. cardiogenic shock or persistent arterial hypotension due to overt right ventricular failure. The treatment of these patients should definitely include immediate thrombolysis or mechanical removal of the thrombus in addition to standard heparin anticoagulation (7,8). On the other hand, the optimal management of initially normotensive patients with "non-high risk" PE is less clearly defined. In particular, further risk stratification of this seemingly stable group, focusing on the identification of patients who present with (subclinical) right ventricular (RV) dysfunction or myocardial injury and may have an "intermediate" death risk of 3-15% (9-11), continues to pose a challenge in clinical practice.

Over the past years, a number of studies evaluated the use of echocardiography, computed tomography and N-terminal pro-brain natriuretic peptide (NT-proBNP) for the detection of RV dysfunction, and of the cardiac troponins T and I for diagnosis of myocardial injury resulting from acute PE. Recent meta-analyses of these studies generally confirmed the prognostic value of these modalities, but also brought into light the marked heterogeneity and the numerous methodological limitations of the individual studies (7,10-12). An important obstacle to translating their data into a prognostic algorithm for clinical practice is that the vast majority of these studies included

unselected, i.e. both high-risk and non-high-risk patients with PE, instead of focusing on the risk stratification of the normotensive group.

Heart-type fatty acid-binding protein (H-FABP) is an early, highly sensitive marker of myocardial injury which has been evaluated for emergency triage of patients with acute coronary syndromes (13). Fatty acid-binding proteins are relatively small cytoplasmic proteins (12-15 kDa) which are abundant in tissues with active fatty acid metabolism, including the heart (14). Following myocardial cell damage, H-FABP diffuses much more rapidly than troponins through the interstitial space and appears in the circulation as early as 90 minutes after symptom onset, reaching its peak within 6 hours (13). Recent studies in unselected patients with acute PE suggested that H-FABP levels on admission may predict an adverse early clinical outcome with a sensitivity and specificity superior to that of cardiac troponins or natriuretic peptides (15,16). Moreover, H-FABP levels were associated with the risk of death during long-term follow-up in patients with chronic thromboembolic pulmonary hypertension (17). Based on these promising observations, we conducted the present study in order to determine whether H-FABP, alone or in combination with clinical or echocardiographic findings, may reliably predict a poor early and long-term prognosis in normotensive patients with acute PE and thus help identify a true "intermediate-risk" group.

Methods

Patient Population and Study Design. We prospectively followed consecutive patients who were diagnosed with acute symptomatic pulmonary embolism (symptom onset, ≤4 weeks) at the University Hospital of Goettingen over a 42-month period (between 2003 and 2007) and who were normotensive on admission. Of 187 patients with confirmed PE, 61 were not considered for further analysis because they met at least one of the following exclusion criteria: 1) hemodynamic instability, i.e. persistent arterial hypotension or shock, defined as systolic blood pressure <90 mm Hg or a pressure drop of ≥40 mm Hg for >15 min at presentation, if not caused by new-onset arrhythmia, hypovolemia or sepsis (6) (24 patients); 2) denial or withdrawal of written consent for participation in the study (4 patients); 3) lost to follow-up (14 patients); and 4) unexpected or accidental diagnosis of PE (patients undergoing diagnostic tests for another suspected disease), or PE coinciding with acute decompensation of left ventricular failure or acute myocardial infarction (19 patients).

The time period covered by the present study (2003-2007) partly overlapped with that (2003-2005) of a previous publication by our own group (15); of that latter patient population (107 patients), 73 patients were also included in the present study while 34 were excluded due to hemodynamic instability (10 patients), loss to follow-up (14 patients), and acute PE coinciding with acute decompensation of left ventricular failure or acute myocardial infarction (10 patients). Between 2005 and 2007, 53 additional patients were included. Thus, a total of 126 patients were finally considered for analysis.

The diagnostic workup for patients with suspected acute PE complied with existing guidelines during the study period (18). Patients with high clinical (pre-test) probability of PE based on the standardized Wells Score (19), and those with intermediate or low clinical probability

and a positive D-dimer test using a quantitative assay (Tina-quant, Roche Diagnostics, Germany), underwent an imaging procedure, preferably multidetector-row (64-slice) computed tomography, to confirm the disease (88 patients; 70% of the study population). Alternatively, in 31 (25%) patients PE was confirmed by a diagnostic ventilation-perfusion lung scan. In five patients (4%), the diagnosis was based on the patients' clinical presentation and the confirmation of deep vein thrombosis by compression ultrasonography. Pulmonary angiography was rarely necessary to confirm PE (2 patients; 2%).

The study protocol strongly recommended a transthoracic echocardiogram within two hours of PE diagnosis. Of 112 patients (89% of the study population) who underwent cardiac ultrasound, 44 (39%) were diagnosed with right ventricular dysfunction. The latter finding was prospectively defined as dilatation of the right ventricle (end-diastolic diameter >30 mm from the parasternal view, or a right ventricle/left ventricle diameter ratio >1.0 from the subcostal or apical views), combined with right atrial hypertension (absence of the inspiratory collapse of the inferior vena cava) in the absence of left ventricular or mitral valve disease (15).

In all cases, blood was drawn immediately for measurement of baseline (admission) biomarker levels prior to further diagnostic workup. Following confirmation of the diagnosis, patients were asked to sign the informed consent form. Subsequently, complete data on baseline clinical, hemodynamic, and laboratory parameters were obtained using a standardized questionnaire by investigators unaware of the patients' biomarker levels.

Thirty-day clinical follow-up data were obtained from all patients included in the study. A complicated 30-day outcome was defined as death or at least one of the following major adverse events: 1) need for catecholamine administration (except for dopamine at a rate of <5 μg/kg/min) to maintain adequate tissue perfusion and prevent or treat cardiogenic shock; 2) endotracheal

intubation; or 3) cardiopulmonary resuscitation. Long-term survival was assessed by follow-up examinations at 6-month intervals after PE diagnosis.

Biomarker levels were not communicated to the clinicians involved in the care of the study patients, and they were not used to guide patient management or to monitor the effects of treatment during the hospital stay or at any time during the follow-up period. The study protocol was approved by the ethics committee of the University of Goettingen.

Laboratory Parameters and Biomarker Testing. Venous plasma and serum samples were collected on admission and 24 hours thereafter, and immediately stored at -80°C. Samples were later analyzed in batches after a single thaw. Plasma levels of H-FABP (dilution 1:5) were measured by a solid-phase ELISA based on the sandwich principle (HyCult Biotechnology, Uden, The Netherlands). Cardiac troponin T (cTnT) and NT-proBNP levels were determined in plasma samples using quantitative electrochemiluminescence immunoassays (Elecsys 1010/2010 analyzer, Roche Diagnostics, Mannheim, Germany) as described (20,21). All other laboratory measurements were performed at the Department of Clinical Chemistry, University of Goettingen, using standard laboratory techniques. Renal insufficiency was defined as a glomerular filtration rate (GFR) <60 ml/min/1.73 m^2. GFR was calculated from the "four-variable" MDRD Study equation (22).

Statistical analysis. Using the modified Kolmogorov-Smirnov test (Lilliefors test), the continuous variables tested in the present study were found not to follow a normal distribution; therefore, they are presented as medians with corresponding 25^{th} and 75^{th} percentiles and were compared using the unpaired Mann-Whitney U-test. Categorical variables were compared using Fisher's exact test. Prognostically relevant cutoff values of prespecified clinical (heart rate) and laboratory (H-FABP) parameters were derived from receiver operating characteristic (ROC) curve analysis, which also

was used to determine the area under the curve (c-statistic). The optimal cut-off point was chosen as the cut-off value at which 0.5x(sensitivity+specificity) was maximal. On the other hand, a value of ≥0.04 ng/ml was prospectively defined as indicating an elevated cTnT concentration as proposed by the manufacturer; for NT-proBNP, the cutoff level was prospectively set at 1,000 pg/ml based on our previous findings in patients with PE (20,23).

The prognostic relevance of H-FABP levels and other baseline parameters with regard to 30-day outcome was estimated using logistic regression analysis with the calculated or prospectively defined cutoff values. The results are presented as odds ratios with the corresponding 95% confidence intervals. To identify predictors of long-term mortality, Cox's proportional hazards regression analysis was performed using Wald's test; these results are presented as hazard ratios with corresponding 95% confidence intervals. Survival rates were estimated by the Kaplan-Meier method, and statistical comparison was performed using the log-rank test. All tests were two-sided and used a significance level of 0.05.

ROC curves from different biomarkers were compared using the software Analyse-it (version 2.21 Excel 12+; Analyse-it Software, Ltd.) which applies the method of DeLong et al. (24). All other analyses were performed using the SPSS 17.0 software (SPSS Inc.) and GraphPad Prism 4 (GraphPad Software).

Results

H-FABP levels on admission predict 30-day outcome in normotensive patients with PE. The baseline clinical characteristics and biomarker levels of the study population are summarized in Table 1. H-FABP concentrations on admission ranged from 0.39 to 217.5 ng/ml with a median value of 3.4 ng/ml (interquartile range, 2.2-5.4 ng/ml). During the first 30 days, 9 (7%) patients suffered major complications: 6 patients died, 5 underwent cardiopulmonary resuscitation, and 7 required catecholamines and/or endotracheal intubation. Patients who developed complications had elevated H-FABP values on admission (median, 11.2 ng/ml; IQR, 8.0-36.8 ng/ml) compared to patients with an uncomplicated course (3.4 [2.1-4.9] ng/ml; $p<0.001$). In contrast, neither the baseline cTnT concentrations nor those of NT-proBNP differed significantly between patients suffering complications within 30 days and those with an uncomplicated course (cTnT, 0.12 [0.009-0.26] vs. 0.009 [0.009-0.04] ng/ml; p=0.072; NT-proBNP, 1,914 [525-25,462] vs. 980 [181-2,630] pg/ml]; p=0.10).

Receiver operating characteristic analysis further suggested that H-FABP levels on admission are a powerful predictor of 30-day outcome in normotensive patients with acute PE (Figure 1). The calculated area under the curve (AUC) for H-FABP was 0.89 (95% CI, 0.77 to 1.01), for cTnT (0.68 [0.47 to 0.9]) and for NT-proBNP (0.67 [0.48 to 0.85]). Comparing all three AUCs (24), the AUC for H-FABP was significantly higher than the AUC for NT-proBNP (p=0.017; other p values were 0.085 for H-FABP/cTnT and 0.834 for cTnT/NT-proBNP). Using ROC analysis, a concentration of 6.09 ng/ml was identified as the best cutoff level for H-FABP in our study population. Notably, this is almost identical to the cutoff value of 6 ng/ml found in previous studies which tested H-FABP in unselected patients with acute PE (15), and in patients with acute coronary syndromes (25,26).

In the present study, 29 (23%) normotensive patients with acute PE had H-FABP concentrations in plasma ≥6 ng/ml on admission. As shown in Table 1, patients with elevated H-FABP were older, had higher baseline circulating levels of cTnT or NT-proBNP, and were more likely to present with syncope as the leading symptom and with acute right ventricular dysfunction in the echocardiogram. During the first 30 days, 8 (28%) patients with initially elevated H-FABP had a complicated course; 4 of them died during this period. In contrast, only one of the 97 patients with H-FABP <6 ng/ml suffered complications ($p<0.0001$). Thus, using the cutoff value of 6 ng/ml, H-FABP had a sensitivity of 0.89 (95% CI, 0.52 to 0.99), a specificity of 0.82 (0.74 to 0.89), a positive predictive value of 0.28 (0.13 to 0.47) and a negative predictive value of 0.99 (0.94 to 0.99) with regard to an adverse 30-day outcome.

Univariable logistic regression demonstrated that patients with H-FABP ≥6 ng/ml at presentation had a 36.6-fold increased risk for 30-day complications ($p=0.001$; Table 2). The only other baseline parameters found to predict an adverse outcome were an elevated heart rate ≥94 beats/min (cutoff value derived by ROC analysis; AUC, 0.74 [0.651 to 0.89]) and syncope. In contrast, neither NT-proBNP ($p=0.331$) nor cTnT ($p=0.087$) concentrations above the predefined cutoff values of 1,000 pg/ml and 0.04 ng/ml respectively appeared to predict 30-day outcome in normotensive patients with PE. When tested by multivariable analysis (including only the significant predictors from the univariable model), H-FABP remained an independent predictor of complicated 30-day outcome (H-FABP elevation, OR 25.9 [2.9 to 229.3], $p=0.003$; tachycardia ≥ 94 beats/min, OR 7.9 [0.9 to 73.9], $p=0.068$; syncope: OR 2.7 [0.5 to 14.6], $p=0.259$).

Finally, repeated biomarker measurements revealed that none of the 62 tested patients who had H-FABP levels <6 ng/ml on admission developed a positive test 24 hours later or suffered cardiovascular complications during the first day in hospital. Thus, a normal H-FABP on admission appeared sufficient to rule out an adverse 30-day outcome in normotensive patients with

acute PE. In contrast, the biomarker test became positive after 24 hours in 5 of 60 patients with an initially negative cTnT test, and in 8 of 42 patients with initially "low" (<1,000 pg/ml) NT-proBNP levels. In each one of these latter groups, one patient suffered complications during the first 24 hours, i.e. between the first and the second biomarker test.

Combined approach using clinical parameters and biomarker levels for risk assessment of normotensive PE. We tested the hypothesis that biomarker levels and particularly H-FABP may have an additive prognostic value when combined with baseline clinical parameters in patients with acute PE. As mentioned above and shown in Table 2, a heart rate of ≥94 beats/min was univariably associated with a 10.6-fold increase in the risk of short-term complications compared to patients with a lower heart rate. However, of 40 patients with tachycardia but normal (<6 ng/ml) H-FABP levels on admission, only one (2.5%) developed complications, while 39% of patients with tachycardia and H-FABP ≥6 ng/ml had a complicated course (Figure 2). Logistic regression confirmed that patients with the combination of tachycardia and H-FABP ≥6 ng/ml had a 33.4-fold elevated risk of an adverse 30-day outcome ($p<0.0001$). H-FABP concentrations at baseline also appeared to increase the prognostic value of other clinical (e.g. syncope) or echocardiographic (RV dysfunction) findings in normotensive patients with PE (Figure 2).

H-FABP levels on admission also predict long-term prognosis after pulmonary embolism. The median follow-up time after the index episode of acute PE was 499 days (IQR, 204-1166 days). Twenty six patients (21%) died during this period. Patients who died during follow-up had significantly higher baseline levels of H-FABP (median, 5.5 ng/ml; IQR, 1.4-11.2 ng/ml) compared to survivors (3.4 [2.0-4.8] ng/ml; $p=0.006$). Baseline NT-proBNP values also were higher in non-survivors as opposed to the patients who survived (2,233 [14-12,180] pg/ml vs. 788

[173-2,374] pg/ml; p=0.001), while cTnT levels on admission did not differ between non-survivors and survivors (0.013 [0.007-0.19] ng/ml vs. 0.009 [0.009-0.04] ng/ml; p=0.55). By univariable Cox regression analysis, patients with H-FABP ≥6 ng/ml on admission had a 4.5-fold increased risk for death during long-term follow up as calculated (p<0.0001; Table 3). Further baseline parameters univariably predicting long-term mortality were tachycardia ≥94 beats/min and the presence of a malignant tumor (Table 3), but not the diagnosis of RV dysfunction on echocardiography (p=0.664). Multivariable analysis including the significant predictors from the univariable model revealed that elevated H-FABP levels on admission remained, besides the presence of a malignant tumor, an independent predictor of long-term mortality (H-FABP ≥6 ng/ml, OR 3.6 [1.6 to 8.2], p=0.002; malignant tumor, OR 5.3 [2.4 to 11.5], p<0.0001; tachycardia ≥94 beats/min, OR 1.9 [0.8 to 4.7], p=0.138). Kaplan-Meier analysis further showed that patients with baseline H-FABP levels ≥6 ng/ml had a reduced probability of long-term survival (Figure 3, upper panel). In contrast, neither elevation of cTnT nor of NT-proBNP at presentation predicted an increased probability of death during the follow-up period (Figure 3).

Discussion

This study evaluated the usefulness of cardiac biomarkers and particularly heart-type fatty acid-binding protein in the risk stratification of acute PE. In contrast to previously published studies which included unselected patients across the entire clinical spectrum of PE severity (10-12), the present study focused on initially normotensive patients and directly addressed the possible existence of an "intermediate-risk" group as proposed by recent guidelines (7). In 126 consecutive patients with confirmed PE who presented without hemodynamic instability, i.e. persistent arterial hypotension or shock, we found that elevated (≥6 ng/ml) H-FABP levels on admission were strongly associated with the 30-day death and complication rate. The prognostic value of H-FABP appeared superior to that of previously validated biomarkers such as cardiac troponins and natriuretic peptides, and to the detection of right ventricular dysfunction on echocardiography. Moreover, elevated H-FABP concentrations at presentation were related to long-term mortality after acute PE.

In acute PE, persistent arterial hypotension or cardiogenic shock on admission is clearly associated with high in-hospital mortality (5,27). However, the majority of patients subsequently diagnosed with acute PE present with normal arterial pressure. Although further risk stratification of these patients into an "intermediate-risk" and a "low-risk" group is supported by current guidelines (7), the optimal tools and strategies to achieve this goal remain controversial. Echocardiography is an appropriate modality for diagnosing RV dysfunction in a patient with cardiogenic shock suspected of having massive PE, and it may also be of prognostic value in normotensive patients (9). On the other hand, echocardiographic studies in PE have been criticized for their heterogeneity and lack of standardized criteria (28), and a recent meta-analysis reported a low overall specificity (57%) and positive predictive value (58%) of the echocardiogram in

predicting an adverse outcome (12). In the present study, 39% of normotensive patients had echocardiographic findings suggesting RV dysfunction, but overall echocardiography was, by itself, not found to predict a significantly elevated risk of death or complications within the first 30 days. RV dysfunction can also be assessed based on the circulating levels of brain natriuretic peptides. However, although elevated BNP and NT-proBNP concentrations are generally related to a poor in-hospital outcome (11), their positive predictive value is low, and prospectively validated cutoff values are lacking (11,29,30). Furthermore, elevated concentrations of brain natriuretic peptides can be found in other conditions and comorbidities including left ventricular dysfunction, older age, renal impairment, and chronic lung disease (31).

Besides RV dysfunction, evidence of myocardial injury also has been shown to be of prognostic relevance in patients with PE. Cardiac troponins are highly sensitive and specific indicators of myocardial cell damage, and elevated troponin levels were correlated with in-hospital mortality or complications in unselected patients with acute PE (21). A recent meta-analysis generally confirmed the prognostic value of elevated troponin levels in acute PE (10). However, repetitive troponin measurements, i.e. beyond those obtained on admission, may be required to increase the negative predictive value of this biomarker (15,32). Moreover, and importantly, cardiac troponins possess a low positive predictive value (30), and the results of the present study indicate that they may be less suitable for predicting either short-term or long-term outcome in the subgroup of initially normotensive (non-high-risk) patients with acute PE.

H-FABP is an early indicator of myocardial injury which has been evaluated in the diagnosis and triage of acute coronary syndromes. Compared to cardiac troponins, H-FABP testing offers a number of potential advantages (discussed in (15)) which are related to its small molecular size (very early release after injury), its relative myocardial specificity which resembles that of the MB isoenzyme of creatine kinase, and its confinement to the cytoplasmic space. The release

characteristics of H-FABP from injured myocardium closely resemble those of myoglobin, but H-FABP appears to possess both higher sensitivity and higher cardiospecificity compared to the latter biomarker. The concentration of 6 ng/ml has been proposed as an upper reference level of H-FABP in previous studies (25,26).

Recently, H-FABP was tested in two studies which included unselected, i.e. both normotensive and hypotensive patients with PE. Elevated H-FABP values were superior to cTnT, NT-proBNP, and myoglobin in risk assessment with regard to 30-day outcome (15,16). However, patients who present with persistent arterial hypotension or shock are clearly at high risk of early death and do not necessitate further risk stratification with biomarker testing. Therefore, and in contrast to the previous reports, we now focussed on the outcome of initially normotensive patients with PE in order to distinguish the intermediate-risk from the low-risk group (7). In this patient population, we could demonstrate that elevated H-FABP is a strong predictor both of an adverse 30-day outcome and of long-term mortality. In fact, H-FABP ≥6 ng/ml at baseline was associated with a 37-fold increase in the 30-day complication risk and a 4.5-fold increase in the risk of death at long-term follow-up (median period, 499 days), while normal H-FABP values virtually excluded an adverse clinical outcome (negative predictive value, 99%). Importantly, negative H-FABP values on admission remained negative over the first 24 hours and thus repetitive measurements of the biomarker may not be necessary to increase its prognostic value.

At the present stage, we can only speculate on how exactly elevated H-FABP levels on admission may (also) have affected long-term outcome after acute PE. In this regard, the exclusion of 14 patients who were lost to follow-up may be a potential limitation of our study. It is postulated that some novel biomarkers are capable of integrating prognostic information related to various comorbidities, including cancer, and may thus serve as “global” indicators of poor outcome after acute PE (23). Although preliminary data suggest that H-FABP may also reflect the

aggressiveness and prognosis of some carcinomas, the most plausible explanation of our findings may be related to the persistence of pulmonary hypertension after acute PE. In this regard, we have previously shown that elevated H-FABP levels on admission independently predicted an adverse outcome in patients with chronic thromboembolic pulmonary hypertension (17).

Weighted scores combining baseline clinical parameters have been evaluated in the risk stratification of acute PE and appear particularly useful for the identification of low-risk patients who may be eligible for early discharge and home treatment (5,33). In search of an optimal strategy for identifying a true "intermediate-risk" group with right ventricular dysfunction despite normal blood pressure on admission, we found that the combination of a positive (≥6 ng/ml) H-FABP-test with an elevated heart rate (≥94 beats/min) at presentation was a strong, highly significant predictor of death or complications in the acute phase. This simplified "risk score" may be a particularly attractive option for clinicians as bedside H-FABP tests are now commercially available.

It should be noted that, although the incidence of death or major complications in our study corresponds to that previously reported for normotensive (non-high risk) PE patients (9-11), the low absolute numbers of end points during short- and long-term follow-up (9 and 26 events, respectively), may limit the interpretation of our multivariable regression models.

In conclusion, H-FABP appears to be a useful biomarker for risk stratification in normotensive patients with acute PE. A single measurement on admission, as early as 60-90 minutes after the onset of symptoms, may be sufficient to classify normotensive patients with confirmed PE into a low-risk and an intermediate-risk group, and may thus guide management strategies in the absence of shock. Based on our results and those of previous studies, the therapeutic implications of a positive H-FABP test, alone or in combination with baseline clinical parameters, deserve to be addressed by a prospective management study.

FIGURE LEGENDS

Figure 1. *Prognostic sensitivity and specificity of heart-type fatty acid-binding protein (H-FABP), cardiac troponin T (cTnT) and N-terminal pro-brain natriuretic peptide (NT-proBNP)*. Displayed are receiver operating characteristic curves for H-FABP, cTnT, and NT-proBNP levels on admission with regard to a complicated 30-day outcome. AUC, area under the curve.

Figure 2. *Combination of H-FABP with clinical parameters.* The number of patients with complications and the overall number of patients are given, along with percentages, for each column.

Figure 3. *Probability of long-term survival in patients with or without elevation of H-FABP, cTnT and NT-proBNP*. Biomarker levels were dichotomized, and elevated concentrations were defined as those ≥6 ng/ml for H-FABP, ≥0.04 ng/ml for cTnT, and ≥1,000 pg/ml for NT-proBNP. Red lines, elevated values; blue lines, normal values; p values were calculated by the log-rank test.

Table 1. Baseline Characheristics of the Study Population

Parameter	**All patients** (n=126)	**H-FABP ≥6 ng/ml** (n=29)	**H-FABP <6 ng/ml** (n=97)	**p Value**
Age (years)	67 (51-74)	71 (57-80)	65 (47-72)	0.02
Surgery within 14 days	20 (16%)	5 (17%)	15 (15%)	0.78
Trauma within 14 days	7 (6%)	2 (7%)	5 (5%)	0.66
Malignant tumor	21 (17%)	6 (21%)	15 (15%)	0.57
History of DVT	42 (33%)	7 (24%)	35 (36%)	0.27
History of PE	20 (16 %)	0	20 (21%)	0.007
Dyspnea	117 (93%)	25 (86%)	92 (95%)	0.21
Syncope	20 (16%)	9 (31%)	11 (11%)	0.019
Heart rate (beats/min)	92 (80-110)	100 (85-110)	90 (78-110)	0.12
GFR (ml/min/1.73 m^2)	76.4 (55.1-94.9)	57.1 (41.1-83.2)	78.3 (61.8-95.5)	0.010
H-FABP (ng/ml)	3.4 (2.1-5.4)	9.9 (6.7-14.0)	3.0 (1.7-3.8)	-
NT-proBNP (pg/ml)	1,046 (188-2,685)	1,988 (425-7,930)	810 (173-2,431)	0.005
cTnT (ng/ml)	0.009 (0.009-0.048)	0.03 (0.009-0.24)	0.009 (0.009-0.03)	0.004
RV dysfunction on echocardiography	44/112 (39%)	17/28 (61%)	27/84 (32%)	0.013

Categorical variables are expressed as absolute numbers (percentages); continuous variables, as medians with the corresponding interquartile range (25^{th}-75^{th} percentile).

cTnT denotes cardiac troponin T; DVT, deep venous thrombosis; GFR, glomerular filtration rate; H-FABP, heart-type fatty acid-binding protein; PE, pulmonary embolism; RV dysfunction, right ventricular dysfunction.

Table 2. Predictors of Complicated 30-Day Outcome

Parameter	OR (95% CI)	p Value
Heart rate ≥94 beats/min	10.6 (1.3 to 87.2)	0.029
Syncope	5.1 (1.2 to 20.8)	0.025
Malignant tumor	2.8 (0.6 to 12.0)	0.179
H-FABP ≥6 ng/ml	36.6 (4.3 to 308)	0.001
cTnT ≥0.04 ng/ml	3.3 (0.4 to 13.1)	0.087
GFR <60 ml/min	3.2 (0.8 to 12.7)	0.097
RV dysfunction (echocardiography)	2.8 (0.6 to 12.3)	0.178

Univariable logistic regression analysis. CI denotes confidence interval; OR, odds ratio; other abbreviations as in Table 1.

Table 3. Baseline Parameters Predicting Long-Term Mortality After Acute PE

Parameter	HR (95% CI)	p Value
Heart rate rate ≥94 beats/min	2.8 (1.2 to 6.5)	0.015
Syncope	2.2 (0.9 to 5.1)	0.082
Malignant tumor	5.6 (2.6 to 12.3)	<0.0001
H-FABP ≥6 ng/ml	4.5 (2.0 to 9.8)	<0.0001
NT-proBNP ≥1,000 pg/ml	2.1 (0.9 to 4.7)	0.089

Univariable Cox regression analysis. CI denotes confidence interval; HR, hazards ratio; other abbreviations as in Table 1.

References

1. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet 1999;353:1386-9.

2. Oger E. Incidence of venous thromboembolism: a community-based study in Western France. EPI-GETBP Study Group. Groupe d'Etude de la Thrombose de Bretagne Occidentale. Thromb Haemost 2000;83:657-60.

3. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, III. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med 1998;158:585-93.

4. Office of the Surgeon General. The Surgeon General's call to action to prevent deep vein thrombosis and pulmonary embolism. http://www.surgeongeneral.gov/news/pressreleases/pr20080915.html . 2008. Ref Type: Electronic Citation

5. Konstantinides S. Clinical practice. Acute pulmonary embolism. N Engl J Med 2008;359:2804-13.

6. Kasper W, Konstantinides S, Geibel A et al. Management strategies and determinants of outcome in acute major pulmonary embolism: results of a multicenter registry. J Am Coll Cardiol 1997;30:1165-71.

7. Torbicki A, Perrier A, Konstantinides SV et al. Guidelines on the diagnosis and management of acute pulmonary embolism: The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Eur Heart J 2008;29:2276-315.

8. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:454S-545S.

9. Kucher N, Rossi E, De Rosa M, Goldhaber SZ. Prognostic role of echocardiography among patients with acute pulmonary embolism and a systolic arterial pressure of 90 mm Hg or higher. Arch Intern Med 2005;165:1777-81.

10. Becattini C, Vedovati MC, Agnelli G. Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. Circulation 2007;116:427-33.

11. Klok FA, Mos IC, Huisman MV. Brain-type natriuretic peptide levels in the prediction of adverse outcome in patients with pulmonary embolism: a systematic review and meta-analysis. Am J Respir Crit Care Med 2008;178:425-30.

12. Sanchez O, Trinquart L, Colombet I et al. Prognostic value of right ventricular dysfunction in patients with haemodynamically stable pulmonary embolism: a systematic review. Eur Heart J 2008;29:1569-77.

13. Alhadi HA, Fox KA. Do we need additional markers of myocyte necrosis: the potential value of heart fatty-acid-binding protein. QJM 2004;97:187-98.

14. Storch J, Thumser AE. The fatty acid transport function of fatty acid-binding proteins. Biochim Biophys Acta 2000;1486:28-44.

15. Puls M, Dellas C, Lankeit M et al. Heart-type fatty acid-binding protein permits early risk stratification of pulmonary embolism. Eur Heart J 2007;28:224-9.

16. Kaczynska A, Pelsers MM, Bochowicz A, Kostrubiec M, Glatz JF, Pruszczyk P. Plasma heart-type fatty acid binding protein is superior to troponin and myoglobin for rapid risk stratification in acute pulmonary embolism. Clin Chim Acta 2006;371:117-23.

17. Lankeit M, Dellas C, Panzenbock A et al. Heart-type fatty acid-binding protein for risk assessment of chronic thromboembolic pulmonary hypertension. Eur Respir J 2008;31:1024-9.

18. European Society of Cardiology TFoPE. Guidelines on diagnosis and management of acute pulmonary embolism. Eur Heart J 2000;21:1301-36.

19. Wells PS, Anderson DR, Rodger M et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. Thromb Haemost 2000;83:416-20.

20. Binder L, Pieske B, Olschewski M et al. N-terminal pro-brain natriuretic peptide or troponin testing followed by echocardiography for risk stratification of acute pulmonary embolism. Circulation 2005;112:1573-9.

21. Konstantinides S, Geibel A, Olschewski M et al. Importance of cardiac troponins I and T in risk stratification of patients with acute pulmonary embolism. Circulation 2002;106:1263-8.

22. National Kidney Foundation. K/DOQI Clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis 2002;39:S1-S000.

23. Lankeit M, Kempf T, Dellas C et al. Growth differentiation factor-15 for prognostic assessment of patients with acute pulmonary embolism. Am J Respir Crit Care Med 2008;177:1018-25.

24. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver opearating characteristic curves: a nonparametric approach. Biometrics 1988;44:837-45.

25. Pelsers MM, Chapelle JP, Knapen M et al. Influence of age and sex and day-to-day and within-day biological variation on plasma concentrations of fatty acid-binding protein and myoglobin in healthy subjects. Clin Chem 1999;45:441-3.

26. Pagani F, Bonora R, Bonetti G, Panteghini M. Evaluation of a sandwich enzyme-linked immunosorbent assay for the measurement of serum heart fatty acid-binding protein. Ann Clin Biochem 2002;39:404-5.

27. Kucher N, Rossi E, De Rosa M, Goldhaber SZ. Massive pulmonary embolism. Circulation 2006;113:577-82.

28. ten Wolde M, Sohne M, Quak E, Mac Gillavry MR, Buller HR. Prognostic value of echocardiographically assessed right ventricular dysfunction in patients with pulmonary embolism. Arch Intern Med 2004;164:1685-9.

29. Giannitsis E, Katus HA. Risk stratification in pulmonary embolism based on biomarkers and echocardiography. Circulation 2005;112:1520-1.

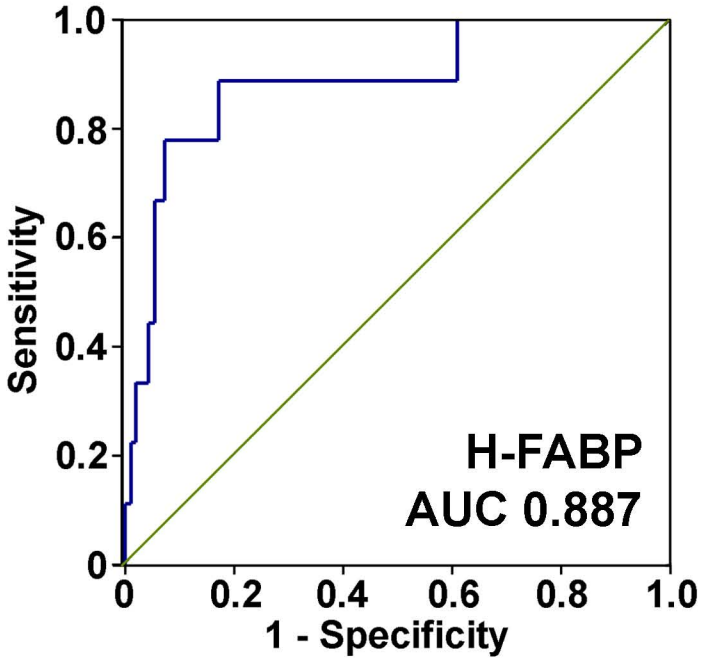
30. Kucher N, Goldhaber SZ. Cardiac biomarkers for risk stratification of patients with acute pulmonary embolism. Circulation 2003;108:2191-4.

31. de Lemos JA, McGuire DK, Drazner MH. B-type natriuretic peptide in cardiovascular disease. Lancet 2003;362:316-22.

32. Pruszczyk P, Bochowicz A, Torbicki A et al. Cardiac troponin T monitoring identifies high-risk group of normotensive patients with acute pulmonary embolism. Chest 2003;123:1947-52.

33. Aujesky D, Roy PM, Le Manach CP et al. Validation of a model to predict adverse outcomes in patients with pulmonary embolism. Eur Heart J 2006;27:476-81.

Figure 1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0.6
0.4
0.2
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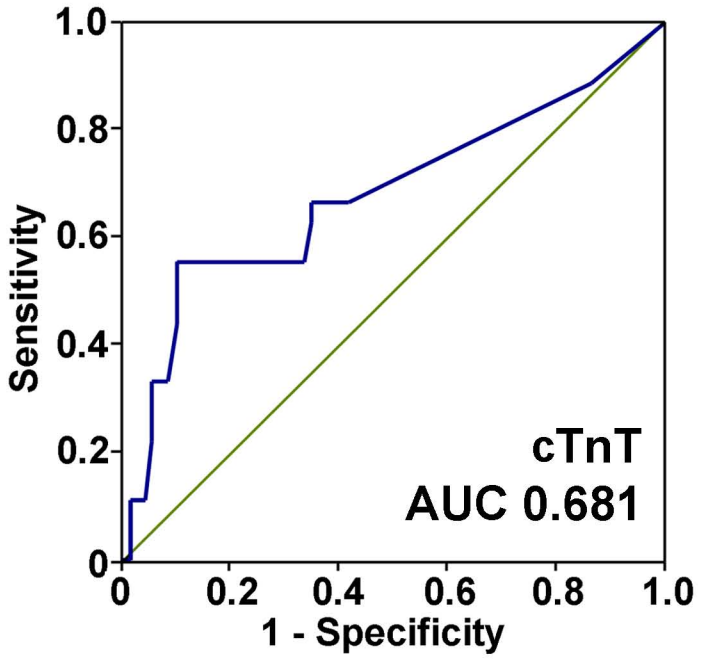
Sensitivity
0
0.2
0.4
0.6
0.8
1.0
1 - Specificity
H-FABP
AUC 0.887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0.6
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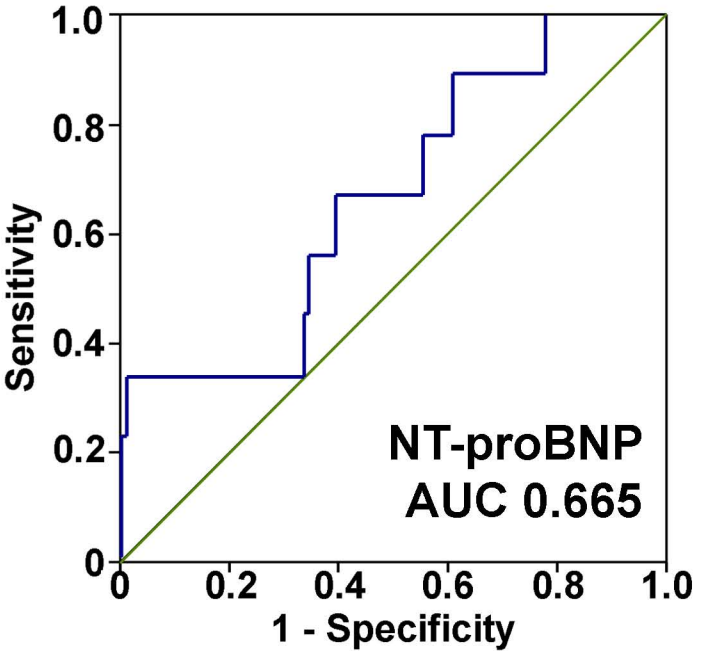
1 - Specificity
cTnT
AUC 0.681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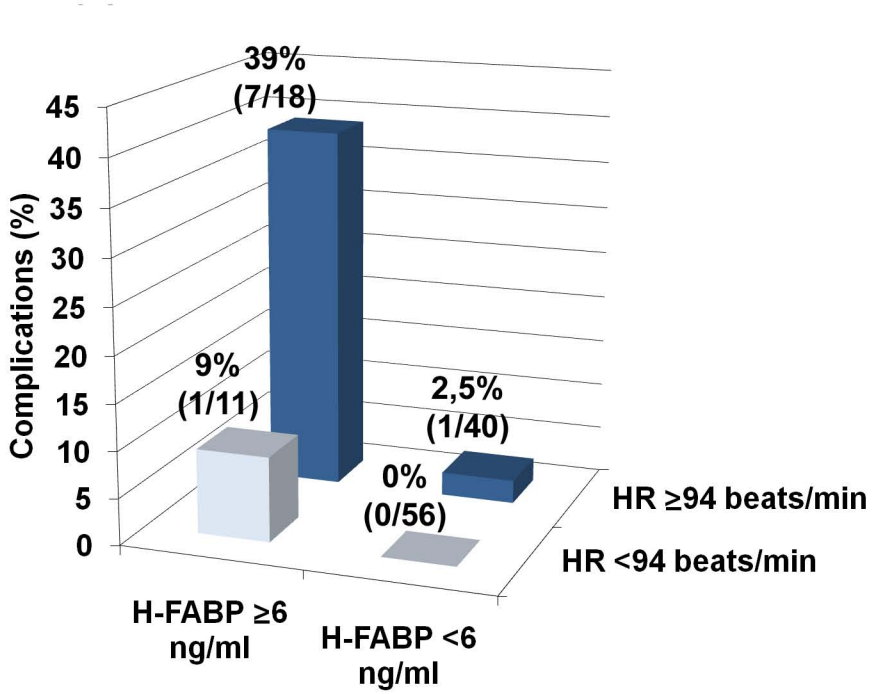
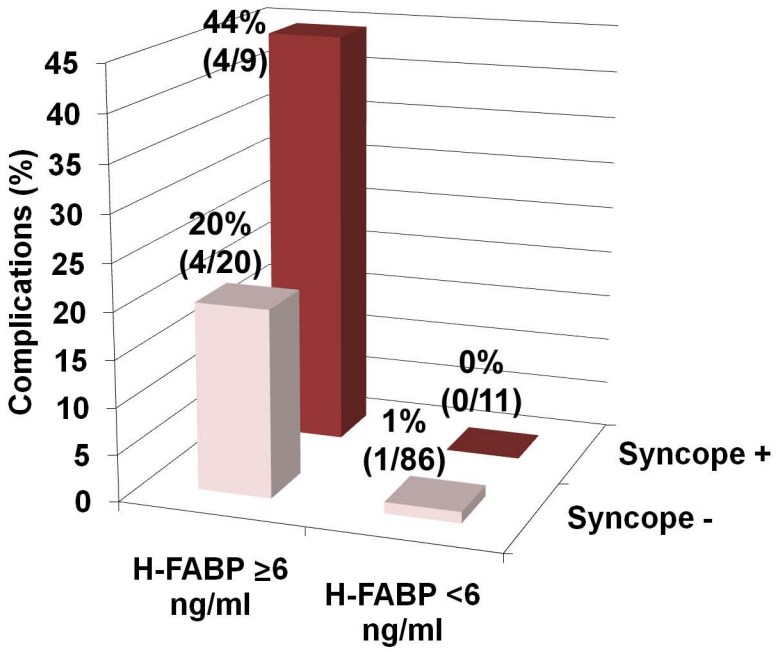
0.8
0.6
0.4
0.2
0
Sensitivity
0
0.2
0.4
0.6
0.8
1.0
1 - Specificity
NT-proBNP
AUC 0.665

Figure 2


39%
(7/18)
9%
(1/11)
2,5%
(1/40)
0%
(0/56)
Complications (%)
45
40
35
30
25
20
15
10
5
0
HR ≥94 beats/min
HR <94 beats/min
H-FABP ≥6 ng/ml
H-FABP <6 ng/ml


44%
(4/9)
20%
(4/20)
0%
(0/11)
1%
(1/86)
Complications (%)
45
40
35
30
25
20
15
10
5
0
Syncope +
Syncope -
H-FABP ≥6 ng/ml
H-FABP <6 ng/ml

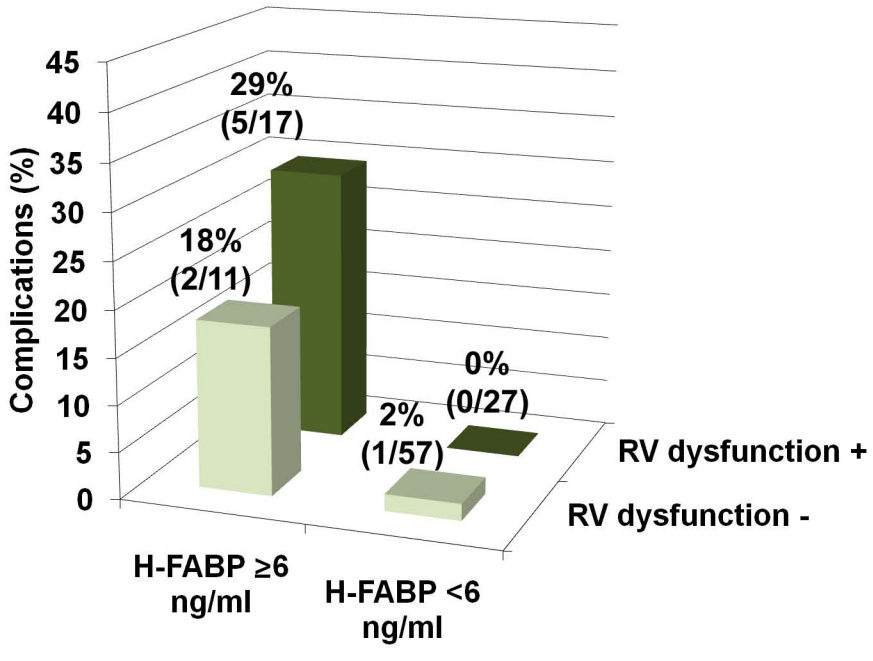
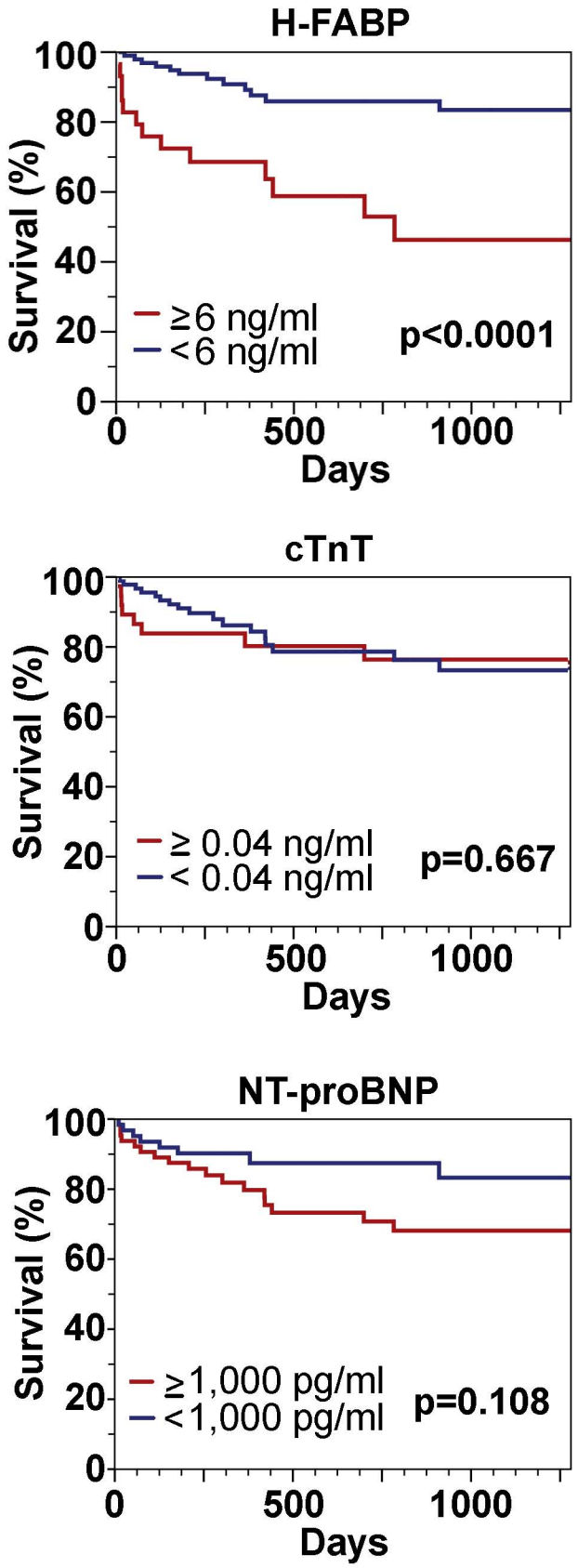

29%
(5/17)
18%
(2/11)
0%
(0/27)
2%
(1/57)
Complications (%)
45
40
35
30
25
20
15
10
5
0
RV dysfunction +
RV dysfunction -
H-FABP ≥6 ng/ml
H-FABP <6 ng/ml

Figure 3


H-FABP
Survival (%)
100
80
60
40
20
0
≥6 ng/ml
<6 ng/ml
p<0.0001
0
500
1000
Days
cTnT
Survival (%)
100
80
60
40
20
0
≥ 0.04 ng/ml
< 0.04 ng/ml
p=0.667
0
500
1000
Days
NT-proBNP
Survival (%)
100
80
60
40
20
0
≥1,000 pg/ml
<1,000 pg/ml
p=0.108
0
500
1000
Days