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

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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 on the basis of 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 [interquartile range: 8.0 to 36.8 ng/ml]) compared with patients with an uncomplicated course (3.4 ng/ml [2.1 to 4.9 ng/ml]; p < 0.001). H-FABP values were above the calculated (by receiver operating characteristic curve 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 (＞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 (interquartile range: 204 to 1,166) days (hazard ratio: 3.6; 95% confidence interval: 1.6 to 8.2; p = 0.003).

Conclusions
The H-FABP might be a useful biomarker for risk stratification of normotensive patients with acute PE. (J Am Coll Cardiol 2010;55:2150–7) © 2010 by the American College of Cardiology Foundation

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 might vary widely, mostly depending on the clinical severity of PE at presentation (1,6). Accordingly, recent guidelines have proposed immediately classifying 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 [RV] 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). By contrast, 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) RV dysfunction or myocardial injury and might have an “intermediate” death risk of 3% to 15% (9–11), continues to pose a challenge in clinical practice.

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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 the use 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 to 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 that has been evaluated for emergency triage of patients with acute coronary syndromes (13). Fatty acid-binding proteins are relatively small cytoplasmic proteins (12 to 15 kDa) that are abundant in tissues with active fatty acid metabolism, including the heart (14). After myocardial cell damage, H-FABP diffuses much more rapidly than troponins through the interstitial space and appears in the circulation as early as 90 min after symptom onset, reaching its peak within 6 h (13). Recent studies in unselected patients with acute PE suggested that H-FABP levels on admission might 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). On the basis of these promising observations, we conducted the present study to determine whether H–FABP, alone or in combination with clinical or echocardiographic findings, might 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 PE (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 1 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) (n = 24); 2) denial or withdrawal of written consent for participation in the study (n = 4); 3) lost to follow-up (n = 14); and 4) unexpected or accidental diagnosis of PE (patients undergoing diagnostic tests for another suspected disease) or PE coinciding with acute decompen- sation of left ventricular (LV) failure or acute myocardial infarction (n = 19).

The time period covered by the present study (2003 to 2007) partly overlapped with that (2003 to 2005) of a previous publication by our own group (15); of that latter patient population (n = 107), 73 patients were also included in the present study, whereas 34 were excluded due to hemodynamic instability (n = 10), loss to follow-up (n = 14), and acute PE coinciding with acute decompen- sation of LV failure or acute myocardial infarction (n = 10). 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 on the basis of 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 5 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 transtho- racic echocardiogram within 2 h of PE diagnosis. Of 112 patients (89% of the study population) who underwent cardiac ultrasound, 44 (39%) were diagnosed with RV dysfunction. The latter finding was prospectively defined as dilatation of the RV (end-diastolic diameter ≥30 mm from the parasternal view or a RV/LV 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 LV or mitral valve disease (15).

In all cases, blood was drawn immediately for measurement of baseline (admission) biomarker levels before further diagnostic workup. After confirmation of the diagnosis, patients were asked to sign the informed consent form. Subsequently, complete data on baseline clinical, hemody- namic, and laboratory parameters were obtained with 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 1 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 h 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 enzyme-linked immunosorbent assay on the basis of the sandwich principle (HyCult Biotechnology, Uden, the Netherlands). Cardiac troponin T (cTnT) and NT-proBNP levels were determined in plasma samples with 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, with standard laboratory techniques. Renal insufficiency was defined as a glomerular filtration rate <60 ml/min/1.73 m². Glomerular filtration rate was calculated from the “four-variable” Modification of Diet in Renal Disease Study equation (22).

**Statistical analysis.** With 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 25th and 75th percentiles and were compared with the unpaired Mann-Whitney U test. Categorical variables were compared with Fisher 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 (AUC) (c-statistic). The optimal cutoff point was chosen as the cutoff value at which 0.5 × (sensitivity + specificity) was maximal. By contrast, 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 on the basis of 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 with logistic regression analysis with the calculated or prospectively defined cutoff values. The results are presented as odds ratios (ORs) with the corresponding 95% confidence intervals (CIs). To identify predictors of long-term mortality, Cox proportional hazards regression analysis was performed with Wald’s test; these results are presented as hazard ratios with corresponding 95% CIs. Survival rates were estimated by the Kaplan-Meier method, and statistical comparison was performed with the log-rank test. All tests were 2-sided and used a significance level of 0.05.

The ROC curves from different biomarkers were compared with the software Analyse-it (version 2.21 Excel 12+, Analyse-it Software, Ltd., Leeds, United Kingdom), which applies the method of DeLong et al. (24). All other analyses were performed with the SPSS 17.0 software (SPSS, Inc., Chicago, Illinois) and GraphPad Prism 4 (GraphPad Software, San Diego, California).

**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. The 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 [IQR] 2.2 to 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 to 36.8 ng/ml) compared with patients with an uncomplicated course (3.4 [IQR 2.1 to 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 to 0.26] ng/ml vs. 0.009 [0.009 to 0.04] ng/ml; p = 0.072; NT-proBNP, 1.914 [IQR 525 to 25,462] pg/ml vs. 980 [IQR 181 to 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 (Fig. 1). The calculated AUC was 0.89 (95% CI: 0.77 to 1.01) for H-FABP, 0.68 (95% CI: 0.47 to 0.9) for cTnT, and 0.67 (95% CI: 0.48 to 0.85) for NT-proBNP. The AUC for H-FABP was significantly higher than the AUC for NT-proBNP (p = 0.017), in a comparison of all 3 AUCs (24); other p values were p = 0.085 for H-FABP/cTnT and p = 0.834 for cTnT/NT-proBNP. With 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 that 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 RV 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 1 of the 97 patients with H-FABP ≤6 ng/ml suffered complications (p < 0.0001). Thus, with the cutoff value of 6 ng/ml, H-FABP had a sensitivity of 0.89 (95% CI: 0.52 to 0.99), specificity of 0.82 (95% CI: 0.74 to 0.89), positive predictive value of 0.28 (95% CI: 0.13 to 0.47), and negative predictive value of 0.99 (95% CI: 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 [95% CI: 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, seemed 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 [95% CI: 2.9 to 229.3], p = 0.003; tachycardia ≥94 beats/min, OR: 7.9 [95% CI: 0.9 to 73.9], p = 0.068; syncope: OR: 2.7 [95% CI: 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 h later or suffered cardiovascular complications during the first day in the hospital. Thus, a normal H-FABP on admission seemed sufficient to rule out an adverse 30-day outcome in normotensive patients with acute PE. In contrast, the biomarker test became positive after 24 h 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, 1 patient suffered complications during the first 24 h (i.e., between the first and the second biomarker test).

### Combined approach with clinical parameters and biomarker levels for risk assessment of normotensive PE

We tested the hypothesis that biomarker levels and particularly H-FABP might have an additive prognostic value when combined with baseline clinical parameters in patients with acute PE. As mentioned in the preceding text 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 with patients with a lower heart rate. However, of 40 patients with tachycardia but normal (<6 ng/ml) H-FABP levels on admission, only 1 (2.5%) developed complications, whereas 39% of patients with tachycardia and H-FABP ≥6 ng/ml had a complicated course (Fig. 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). The H-FABP concentrations at baseline also seemed to increase the prognostic value of other clinical (e.g., syncope) or echocardiographic (RV dysfunction) findings in normotensive patients with PE (Fig. 2).

### H-FABP levels on admission also predict long-term prognosis after PE

The median follow-up time after the index episode of acute PE was 499 days (IQR 204 to 1,166 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 to

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**Table 1** Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All Patients (n = 126)</th>
<th>H-FABP ≥6 ng/ml (n = 29)</th>
<th>H-FABP &lt;6 ng/ml (n = 97)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>67 (51–74)</td>
<td>71 (57–80)</td>
<td>65 (47–72)</td>
<td>0.02</td>
</tr>
<tr>
<td>Surgery within 14 days</td>
<td>20 (16%)</td>
<td>5 (17%)</td>
<td>15 (15%)</td>
<td>0.78</td>
</tr>
<tr>
<td>Trauma within 14 days</td>
<td>7 (6%)</td>
<td>2 (7%)</td>
<td>5 (5%)</td>
<td>0.66</td>
</tr>
<tr>
<td>Malignant tumor</td>
<td>21 (17%)</td>
<td>6 (21%)</td>
<td>15 (15%)</td>
<td>0.57</td>
</tr>
<tr>
<td>History of DVT</td>
<td>42 (33%)</td>
<td>7 (24%)</td>
<td>35 (36%)</td>
<td>0.27</td>
</tr>
<tr>
<td>History of PE</td>
<td>20 (16%)</td>
<td>0</td>
<td>20 (21%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>117 (93%)</td>
<td>25 (86%)</td>
<td>92 (95%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Syncope</td>
<td>20 (16%)</td>
<td>9 (31%)</td>
<td>11 (11%)</td>
<td>0.019</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>92 (80–110)</td>
<td>100 (85–110)</td>
<td>90 (78–110)</td>
<td>0.12</td>
</tr>
<tr>
<td>GFR (ml/min/1.73 m²)</td>
<td>76.4 (55.1–94.9)</td>
<td>57.1 (41.1–83.2)</td>
<td>78.3 (61.8–95.5)</td>
<td>0.010</td>
</tr>
<tr>
<td>H-FABP (ng/ml)</td>
<td>3.4 (2.1–5.4)</td>
<td>9.9 (6.7–14.0)</td>
<td>3.0 (1.7–3.8)</td>
<td>—</td>
</tr>
<tr>
<td>NT-proBNP (pg/ml)</td>
<td>1.046 (188–2.685)</td>
<td>1.988 (425–7.930)</td>
<td>810 (173–2.431)</td>
<td>0.005</td>
</tr>
<tr>
<td>cTnT (ng/ml)</td>
<td>0.009 (0.009–0.048)</td>
<td>0.03 (0.009–0.24)</td>
<td>0.009 (0.009–0.03)</td>
<td>0.004</td>
</tr>
<tr>
<td>RV dysfunction on echocardiography</td>
<td>44/112 (39%)</td>
<td>17/28 (61%)</td>
<td>27/84 (32%)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Categorical variables are expressed as absolute n (%); continuous variables are expressed as medians with the corresponding interquartile range (25th to 75th percentile).

cTnT = cardiac troponin T; DVT = deep venous thrombosis; GFR = glomerular filtration rate; H-FABP = heart-type fatty acid-binding protein; PE = pulmonary embolism; RV = right ventricular.
11.2 ng/ml) compared with survivors (3.4 [IQR 2.0 to 4.8] ng/ml; p = 0.006). Baseline NT-proBNP values also were higher in nonsurvivors as opposed to the patients who survived (2,233 [IQR 14 to 12,180] pg/ml vs. 788 [IQR 173 to 2,374] pg/ml; p = 0.001), whereas cTnT levels on admission did not differ between nonsurvivors and survivors (0.013 [IQR 0.007 to 0.19] ng/ml vs. 0.009 [IQR 0.009 to 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 [95% CI: 1.6 to 8.2], p = 0.002; malignant tumor, OR: 5.3 [95% CI: 2.4 to 11.5], p < 0.0001; tachycardia ≥94 beats/min, OR: 1.9 [95% CI: 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 (Fig. 3, upper panel). In contrast, neither elevation of cTnT nor elevation of NT-proBNP at presentation predicted an increased probability of death during the follow-up period (Fig. 3).

**Discussion**

This study evaluated the usefulness of cardiac biomarkers and particularly H-FABP in the risk stratification of acute PE. In contrast to previously published studies that 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 seemed superior to that of previously validated biomarkers such as cardiac troponins and natriuretic peptides and to the detection of RV 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

**Table 2**

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

Univariable logistic regression analysis. CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.
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 might also be of prognostic value in normotensive patients (9). By contrast, 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. Right ventricular dysfunction can also be

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

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

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

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. Abbreviations as in Figure 1.
assessed on the basis of the circulating levels of brain natriuretic peptides. However, although elevated brain natriuretic peptides 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 LV 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) might 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 might 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.

Heart-type fatty acid-binding protein is an early indicator of myocardial injury that has been evaluated in the diagnosis and triage of acute coronary syndromes. Compared with cardiac troponins, H-FABP testing offers a number of potential advantages (discussed in Puls et al. [15]) that are related to its small molecular size (very early release after injury), its relative myocardial specificity that resembles that of the myocardial band 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 seems to possess both higher sensitivity and higher cardiospecificity compared with 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 2 studies that 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 focused on the outcome of initially normotensive patients with PE 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), whereas 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 h, and thus repetitive measurements of the biomarker might 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 might (also) have affected long-term outcome after acute PE. In this regard, the exclusion of 14 patients who were lost to follow-up might 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 might thus serve as “global” indicators of poor outcome after acute PE (23).

Although preliminary data suggest that H-FABP might also reflect the aggressiveness and prognosis of some carcinomas, the most plausible explanation of our findings might 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 seem particularly useful for the identification of low-risk patients who might be eligible for early discharge and home treatment (5,33). In search of an optimal strategy for identifying a true “intermediate-risk” group with RV 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” might be a particularly attractive option for clinicians, because 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) might limit the interpretation of our multivariable regression models.

Conclusions

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

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