Highly sensitive troponin T assay in normotensive patients with acute pulmonary embolism

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Received 8 April 2010; revised 8 June 2010; accepted 17 June 2010; online publish-ahead-of-print 28 June 2010

Aims
To assess the role of cardiac troponin T (cTnT) levels on admission using a new, highly sensitive assay (hsTnT) in the risk assessment of normotensive patients with acute pulmonary embolism (PE).

Methods and results
We prospectively studied 156 consecutive normotensive patients with confirmed PE. The prognostic value of hsTnT at baseline was compared with the conventional cTnT troponin assay and with N-terminal pro-brain natriuretic peptide concentrations. Long-term follow-up was available for 153 patients (98.1%). Highly sensitive troponin T values ranged from 0.001 to 357.2 pg/mL [median 27.2 (25th–75th percentile 9.4–69.4) pg/mL]. Overall, 100 patients (64%) had hsTnT ≥14 pg/mL. Baseline hsTnT was higher in patients with an adverse 30-day outcome (≥1: death, need for catecholamines, endotracheal intubation, or cardiopulmonary resuscitation) compared with an uncomplicated course [71.7 (35.5–117.9) vs. 26.4 (9.2–68.2) pg/mL; P = 0.027]. The cut-off value of 14 pg/mL showed an excellent prognostic sensitivity and negative predictive value (both 100%). In comparison, as many as 50% of the patients with an adverse early outcome would have been misclassified as low risk by cTnT (cut-off 0.03 ng/mL). Logistic regression indicated a two-fold increase in the risk of an adverse outcome for each increase of hsTnT by 1SD of the natural logarithm (P = 0.037). Patients with elevated hsTnT levels had a reduced probability of long-term survival (P = 0.029 by log-rank); by Cox’s regression analysis, hsTnT was the only laboratory biomarker predicting an elevated risk of death over the long term.

Conclusion
Highly sensitive troponin T assays may be capable of improving risk stratification of non-high-risk PE.

Keywords
Pulmonary embolism • Highly sensitive troponin • Natriuretic peptides • Biomarkers • Prognosis • Risk assessment

Introduction
Recent guidelines emphasize the importance of early risk stratification of patients with acute pulmonary embolism (PE).1 Consensus exists that patients presenting with refractory arterial hypotension (systolic blood pressure <90 mmHg or a pressure drop ≥40 mmHg for ≥15 min) or shock indicating overt right ventricular (RV) failure are particularly at high risk of early death and should therefore undergo prompt recanalization treatment.1,3 On the other hand, the strategies for prognostic assessment of patients who are haemodynamically stable on admission (non-high-risk PE) remain controversial to date.3 Laboratory biomarkers and particularly elevated circulating levels of cardiac troponins T and I were associated with an increased risk of death or complications during the acute phase of PE, but most of the studies published thus far failed to exclude haemodynamically unstable patients who are at high risk anyway and do not necessitate further risk stratification.4 In fact, a recent cohort study5 as well as a meta-analysis6 focusing on patients with non-high-risk PE questioned the prognostic value of cardiac troponins in the absence of arterial hypotension. Moreover, cardiac troponin concentrations on admission did not appear to predict the patients’ outcome beyond discharge from the hospital.7
Conventional troponin assays are characterized by inadequate precision at the lower detection limit. As a consequence of the low prognostic sensitivity and negative predictive value of these assays, repeated troponin measurements may be required for risk assessment both in patients with acute chest pain and in those with confirmed acute PE. In order to overcome these limitations, a new generation of highly sensitive troponin assays were developed which are capable of defining the 99th percentile of a normal (healthy) reference population with a coefficient of variation (CV) of <10%. Recent studies in patients with acute myocardial infarction indicated an excellent diagnostic performance of these assays and the potential to improve early risk stratification.

In the present study, we assessed the prognostic value of baseline cardiac troponin T (cTnT) levels measured by a highly sensitive assay in normotensive patients with acute PE. More specifically, we sought to determine whether the new assay improves the prognostic sensitivity and negative predictive value of troponin testing, whether it increases the additive value of this biomarker to other determinants of early outcome, and whether it may also be capable of predicting long-term prognosis.

**Methods**

**Patient population and study design**

We prospectively studied consecutive patients who were diagnosed with acute PE at the Universities of Göttingen and Heidelberg between March 2007 and April 2009 and gave informed consent. For inclusion in the study, patients had to fulfill the following criteria: (i) high clinical probability of PE as documented by the Wells score, or low/intermediate probability and a positive (≥0.5 mg/L) D-dimer test and (ii) confirmation of PE by an imaging procedure (contrast-enhanced computed tomography, ventilation–perfusion lung scan, pulmonary angiography, or sonographic/phlebographic examination of the leg veins) based on the diagnostic algorithms proposed by recent guidelines and those existing before 2008.

According to the study protocol, and as described in a previous publication, preliminary consent was obtained upon admission from all patients clinically suspected of having acute PE, and blood was drawn immediately for the measurement of baseline 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, haemodynamic, and laboratory parameters were obtained using a standardized questionnaire.

Patients were excluded from analysis if they met at least one of the following criteria: (i) denial of preliminary consent or withdrawal of previously given consent for participation in the study; (ii) haemodynamic instability at presentation, defined as the presence of the following: need for cardiopulmonary resuscitation, systolic blood pressure <90 mmHg or drop of systolic blood pressure by ≥40 mmHg for ≥15 min with signs of end-organ hypoperfusion, or need for catecholamine administration to maintain adequate organ perfusion and a systolic blood pressure ≥90 mmHg; (iii) severe renal insufficiency or failure, defined as an estimated glomerular filtration rate (GFR) <30 mL/min/1.73 m² on admission; and (iv) PE as an accidental finding obtained during diagnostic workup for another suspected disease. The study protocol strongly recommended a transthoracic echocardiogram within 2 h of PE diagnosis. Right ventricular dysfunction was defined as dilatation of the rightventricle (end-diastolic diameter >30 mm from the parasternal view, or a right/left ventricle diameter ratio >1.0 from the subcostal or apical view), 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.

Thirty-day clinical follow-up data were obtained from all patients included in the study. An adverse 30-day outcome was defined as death or at least one of the following major complications: 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; endotracheal intubation; and cardiopulmonary resuscitation. Long-term survival was assessed by clinical examination of the patient at follow-up visits or by a telephone conversation with the patient or his/her treating physician at 6-month intervals after PE diagnosis. All causes of death were adjudicated by two of the authors by reviewing the patients’ medical records and the results of autopsy if performed. Biomarker levels were not used to guide the patients’ management or to monitor the effects of treatment during the hospital stay or at any time during the follow-up period, as such policy is not recommended by current guidelines. The study protocol was approved by the Ethics Committees of the Universities of Göttingen and Heidelberg.

**Laboratory parameters and biomarker testing**

Venous plasma and serum samples were collected on admission and immediately stored at −80°C. Samples were later analysed in batches after a single thaw. Concentrations of cTnT were measured by a new, highly sensitive troponin T (hsTnT) quantitative electrochemiluminescence immunoassay (Elecsys 2010 analyser, Roche Diagnostics, Mannheim, Germany) as described previously. The assay is specific for troponin T without relevant interferences and has an analytic range of 3–10 000 pg/mL. A concentration of 14 pg/mL has been identified as the 99th percentile of a healthy reference population with a CV of <10% (Roche Diagnostics; data on file). In the present study, which is the first to examine hsTnT in patients with acute PE, the concentration of 14 pg/mL was prospectively defined as distinguishing between normal and elevated biomarker levels in the study population in accordance with previous studies in patients with coronary artery disease.

Routine laboratory parameter measurements including the conventional assay for cTnT, N-terminal pro-brain natriuretic peptide (NT-proBNP), D-dimers, and creatinine were performed at the Department of Clinical Chemistry of the University of Göttingen and in the core laboratory of the University Hospital of Heidelberg. N-terminal pro-brain natriuretic peptide and cTnT levels were determined in plasma samples using quantitative electrochemiluminescence immunoassays (Elecsys 1010/2010 analyser, Roche Diagnostics). For cTnT, the detection limit is 0.01 ng/mL and the concentration with a CV of <10% is 0.03 ng/mL as specified by the manufacturer; this latter value was prospectively set as the cut-off level defining cTnT elevation. D-dimer levels were measured with a quantitative immunoturbidimetric assay (Tina-quant, Roche Diagnostics). The GFR was estimated using the Modification of Diet in Renal Disease (MDRD) study equation; renal insufficiency/chronic kidney disease was defined as GFR 30–60 mL/min/1.73 m² body-surface area, and severe renal insufficiency or kidney failure as GFR <30 mL/min/1.73 m².

**Statistical analysis**

Continuous variables were found not to follow a normal distribution as tested with the modified Kolmogorov–Smirnov test (Lilliefors’s test).
<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics of 156 normotensive (non-high-risk) patients with acute pulmonary embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>All study patients (n = 156)</td>
<td>hsTnT &lt;14 pg/mL (n = 56)</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>70 (45%)/86 (55%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67 (53–75)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.6 (24.3–31.5) (n = 151)</td>
</tr>
<tr>
<td>Symptoms on admission</td>
<td></td>
</tr>
<tr>
<td>Reported symptom onset (&lt;24 h)</td>
<td>92 (59.0%)</td>
</tr>
<tr>
<td>Tachycardia (heart rate ≥100 b.p.m.)</td>
<td>55 (35.3%)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>134 (85.9%)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>83 (53.2%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>28 (17.9%)</td>
</tr>
<tr>
<td>Comorbidities and risk factors for VTE</td>
<td></td>
</tr>
<tr>
<td>Previous history of DVT or PE</td>
<td>44 (28.2%)</td>
</tr>
<tr>
<td>Immobilization within 14 days</td>
<td>58 (37.2%)</td>
</tr>
<tr>
<td>Malignant tumour</td>
<td>30 (19.2%)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>10 (6.4%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>23 (14.7%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>20 (12.8%)</td>
</tr>
<tr>
<td>COPD or asthma</td>
<td>18 (11.5%)</td>
</tr>
<tr>
<td>Laboratory parameters and biomarkers</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.8 (0.7–1.0)</td>
</tr>
<tr>
<td>GFR &lt;60 mL/min/1.73m²</td>
<td>31 (19.9%)</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>1000 (177–2445)</td>
</tr>
<tr>
<td>NT-proBNP ≥1000 pg/mL</td>
<td>78 (50.0%)</td>
</tr>
<tr>
<td>cTnT (ng/mL)</td>
<td>0.01 (0.01–0.05)</td>
</tr>
<tr>
<td>cTnT ≥0.03 ng/mL</td>
<td>52 (33.3%)</td>
</tr>
<tr>
<td>RV dysfunction&lt;sup&gt;c&lt;/sup&gt;</td>
<td>59 (44.7%) (n = 132)</td>
</tr>
<tr>
<td>Thrombolysis&lt;sup&gt;d&lt;/sup&gt;</td>
<td>23 (14.7%)</td>
</tr>
</tbody>
</table>

Patients were stratified according to the prospectively defined cut-off value (14 pg/mL) of the highly sensitive cardiac troponin T (hsTnT) assay. Data are presented as absolute numbers (percentages) or medians (25th–75th percentile); (n) refers to the number of patients with available data.

<sup>a</sup> P-values were calculated by Fisher’s exact test.

<sup>b</sup> P-values were calculated by the Mann–Whitney U test.

<sup>c</sup> Right ventricular (RV) dysfunction was echocardiographically defined as dilatation of the right ventricle (end-diastolic diameter >30 mm from the parasymmetrical view, or right/left ventricle diameter ratio >1.0 from the subcostal or apical view) combined with evidence of right atrial hypertension (absence of the inspiratory collapse of the inferior vena cava), and in the absence of left ventricular or mitral valve disease.

<sup>d</sup> These were all initially normotensive, i.e. non-high-risk patients with acute PE. The decision to perform thrombolysis was left to the clinicians’ discretion without any influence whatsoever by the study protocol.

BMI, body mass index; b.p.m., beats per minute; VTE, venous thrombo-embolism; DVT, deep vein thrombosis; PE, pulmonary embolism; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate (estimated); cTnT, cardiac troponin T (conventional assay); NT-proBNP, N-terminal pro-brain natriuretic peptide.
They were therefore expressed as medians with corresponding 25th and 75th percentiles and compared using the unpaired Mann–Whitney U test. Categorical variables were compared using Fisher’s exact test. The following cut-off values were prospectively defined as indicating elevated biomarker concentrations: hsTnT ≥ 14 pg/mL\(^1\), cTnT ≥ 0.03 ng/mL\(^2\) and NT-proBNP ≥ 1000 pg/mL\(^3\).

Receiver operating characteristic (ROC) analysis was used to determine the area under the curve (AUC) of baseline biomarker concentrations with regard to an adverse 30-day outcome, and sensitivity, specificity, and the positive and negative predictive value of elevated biomarker levels were calculated. In addition, we calculated the net reclassification improvement (NRI) and the integrated discrimination improvement (IDI) through the use of hsTnT (compared with the conventional assay) as proposed recently\(^4\). The prognostic relevance of hsTnT levels and other baseline parameters with regard to 30-day outcome was estimated using logistic regression analysis after logarithmic transformation of the not normally distributed continuous variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. 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% CIs. 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. Comparison of the areas under the curve (ROC) was performed using MedCalc statistical software (version 9.4.1.0, Mariakerke, Belgium). All other analyses were performed using the PASW software (version 17.0, Chicago, IL, USA).

**Results**

**Baseline clinical and laboratory findings**

A total of 448 patients who were admitted to the University Hospitals of Göttingen and Heidelberg with clinical suspicion of acute PE during the study period gave preliminary consent to participate in the study. Pulmonary embolism was finally confirmed in 186 (41.5%) of these cases, and blood samples from the remaining patients were discarded. Subsequently, 30 patients (16.1%) were excluded from further analysis due to: (i) haemodynamic instability on admission (n = 17); (ii) renal failure with a GFR of < 30 mL/min/1.73 m\(^2\) (n = 8), or (iii) PE being an accidental finding on computed tomography performed for tumour staging (n = 5). None of the patients withdrew his/her consent. Thus, the final study population comprised 156 normotensive patients with acute PE.

The baseline clinical characteristics of the study patients are summarized in Table 1, second column from the left. The diagnosis of PE was confirmed by contrast-enhanced computed tomography (n = 134, 85.9%), ventilation–perfusion lung scan (n = 17, 10.9%), pulmonary angiography (n = 5, 3.2%), and sonographic or phlebographic examination of the leg veins (n = 71, 45.5%), alone or in combination. A transthoracic echocardiogram (strongly recommended by the study protocol) was performed in 132 patients (84.6%). Of these, 59 (44.7%) were diagnosed with RV dysfunction.

The distribution of hsTnT levels in the study population is displayed in Figure 1. Highly sensitive troponin T values ranged from 0.001 to 357.2 pg/mL with a median value of 27.2 (25th–75th percentile 9.4–69.4) pg/mL. Overall, 100 normotensive patients with acute PE (64.1%) had hsTnT levels above the cut-off value of 14 pg/mL. As shown in Table 1 (compare the third with the fourth column), patients with hsTnT levels ≥ 14 pg/mL were older and more likely to present with tachycardia and syncope. They also were more frequently diagnosed with congestive heart failure, a finding in accordance with the results of a previous study\(^5\), and with a GFR of < 60 mL/min/1.73 m\(^2\). By comparison, cTnT levels as determined using the conventional assay were detectable in 71 patients (45.5% of the study population) with a median value of 0.01 (25th–75th percentile 0.01–0.05) ng/mL. Furthermore, and importantly, elevated cTnT levels, defined as those lying above the cut-off value of 0.03 ng/mL, were detected in only 52 patients (33.3%) on admission. Thus, and as shown in Table 1, only 52.0% of the patients with hsTnT ≥ 14 pg/mL also had elevated troponin levels using the conventional assay.

N-terminal pro-brain natriuretic peptide levels ranged from 6 to 26 524 pg/mL with a median value of 1000 (25th–75th percentile 177–2445) pg/mL. Patients with elevated hsTnT had significantly higher levels of NT-proBNP (P < 0.001; Table 1).

**Highly sensitive troponin T compared with cardiac troponin T for predicting early outcome after acute pulmonary embolism**

Initial treatment of the study patients consisted of either anticoagulation with intravenous unfractionated heparin or subcutaneous low molecular weight heparin or fondaparinux in weight-adjusted dosages. A total of 23 patients (14.7%) received early (primary) thrombolytic therapy. Another two patients (1.3%) underwent surgical embolectomy.

During the acute phase of PE (first 30 days), eight patients (5.1%) had an adverse outcome, i.e. suffered at least one of the major complications defined in the Methods. More specifically, four patients needed catecholamine administration, whereas seven patients underwent endotracheal intubation, and one patient cardiopulmonary resuscitation; two patients (1.3%) died, both of acute PE. Baseline plasma levels of hsTnT were significantly

![Figure 1](image-url)
higher in patients with an adverse 30-day outcome (median 71.7; 25th–75th percentile 35.5–117.9 pg/mL) compared with those with an uncomplicated course (median 26.4; 25th–75th percentile 9.2–68.2 pg/mL; P = 0.027). As shown in Table 2, ROC analysis suggested that hsTnT was a reliable indicator of 30-day outcome in acute PE. The AUC was 0.732 for hsTnT (asymptotic significance P = 0.027) and 0.619 (P = 0.162) for the conventional assay cTnT (P = 0.176 for the comparison between cTnT and hsTnT). In particular, the cut-off value of 14 pg/mL for hsTnT was associated with an excellent prognostic sensitivity and a negative predictive value, which both reached 100% and were superior to those of cTnT using the cut-off value of 0.03 ng/mL (Table 2). Overall, the NRI value from low-risk to intermediate-risk PE through the use of the new, highly sensitive assay was 20.9% (P = 0.406); the IDI value, which reflects the new assay’s ability to improve average (integrated) sensitivity without sacrificing average specificity, was calculated at 2.4% (P = 0.056). Seen from the clinician’s perspective, none of the 56 patients (35.9% of the study population) with hsTnT levels of <14 pg/mL on admission developed life-threatening complications during the first 30 days, whereas 50% of the patients with an adverse early outcome would have been misclassified as being at low risk by the conventional (cTnT) assay and using the cut-off value of 0.03 ng/mL. In comparison, NT-proBNP using the previously reported cut-off concentration of 1000 pg/mL also showed an excellent prognostic sensitivity and negative predictive value with regard to short-term outcome at ROC analysis (Table 2), and the AUC did not differ significantly between hsTnT and NT-proBNP (P = 0.429). The corresponding event rates (in absolute numbers and percentages) in patient subgroups defined according to biomarker cut-off values on admission are shown in Table 3. Univariable logistic regression analysis further supported the prognostic value of hsTnT by indicating a two-fold increase in the risk of an adverse 30-day outcome for each increase of hsTnT by 1 SD of the natural logarithm (ln; P = 0.037; Table 4). In comparison, the elevation of ln cTnT was not associated with a significantly increased risk of complications (P = 0.758). Besides ln hsTnT, tachycardia, evidence of RV dysfunction in echocardiography, and elevation of ln NT-proBNP also were identified as being univariably correlated with a poor early outcome (Table 4). Finally, echocardiographic findings suggestive of RV dysfunction were reported in six of the patients (14.0%) with hsTnT levels of <14 pg/mL on admission, but none of these patients died or developed major complications during the first 30 days. The overall prognostic sensitivity of the echocardiogram was 88%, the specificity 58%, the positive predictive value 12%, and the negative predictive value 99%; the corresponding event rates (absolute numbers and percentages) are given in Table 3.

### Prognostic value of highly sensitive troponin T on top of echocardiography

We assessed the additive prognostic value of hsTnT in combination with echocardiographic findings of RV dysfunction and compared it with that of the conventional cTnT assay and with NT-proBNP. Right ventricular dysfunction on cardiac ultrasound alone was associated with a nearly 10-fold increase in the risk of complications during the hospital stay (Table 4). Whereas elevated cTnT concentrations (using 0.03 ng/mL as cut-off value) did not appear to provide additive prognostic information, the combination of echocardiography with elevated hsTnT levels increased the OR for an adverse outcome. This was further supported by a 3.9% IDI (P = 0.002) through the combination of echocardiography with the new highly sensitive assay (hsTnT) compared with echocardiography plus cTnT. Similar to (and apparently more pronounced than) hsTnT, the combination of echocardiography with NT-proBNP was associated with an almost 18-fold increased risk to develop complications (Table 4).

### Value of highly sensitive troponin T in the prediction of long-term mortality

Long-term follow-up data were available for 153 of the study patients (98.1% of the study population). Patients were followed at 6-month intervals and over a median period of 965 (25th–75th percentile 375–1521) days. During that time, 22 patients (14.4%) died. Of these, 2 deaths (9.1%) were due to the initial PE episode, 13 (59.1%) were the result of malignancy, and 3 patients (13.6%) died of pneumonia. In three further cases, the cause of death was identified as dilative cardiomyopathy, stroke, and suicide respectively; finally, in one case, the cause of death could not be confirmed with certainty. Figure 2 shows the results of the Kaplan–Meier analysis, which illustrated that patients with elevated hsTnT levels above the cut-off value had a reduced probability of long-term survival (P = 0.029), whereas cTnT ≥ 0.03 ng/mL or NT-proBNP ≥ 1000 pg/mL was not significantly associated with a poor long-term prognosis. Cox’s regression analysis (Table 5) further supported these findings by revealing that hsTnT was, besides the presence of a malignant tumour and

### Table 2  Receiver operating characteristics analysis for the predictive value of biomarkers in acute pulmonary embolism

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>AUC</th>
<th>95% CIs</th>
<th>Cut-off value</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>cTnT</td>
<td>0.647</td>
<td>0.46–0.83</td>
<td>0.03 ng/mL</td>
<td>0.50</td>
<td>0.68</td>
<td>0.08</td>
<td>0.96</td>
</tr>
<tr>
<td>hsTnT</td>
<td>0.732</td>
<td>0.60–0.87</td>
<td>14 pg/mL</td>
<td>1.00</td>
<td>0.38</td>
<td>0.08</td>
<td>1.00</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>0.817</td>
<td>0.72–0.91</td>
<td>1000 pg/mL</td>
<td>1.00</td>
<td>0.53</td>
<td>0.10</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Presented are the areas under the curve (AUC) for each biomarker and assay, also including the corresponding 95% confidence intervals (CI). PPV, positive predictive value; NPV, negative predictive value; cTnT, cardiac troponin T (conventional assay); hsTnT, highly sensitive troponin T (new assay); NT-proBNP, N-terminal pro-brain natriuretic peptide.
congestive heart failure, the only baseline variable associated with an elevated risk of death over the long term.

**Discussion**

Optimizing risk stratification of patients with acute PE before they develop overt haemodynamic instability is one of the greatest challenges in contemporary management of this frequent disease. The present study sought to determine the value of cTnT measured with a new, highly sensitive assay for improving the prognostic assessment of patients with acute PE who are normotensive on admission. Our findings obtained in 156 consecutive patients can be summarized as follows: (i) the prospectively defined cut-off value (14 pg/mL) of hsTnT was associated with an excellent prognostic sensitivity and negative predictive value, both of which reached 100% and were superior to those of cTnT using the cut-off value of 0.03 ng/mL; (ii) 50% of the patients who had an adverse early outcome would have been misclassified as being at low risk by the conventional assay; (iii) hsTnT, but not cTnT, provided additive prognostic information when combined with evidence of RV dysfunction in echocardiography; and (iv) although NT-proBNP also exhibited an excellent prognostic sensitivity, negative predictive value, and additive value in combination with echocardiography when tested for short-term outcome, hsTnT was, besides malignancy and congestive heart failure, the only baseline variable significantly associated with an elevated risk of death over the long term.

Strategies for risk stratification and risk-adjusted management of acute PE have been a major focus of interest during the past decade. Earlier registry data appeared to support the value of echocardiographic findings in the diagnosis of acute RV dysfunction in normotensive patients and the identification of possible candidates for thrombolytic treatment (reviewed in reference 23). However, echocardiographic criteria of RV dysfunction have been characterized by a lack of standardization and homogeneity, which was reflected in an overall moderate positive and negative predictive value of this modality in a recent meta-analysis. In the present study, echocardiographic findings suggestive of RV dysfunction were reported in up to 14% of the patients with normal troponin levels using the highly sensitive assay, but none of these patients died or developed major complications during the first 30 days.

A number of studies have evaluated the prognostic value of cardiac troponins I or T (determined by conventional assays) in acute PE. Overall, the elevation of cardiac troponin levels was associated with an adverse early outcome as confirmed by a meta-analysis of 20 studies conducted between 1998 and 2007. However, conventional troponin assays may be too insensitive and thus incapable of ruling out an adverse outcome when performed during the first hours after symptom onset, thus requiring repeated measurements. Moreover, due to the lack of adequate precision at the lower detection limit, the 99th percentile of a normal reference population could not be defined using conventional troponin assays, and this has precluded the agreement on a cut-off value complying with the stipulated criteria for the definition of myocardial infarction and necrosis. The new highly sensitive troponin assay used in the present study appears to overcome these limitations. Focusing on a population of 156 consecutive patients who were haemodynamically stable at diagnosis, and using a prospectively defined and validated concentration of 14 pg/mL as the cut-off value, we could now show a 100% sensitivity and negative predictive value of baseline hsTnT levels with regard to the 30-day risk of death or major complications. Thus, a negative hsTnT test on admission appeared capable of ruling out an adverse early outcome of acute PE, which was in contrast with the rather poor performance of the conventional assay. As debate continues regarding the feasibility and safety of home treatment of acute PE, the new highly sensitive troponin assays, employed either alone or in combination with clinical scores.
Figure 2. Kaplan–Meier analysis of survival following acute non-high-risk pulmonary embolism. Probability of long-term survival was calculated according to the baseline concentrations of cardiac troponin T using the conventional assay (cTnT; upper panel), highly sensitive cardiac troponin T (hsTnT; middle panel), and N-terminal pro-brain natriuretic peptide (NT-proBNP; lower panel). The displayed $P$-values were calculated using the log-rank test.
might prove useful for identifying low-risk patients who can be discharged early and treated on an outpatient basis.

Previous studies by our group and others have suggested that cardiac troponin levels (determined by the conventional assay) may add to the prognostic value of echocardiography in identifying patients with an elevated PE-related risk. However, it has remained uncertain whether this approach may also improve risk stratification of haemodynamically stable, non-high-risk patients. In the present study, using logistic regression analysis, we found that the addition of hsTnT levels, but not those measured with the conventional assay, possessed an additive value to echocardiography in predicting an adverse outcome and thus defining intermediate-risk PE. These findings were further supported by a significant 3.9% IDI through the combination of echocardiography with the hsTnT compared with the combination of echocardiography with cTnT.

Our results may be of particular relevance with regard to the Pulmonary Embolism International Thrombolysis Trial (PEITHO), an ongoing multinational randomized trial which plans to enrol a total of 1000 patients with acute PE and seeks to determine whether normotensive patients with RV dysfunction on echocardiography (or computed tomography) plus evidence of myocardial injury indicated by a positive troponin test may benefit from early thrombolytic treatment (EudraCT number, 2006-005328-18). The results of the present study suggest that the choice of the assay for measuring baseline cardiac troponin levels and the definition of a prognostically relevant cut-off value of the biomarker may need to be revised in order to successfully address the hypothesis of PEITHO.

Circulating levels of NT-proBNP on admission also exhibited an excellent prognostic sensitivity. This is in agreement with a meta-analysis of 13 studies on the prognostic value of natriuretic peptides in acute PE. In fact, the additive value of NT-proBNP to echocardiography with regard to early outcome appeared to be even higher than that of hsTnT in our study population. Over a median follow-up period of 965 days, which makes the present study the longest prospective follow-up investigation after acute PE to date, elevated hsTnT levels on admission were significantly correlated with long-term survival, whereas NT-proBNP reached borderline significance both in the Cox regression ($P = 0.065$) and Kaplan–Meier analysis ($P = 0.056$). On the other hand, limitations of natriuretic peptide testing in PE include the lack of a widely accepted and prospectively validated cut-off concentration and the confounding effects of pre-existing abnormalities in the left ventricular function.

The relatively low number of events in the acute phase of PE is a potential limitation of the present study, which was not powered to demonstrate a superiority of hsTnT over the conventional assay, or possibly over NT-proBNP, in a direct (head-to-head) comparison. In particular, the 30-day mortality rate was lower than that reported for normotensive patients with RV dysfunction in two large registries. On the other hand, our results are largely in agreement with the mortality rates found in two more recent major thrombolysis trials. Finally, it cannot be excluded that the relatively high rate (14.7%) of early thrombolysis in our study population partly affected the patients’ outcome.

In conclusion, the results of the present study suggest that the use of an hsTnT assay may improve the risk stratification of patients with acute PE. Although our study did not directly assess the impact of troponin T levels on the management of PE, our findings indicate that the highly sensitive assay may help identify (i) low-risk patients and thus possible candidates for home treatment; (ii) patients with an elevated risk of an adverse early outcome, particularly when used in combination with echocardiography; and (iii) patients who may need closer long-term follow-up because of an increased risk of late mortality.

**Acknowledgements**

We are grateful to Dr David Jiménez, Ramón y Cajal Hospital and Alcalá de Henares University, Madrid, Spain, for his assistance in calculating NRI and IDI values. We also thank Dr Klaus Jung, Department of Medical Statistics, University of Göttingen, Germany, for his advice regarding statistical analysis.

**Conflict of interest:** H.K. developed the conventional assay for troponin T and holds a patent jointly with Roche Diagnostics, Germany. H.K. and E.G. received grants, research funding, and honorary for lectures from Roche Diagnostics, Germany.

**References**


