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Predictive Value of the High-Sensitivity Troponin T Assay and the Simplified Pulmonary Embolism Severity Index in Hemodynamically Stable Patients With Acute Pulmonary Embolism A Prospective Validation Study

Mareike Lankeit, MD; David Jiménez, MD; Maciej Kostrubiec, MD; Claudia Dellas, MD; Gerd Hasenfuss, MD; Piotr Pruszczyk, MD; Stavros Konstantinides, MD

Background—The new, high-sensitivity troponin T (hsTnT) assay may improve risk stratification of normotensive patients with acute pulmonary embolism (PE). We externally validated the prognostic value of hsTnT, and of the simplified Pulmonary Embolism Severity Index (sPESI), in a large multicenter cohort.

Methods and Results—We prospectively examined 526 normotensive patients with acute PE; of those, 31 (5.9%) had an adverse 30-day outcome. The predefined hsTnT cutoff value of 14 pg/mL was associated with a high prognostic sensitivity and negative predictive value, comparable to those of the sPESI. Both hsTnT \geq 14 pg/mL (OR, 4.97 [95% CI, 1.71–14.43]; $P=0.003$) and sPESI \geq 1 point(s) (OR, 9.51 [2.24–40.29]; $P=0.002$) emerged, besides renal insufficiency (OR, 2.97 [1.42–6.22]; $P=0.004$), as predictors of early death or complications; in a multivariable model, they remained independent predictors of outcome ($P=0.044$ and 0.012, respectively). A total of 127 patients (24.1%) were identified as low risk by a sPESI of 0 and hsTnT $<$ 14 pg/mL; none of them had an adverse 30-day outcome. During 6-month follow-up, 52 patients (9.9%) died. Kaplan-Meier analysis illustrated that patients with hsTnT \geq 14 pg/mL ($P=0.001$) and those with sPESI \geq 1 ($P<0.001$) had a decreased probability of 6-month survival. Patients with sPESI of 0 and hsTnT $<$ 14 pg/mL at baseline had a 42% reduction in the risk of dying (hazard ratio, 0.58 [0.01–0.42]; $P=0.005$).

Conclusions—The hsTnT assay and the sPESI improve risk stratification of acute PE. Combination of both modalities may yield additive prognostic information and particularly identify possible candidates for out-of-hospital treatment. (*Circulation*. 2011;124:2716-2724.)

Key Words: embolism ■ pulmonary heart disease ■ prognosis ■ complications

Current guidelines emphasize the importance of an early risk stratification of patients with acute pulmonary embolism (PE) to allow assessment of the individual prognosis and guide therapeutic decision-making.¹ Although hypotensive, hemodynamically unstable patients with massive PE can easily be recognized as a high-risk subgroup for which treatment strategies are clearly defined, the best tool (or combination of tools) for stratifying normotensive patients into an intermediate-risk (submassive PE) and a low-risk subgroup remain controversial to date.^{2,3} Laboratory biomarkers and particularly cardiac troponins have been demonstrated to identify patients with an elevated risk of death and

complications during the acute phase of PE.⁴ However, most of the studies failed to exclude hemodynamically unstable patients who clearly need no further risk stratification. Furthermore, and importantly, recent studies did not address whether biomarker levels below the defined cutoff values might also be eligible for the identification of low-risk patients. In this regard, our recent findings in a derivation cohort suggested that circulating troponin T levels determined with a new, highly sensitive assay (high-sensitivity troponin T [hsTnT]) may be capable of improving (in comparison with older assays) the risk stratification of normotensive patients with acute PE, and, in particular, that they

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may identify patients who are at low risk of an adverse early outcome.⁵

Clinical Perspective on p 2724

Besides laboratory markers, clinical prediction rules have also been shown to be helpful in the prognostic assessment of patients with acute PE.^{6–10} The Pulmonary Embolism Severity Index (PESI) is the most extensively studied clinical score to date.^{6,11–14} Recently, it was reported that reliable prognostic information can also be obtained with a simplified version of this score (the sPESI), which reduces the technical complexity of the original prediction rule by focusing on 6 equally weighted variables: age >80 years, history of cancer, history of chronic cardiopulmonary disease, heart rate ≥ 110 bpm, systolic blood pressure <100 mm Hg, and arterial oxyhemoglobin saturation <90%.¹⁵ Patients with ≥ 1 point(s) were classified as high-risk patients, whereas low-risk patients with a score of 0 points exhibited a mortality rate of 1%.¹⁵

The aim of the present study was to externally validate the predictive value of both hsTnT and the sPESI in a multicenter, multinational cohort. We further sought to determine whether combination of the 2 tools is capable of providing important additive prognostic information and particularly whether it permits the identification of low-risk patients with an even higher degree of safety than either test alone.

Methods

Patient Population and Study Design

Between August 2007 and October 2010, we prospectively included consecutive patients who were diagnosed with acute PE at 12 cooperating European centers in 3 countries. The participating sites are listed in the Appendix in the online-only Data Supplement.

All sites followed the same study protocol. For inclusion in the study, patients had to fulfill all of the following criteria⁵: (1) high clinical probability of PE as documented by the Wells score, or low/intermediate probability with a positive (≥ 0.5 mg/L) D-dimer test; and (2) confirmation of PE by contrast-enhanced multidetector computed tomography or ventilation-perfusion lung scan, or by echocardiography showing the presence of mobile thrombi in the right atrium or ventricle, or in the proximal portions of the pulmonary artery. Patients were excluded from the study for the following reasons (at least one present): (1) hemodynamic instability at presentation (need for cardiopulmonary resuscitation; systolic blood pressure <90 mm Hg, or a drop of systolic blood pressure by ≥ 40 mm Hg for ≥ 15 minutes, with signs of end-organ hypoperfusion; or need for catecholamine administration to maintain adequate organ perfusion and a systolic blood pressure ≥ 90 mm Hg); (2) PE being an accidental finding obtained during diagnostic workup for another suspected disease; (3) denial of consent, or withdrawal of previously given consent for participation in the study; and (4) in the case of the University of Göttingen, inclusion of the patient in the derivation cohort for assessment of the prognostic value of hsTnT in acute PE.⁵

The study protocol strongly recommended a transthoracic echocardiogram within 24 hours of PE diagnosis. Right ventricular (RV) dysfunction was defined as dilatation of the right ventricle (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 absence of the inspiratory collapse of the inferior vena cava or an elevated systolic gradient through the tricuspid valve (>30 mm Hg), in the absence of left ventricular or mitral valve disease.^{2,5}

For calculation of the sPESI, one point was given for the presence of each one of the following variables: (1) age >80 years; (2) history

of cancer; (3) history of chronic cardiopulmonary disease (heart failure or pulmonary disease); (4) heart rate ≥ 110 bpm; (5) systolic blood pressure 90 to 100 mm Hg; and (6) arterial oxyhemoglobin saturation <90% measured at the time of PE diagnosis. Missing data were considered to be normal.^{6,15} Patients were classified into either a low-risk (0 points) or a high-risk (≥ 1 point[s]) group.¹⁵

Treatment decisions were made by the physicians caring for the patient and not dictated by the study protocol. All patients were initially treated with intravenous unfractionated heparin, subcutaneous low-molecular-weight heparin, or fondaparinux in activated partial thromboplastin time- or weight-adjusted doses, respectively. Thrombolytic, interventional, or surgical treatment was administered if deemed appropriate by the attending physician. During the hospital stay, an oral vitamin K antagonist (therapeutic international normalized ratio, 2.0–3.0) was initiated unless contraindicated. Biomarker levels were not communicated to the clinicians and thus not used to guide the patients' management or monitor the effects of treatment during the hospital stay or at any time during the follow-up period.

Thirty-day clinical follow-up data were obtained from all patients included in the study. Long-term (6-month) status 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. The primary end point of the study was adverse 30-day outcome, defined as death from any cause or at least one of the following major complications⁵: (1) need for intravenous catecholamine administration (with the exception of dopamine, at a rate of ≤ 5 $\mu\text{g}/\text{kg}$ per min) to maintain adequate tissue perfusion and prevent or treat cardiogenic shock; (2) endotracheal intubation; and (3) cardiopulmonary resuscitation. The secondary end points were (1) symptomatic recurrent PE within 30 days (confirmed by a new perfusion defect involving 75% or more of a lung segment on ventilation-perfusion lung scan, or by the presence of a new at least segmental intraluminal filling defect or an extension of a previous filling defect on computed tomography)¹⁶; (2) major bleeding within 30 days (clinically overt bleeding that was associated with a decrease of hemoglobin levels of 20 g/L or more; led to transfusion of 2 or more units of red blood cells; resulted in hemodynamic compromise requiring emergency intervention (replacement of fluid and/or blood products, inotropic support, or surgical/interventional treatment); was intracranial, retroperitoneal, occurred in a critical site, or contributed to death)¹⁷; and (3) all-cause mortality within 6-month follow-up. The cause of death was adjudicated by three of the authors (M.L., D.J., and M.K.) by reviewing the patients' medical records and the results of autopsy if performed. Death was determined to be PE-related if it was confirmed by autopsy, or if it followed a clinically severe PE episode, either immediately or shortly after an objectively confirmed recurrent event, and in the absence of an alternative diagnosis.

The study protocol was approved by the ethics committees of the participating sites and all patients gave informed consent for their participation in the study.

Laboratory Parameters and Biomarker Testing

Venous plasma and serum samples were collected on admission and immediately stored at -80°C . Samples were later shipped to the core laboratory of the University of Göttingen and analyzed in batches after a single thaw. Concentrations of cardiac troponin T were measured centrally, in the laboratory of the Departments of Clinical Chemistry of the University of Göttingen, by a highly sensitive (hsTnT) quantitative electrochemiluminescence immunoassay (Elecsys 2010 analyzer, Roche Diagnostics, Mannheim, Germany) as previously described.⁵ The assay is specific for troponin T without relevant interferences and has an analytic range from 3 to 10 000 pg/mL.¹⁸ In the derivation cohort examined in a previous study, a concentration of 14 pg/mL was established as distinguishing between normal and elevated biomarker levels in acute PE.⁵

Routine laboratory parameter measurements including D-dimers and creatinine were performed at the Departments of Clinical Chemistry of the University of Göttingen, the Central Laboratory of Infant Jesus Teaching Hospital, Warsaw, Poland, and the Biochemistry Department at Ramón y Cajal Hospital, Madrid, Spain. The

Table 1. Baseline Characteristics, Clinical Symptoms, and Relevant Findings on Admission of 526 Hemodynamically Stable Patients With Acute Pulmonary Embolism

	All Study Patients (n=526)	hsTnT <14 pg/mL (n=214)	hsTnT ≥14 pg/mL (n=312)	P
Sex (male/female)	266 (51%)/260 (49%)	105 (49%)/109 (51%)	161 (52%)/151 (48%)	0.595†
Age, years	71 (55–79)	65 (44–75)	74 (65–81)	0.001*
Age >80 y	108 (20.5%)	19 (8.9%)	89 (28.5%)	<0.001†
Symptoms on admission				
Systolic blood pressure (mm Hg)	130 (115–147) (n=523)	130 (120–150) (n=212)	130 (114–145) (n=311)	0.035*
Systolic blood pressure 90–100 mm Hg	25 (4.8%) (n=523)	2 (0.9%) (n=212)	23 (7.4%) (n=311)	0.001†
Heart rate (bpm)	90 (80–107) (n=524)	86 (75–98) (n=213)	95 (84–110) (n=311)	<0.001*
Tachycardia (HR ≥110 bpm)	117 (22.3%) (n=524)	26 (12.2%) (n=213)	91 (29.3%) (n=311)	<0.001†
Oxyhemoglobin saturation <90%	96 (20.6%) (n=466)	18 (9.7%) (n=186)	78 (27.9%) (n=280)	<0.001†
Dyspnea	424 (80.6%)	160 (74.8%)	264 (84.6%)	0.007†
Chest pain	229 (43.5%)	119 (55.6%)	110 (35.3%)	<0.001†
Syncope	91 (17.3%)	21 (9.8%)	70 (22.4%)	<0.001†
Comorbidities and risk factors for VTE				
History of DVT or PE	115 (21.9%) (n=525)	55 (25.7%)	60 (19.3%) (n=311)	0.087†
Immobilization in the past 14 d	131 (25.0%) (n=525)	38 (17.8%)	93 (29.9%) (n=311)	0.001†
Malignant tumor	85 (16.2%) (n=525)	31 (14.5%)	54 (17.4%) (n=311)	0.401†
Congestive heart failure	61 (11.6%) (n=525)	15 (7.0%)	46 (14.8%) (n=311)	0.008†
Chronic pulmonary disease	67 (12.8%) (n=525)	13 (6.1%)	54 (17.4%) (n=311)	<0.001†
Renal insufficiency‡	175 (33.3%) (n=525)	39 (18.2%)	136 (43.7%) (n=311)	<0.001†
RV dysfunction§	160 (35.1%) (n=456)	34 (18.6%) (n=183)	126 (46.2%) (n=273)	<0.001†
sPESI ≥1 point(s)	328 (62.4%)	87 (40.7%)	241 (77.2%)	<0.001†

Patients were stratified according to the prospectively defined cutoff value (14 pg/mL) of the hsTnT assay on admission. Data are presented as absolute numbers (percentages) or medians (25th–75th percentile); (n) refers to the number of patients with available data; P values were calculated by the Mann-Whitney U test (*) or Fisher Exact test (†). hsTnT indicates high-sensitivity troponin T; HR, heart rate; VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; RV, right ventricular; sPESI, simplified Pulmonary Embolism Severity Index; and GFR, glomerular filtration rate (estimated).

‡Renal insufficiency was defined as GFR <60 mL/min per 1.73 m².

§RV dysfunction was echocardiographically defined as dilatation of the right ventricle (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 absence of the inspiratory collapse of the inferior vena cava or an elevated systolic gradient through the tricuspid valve (>30 mm Hg), in the absence of left ventricular or mitral valve disease.

||The sPESI assigns 1 point for each of the following variables: age >80 years, heart rate ≥110 bpm, systolic blood pressure <100 mm Hg, oxyhemoglobin saturation <90%, congestive heart failure or chronic pulmonary disease, and malignant tumor, and it allows categorization in patients with low risk (0 points) and patients with high risk (≥1 point[s]). Missing variables were considered to be normal.^{6,15}

glomerular filtration rate was estimated by the use of the Modification of Diet in Renal Disease study equation; renal insufficiency was defined as glomerular filtration rate <60 mL/min per 1.73 m² body-surface area.

Statistical Analysis

Continuous variables were found not to follow a normal distribution as tested with the modified Kolmogorov-Smirnov test (Lilliefors test). They were therefore expressed as medians with corresponding 25th and 75th percentiles and compared using the unpaired Mann-Whitney U test. Categorical variables were expressed as absolute numbers or percentages with the corresponding 95% confidence interval (CI) and compared using the Fisher exact test or χ^2 test, as appropriate. Receiver operating characteristic analysis was used to determine the area under the curve of hsTnT and the dichotomized sPESI with regard to an adverse 30-day outcome, and sensitivity, specificity, and the positive and negative predictive value of elevated hsTnT levels and the sPESI were calculated. The prognostic relevance of hsTnT levels, the sPESI, and other baseline parameters (listed in Table 1) with regard to 30-day outcome was estimated by using logistic regression analysis. Odds ratios (OR) and the corresponding 95% CIs were calculated. To identify predictors of 6-month mortality, Cox proportional hazards regression analysis was performed; these results are presented as hazard ratios with corre-

sponding 95% CIs. Survival rates were estimated by the Kaplan-Meier method, and statistical comparison was performed by using the log-rank test.

All tests were 2-sided and used a significance level of 0.05. All analyses were performed using the PASW software (version 18.0, Chicago, IL).

Results

Baseline Clinical and Laboratory Findings

The baseline clinical characteristics of the 526 study patients are summarized in Table 1. Diagnosis of PE was confirmed by multidetector contrast-enhanced computed tomography in 511 cases (97.1%), and by ventilation-perfusion lung scan in 13 (2.5%). In 2 patients (0.4%), the diagnosis of PE was established by echocardiographic criteria (explained in the Methods section). Overall, a transthoracic echocardiogram was performed in 456 patients (86.7%); of these, 160 (35.1%) were diagnosed with RV dysfunction.

On admission, cardiac troponin T levels, determined with the highly sensitive assay, ranged from 2.9 to 3460 pg/mL, with a median value of 19.3 pg/mL (25th–75th percentile,

Table 2. Outcome of the Study Patients According to the Baseline Levels of hsTnT and the sPESI

	hsTnT <14 pg/mL (n=214)	hsTnT ≥14 pg/mL (n=312)	<i>P</i>	sPESI 0 Points (n=198)	sPESI ≥1 Point(s) (n=328)	<i>P</i>	sPESI 0 Points and hsTnT <14 pg/mL (n=127)	sPESI ≥1 Point(s) or hsTnT ≥14 pg/mL (n=158)	sPESI ≥1 Point(s) and hsTnT ≥14 pg/mL (n=241)	<i>P</i>
Adverse 30-d outcome	4 (1.9%)	27 (8.7%)	0.001*	2 (1.0%)	29 (8.8%)	<0.001*	0	6 (3.8%)	25 (10.4%)	<0.001†
All-cause death	3 (1.4%)	24 (7.7%)	0.001*	1 (0.5%)	26 (7.9%)	<0.001*	0	4 (2.5%)	23 (9.5%)	<0.001†
PE-related death	0	8 (2.6%)	0.024*	0	8 (2.4%)	0.028*	0	0	8 (3.3%)	0.008†
Recurrent PE	3 (1.4%)	6 (1.9%)	0.744*	2 (1.0%)	7 (2.1%)	0.494*	1 (0.8%)	2 (1.3%)	5 (2.1%)	0.601†
Major bleeding	3 (1.4%)	12 (3.8%)	0.115*	4 (2.0%)	11 (3.4%)	0.431*	1 (0.8%)	5 (3.2%)	9 (3.7%)	0.261†
Death at 6-mo follow-up	10 (4.7%)	42 (13.5%)	0.001*	5 (2.5%)	47 (14.3%)	<0.001*	1 (0.8%)	13 (8.2%)	38 (15.8%)	<0.001†

P values were calculated by the Fisher Exact test (*) or χ^2 test for trend (†). HsTnT indicates high-sensitivity troponin T; PE, pulmonary embolism; sPESI, simplified Pulmonary Embolism Severity Index.

7.0–46.8 pg/mL). Overall, 312 patients (59.3%) had hsTnT levels above the predefined cutoff value of 14 pg/mL. As shown in Table 1, these patients were older and more frequently previously diagnosed with congestive heart failure, chronic pulmonary disease, or renal insufficiency. They also were more likely to present with systolic blood pressures between 90 and 100 mm Hg, tachycardia (heart rate \geq 110 bpm), dyspnea, and syncope.

The sPESI assigned 328 patients (62.4%) to the high-risk category (\geq 1 point[s]). These patients presented more often with elevated hsTnT levels (73.5%) in comparison with low-risk patients (35.9%; $P<0.001$).

Highly Sensitive Troponin T and Clinical Predictors of an Adverse Early Outcome

Overall, 31 patients (5.9%) reached the primary end point (adverse 30-day outcome). Of these, 27 patients died; the cause of death was directly related to the PE episode in 8 cases. With regard to the secondary end points, 9 patients (1.7%) developed symptomatic recurrent PE (fatal in 5 cases), and 15 patients (2.9%) experienced a major bleeding episode (fatal in 3 cases). In 36 patients (6.8% of the study population) who received thrombolytic therapy within 24 hours of admission, the rate of major bleeding was 8.3% as opposed to 2.4% in the absence of thrombolysis ($P=0.076$).

Table 2 displays the outcomes (mortality, PE recurrence, and major bleeding episodes) of the study patients according to the baseline levels of hsTnT and the sPESI. Patients with an adverse 30-day outcome had significantly higher levels of hsTnT (median, 57.7; 25th–75th percentile, 28.8–88.0 pg/mL) on admission in comparison with those with a favorable course (18.0 [6.4–41.6] pg/mL; $P<0.001$). Receiver operating characteristic analysis further illustrated that hsTnT was an indicator of 30-day outcome in normotensive patients with acute PE (Figure 1). The calculated area under the curve was 0.73 (95% CI, 0.65–0.82) for hsTnT, and 0.67 (0.59–0.75) for the dichotomized sPESI. As shown in Table 3, the cutoff value of 14 pg/mL for hsTnT was associated with a prognostic sensitivity of 87% and a negative predictive value (NPV) of 98%. Of the 214 patients with hsTnT levels <14 pg/mL, 4 (1.9%) had an adverse 30-day outcome and 3 died (Table 2);

none of these deaths was directly related to the PE episode. The sPESI was also associated with a high prognostic sensitivity (94%) and NPV (99%; Table 3); 2 (1.0%) of 198 patients with a sPESI of 0 had an adverse outcome, and one of them died (Table 2). Notably, patients classified as being at high-risk by the sPESI showed an almost identical complication rate as patients with hsTnT \geq 14 pg/mL (8.8 versus 8.7%, respectively; Table 2).

Univariable logistic regression analysis further supported the prognostic value of both the hsTnT assay and the sPESI. Increases of hsTnT concentrations by 1 pg/mL were associated with an increase in the risk of an adverse outcome (OR, 1.00; 95% CI, 1.00–1.01; $P=0.007$); when hsTnT was dichotomized, levels \geq 14 pg/mL were associated with a nearly 5-fold increase in the risk of death or life-threatening complications (OR, 4.97 [1.71–14.43]; $P=0.003$; Table 4). Patients identified as high risk by the sPESI appeared to be at

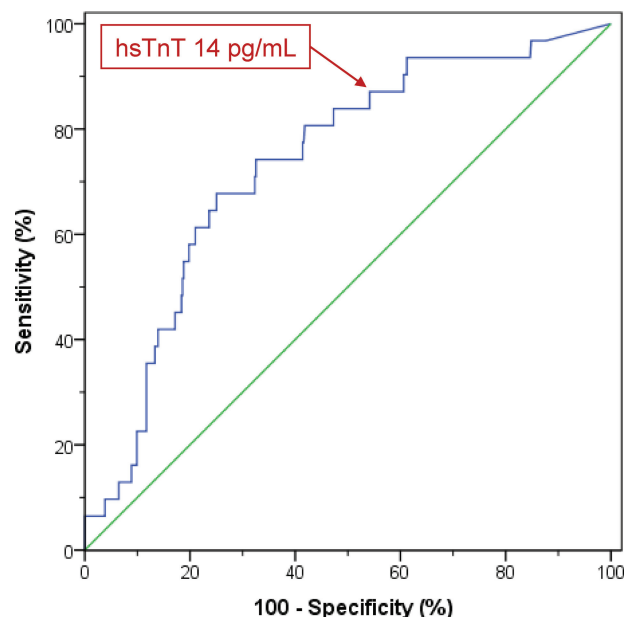


Figure 1. Receiver operating characteristics curve showing the prognostic sensitivity and specificity of hsTnT with regard to an adverse 30-day outcome.

Table 3. Value of hsTnT and the sPESI, Alone and in Combination, for Predicting an Adverse 30-Day Outcome after Acute Pulmonary Embolism

	Sensitivity	Specificity	PPV	NPV
hsTnT ≥ 14 pg/mL	0.87	0.42	0.09	0.98
sPESI ≥ 1 point(s)	0.94	0.40	0.09	0.99
hsTnT ≥ 14 pg/mL and sPESI ≥ 1 point(s)	1.00	0.26	0.08	1.00

PPV indicates positive predictive value; NPV, negative predictive value; hsTnT, high-sensitivity troponin T; and sPESI, simplified Pulmonary Embolism Severity Index.

even higher risk for an unfavorable course (OR, 9.51 [2.24–40.29]; $P=0.002$; Table 4). The prognostic relevance of the clinical score is supported by the observation that several of the clinical baseline variables comprising the sPESI (age >80 years, history of chronic cardiopulmonary disease, arterial oxyhemoglobin saturation $<90\%$) were univariably (and individually) correlated with a poor outcome, as was renal insufficiency (glomerular filtration rate <60 mL/min per 1.73 m²; Table 4). Importantly, when the sPESI and hsTnT were entered into a multivariable model, their predictive values (OR, 3.07 [1.03–9.16] and 6.63 [1.52–28.91], respectively) remained independent from each other ($P=0.044$ and 0.012, respectively). Moreover, the prognostic information provided by hsTnT (4.02 [1.35–11.92]; $P=0.012$) was independent from the presence of renal insufficiency (2.23 [1.05–4.76]; $P=0.038$) in multivariable logistic regression analysis. On the other hand, neither hsTnT ≥ 14 pg/mL nor a sPESI ≥ 1 appeared to predict an elevated risk of symptomatic recurrence ($P=0.652$ and 0.347, respectively) or of major bleeding ($P=0.112$ and 0.378, respectively) by logistic regression analysis.

Table 4. Predictors of an Adverse 30-Day Outcome

	OR	95% CI	<i>P</i>
hsTnT ≥ 14 pg/mL	4.97	1.71–14.43	0.003
GFR <60 mL/min per 1.73 m ²	2.97	1.42–6.22	0.004
Chest pain	0.36	0.15–0.85	0.020
sPESI ≥ 1 point(s)	9.51	2.24–40.29	0.002
Age >80 y	3.04	1.44–6.42	0.004
History of chronic cardiopulmonary disease	4.87	2.32–10.21	<0.001
History of cancer	1.56	0.65–3.74	0.323
Heart rate ≥ 110 bpm	2.01	0.93–4.32	0.075
Systolic blood pressure <100 mm Hg	0.65	0.09–4.97	0.678
Arterial oxyhemoglobin saturation $<90\%$	2.39	1.10–5.21	0.028

Variables found to significantly predict an adverse 30-day outcome by univariable analysis are displayed; in addition, all variables included in the sPESI are shown. Odds ratios (OR) with the respective 95% confidence intervals (CI) for an adverse 30-day outcome were calculated by logistic regression analysis. hsTnT indicates high-sensitivity troponin T; GFR, glomerular filtration rate; and sPESI, simplified Pulmonary Embolism Severity Index.

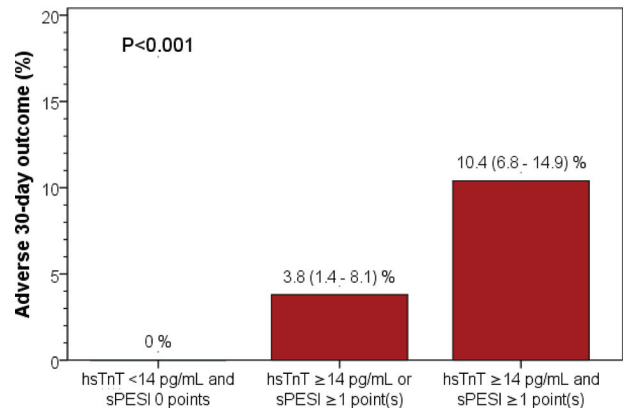


Figure 2. Frequency of an adverse 30-day outcome according to baseline hsTnT levels and the sPESI. Numbers indicate percentages (with corresponding 95% confidence intervals). hsTnT indicates high-sensitivity troponin T assay; sPESI, simplified Pulmonary Embolism Severity Index.

Combining the sPESI and hsTnT for Identification of Low Risk

Overall, 214 patients (40.7%) were identified as being at low risk by the hsTnT assay, in comparison with 198 (37.6%) by the sPESI. Importantly, we found that none of the 127 patients (24.1% of the study population) with a simplified PESI of 0 and hsTnT <14 pg/mL on admission had an adverse outcome within the first 30 days (Figure 2). Interestingly, in 113 of these patients who had an echocardiographic examination at presentation, RV dysfunction was reported on ultrasound in 17 (15.0%), but apparently did not adversely affect the 30-day clinical outcome. Overall, the combination of the biomarker (measured with the high-sensitivity assay) with the clinical score was associated with an excellent prognostic sensitivity and NPV, both of which reached 100%. On the other hand, the complication rate rose from 0% to 3.8% (95% CI, 1.4–8.1) in patients with sPESI ≥ 1 or hsTnT ≥ 14 pg/mL, and further to 10.4% (6.8–14.9) in those with sPESI ≥ 1 and hsTnT ≥ 14 pg/mL ($P<0.001$; Figure 2).

HsTnT and sPESI for Prediction of 6-Month Mortality

Patients were followed for 6 months; only 6 patients (1.1%) did not complete the entire observation period. During the follow-up period, a total of 52 deaths (9.9% of the population) were recorded. Of these, 8 (15.4%) were due to the initial PE event (all within the first 30 days), 5 (9.6%) to fatal recurrent PE (only one occurred after day 30), and 3 (5.8%) to fatal bleeding (all within the first 30 days). In addition, 16 deaths (30.8%) were the result of malignancy, 13 patients (25.0%) died of decompensated cardiac or pulmonary disease, and 3 (5.8%) died of pneumonia. In 2 other cases (3.8%), the cause of death was severe renal insufficiency. Finally, 1 patient died of amyotrophic lateral sclerosis. Of 214 patients with hsTnT <14 pg/mL on admission, 10 (4.7%) died; of 198 patients with a sPESI of 0, 5 (2.5%) died.

Kaplan-Meier analysis illustrated that hsTnT levels above the cutoff value ($P=0.001$) and a sPESI ≥ 1 ($P<0.001$) both were associated with a reduced probability of survival at 6 months (Figure 3, top and middle, respectively). Combination

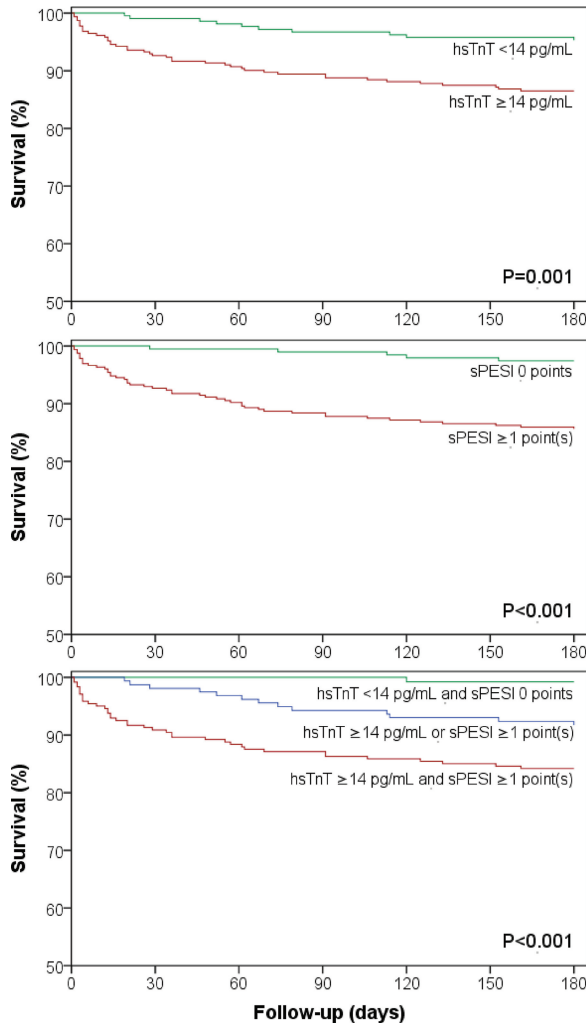


Figure 3. Probability of 6-month survival according to baseline hsTnT levels and the sPESI, alone or in combination. HsTnT indicates high-sensitivity troponin T assay; sPESI, simplified Pulmonary Embolism Severity Index.

of baseline hsTnT levels with the sPESI allowed a more reliable identification of patients with a favorable long-term (6-month) prognosis (Figure 3, bottom, $P<0.001$; and Figure 4). Only 1 patient (0.8 [0.0–4.3]%) with a sPESI of 0 and hsTnT <14 pg/mL died within the 6-month follow-up period. By Cox regression analysis, patients with a sPESI of 0 and hsTnT <14 pg/mL had a 42% reduction in the risk of dying during the first 6 months in comparison with patients with either a sPESI ≥ 1 or hsTnT ≥ 14 pg/mL (hazard ratio, 0.58; 95% CI, 0.01–0.42; $P=0.005$). Univariable Cox regression further revealed that elevated hsTnT levels and the sPESI were, besides the presence of RV dysfunction on echocardiography and renal insufficiency, the only baseline variables predicting an elevated risk of death over the long term (Table 5, univariable model). In fact, all variables included in the sPESI (with the exception of systolic blood pressure between 90 and 100 mm Hg) were univariably identified as predictors of mortality during 6-month follow-up (data not shown). By multivariable analysis (Table 5, multivariable model), the sPESI and renal insufficiency emerged as independent predictors of 6-month mortality.

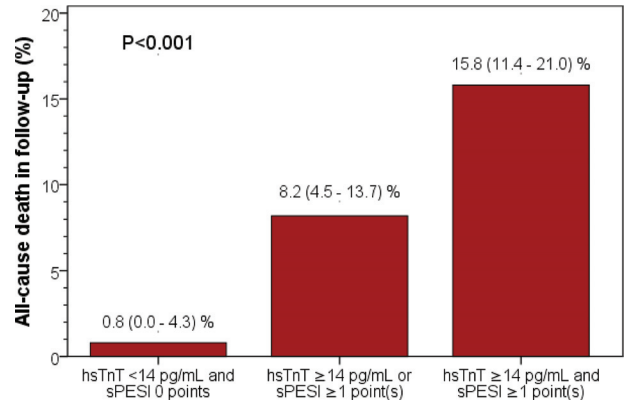


Figure 4. Frequency of all-cause mortality at 6-month follow-up according to baseline hsTnT levels and the sPESI. Numbers indicate percentages (with corresponding 95% confidence intervals). hsTnT indicates high-sensitivity troponin T assay; sPESI, simplified Pulmonary Embolism Severity Index.

Subgroup analysis confirmed that the results presented above with regard to 30-day and 6-month mortality were consistent across the participating countries and sites (data not shown).

Discussion

Our findings in a large multicenter validation cohort of 526 hemodynamically stable (normotensive) patients with acute PE can be summarized as follows: (1) the predefined hsTnT cutoff level of 14 pg/mL exhibited a high prognostic sensitivity and NPV, in particular, for excluding early PE-related death; (2) the prognostic value of hsTnT was comparable to (although it appeared slightly lower than) that of the sPESI; (3) combination of hsTnT with the sPESI improved the prediction of the patients' outcome both in the acute phase (first 30 days) and over the long term.

For an optimal management of hemodynamically stable patients with acute PE, accurate risk stratification is of crucial importance. During the past decade, strategies have mainly focused on the identification of patients with an elevated (in Europe also called intermediate)¹ risk of an early adverse outcome who might benefit from aggressive, eg, thrombolytic, treatment regimens. Laboratory markers of myocardial (right ventricular) dysfunction such as the natriuretic peptides,¹⁹ or injury such as the cardiac troponins^{4,20} or heart-type fatty acid-binding protein,^{21–23} and imaging procedures (echocardiography, computed tomography) for assessment of size and function of the right ventricle²⁴ all were reported to be useful tools in this approach. Nevertheless, their therapeutic implications remain controversial to date,^{3,25} in particular, because none of them was tested in a prospective management trial. In parallel to laboratory markers, clinical scores, such as the sPESI^{6,15} that account for the patients' baseline clinical findings and comorbidity, have been developed; they yielded promising results that appeared to be more reliable on the low-risk side of the severity spectrum.

The introduction of new, highly sensitive assays for the measurement of cardiac troponins has improved their diagnostic sensitivity.^{18,26,27} In a derivation study,⁵ our findings

Table 5. Predictors of 6-Month Mortality

	Univariable Model			Multivariable Model		
	HR	95% CI	<i>P</i>	HR	95% CI	<i>P</i>
hsTnT ≥ 14 pg/mL	3.05	1.53–6.08	0.002	1.48	0.64–3.41	0.358
GFR < 60 mL/min per 1.73 m ²	2.44	1.41–4.21	0.001	2.01	1.07–3.77	0.030
RV dysfunction	2.10	1.14–3.84	0.017	1.64	0.88–3.05	0.119
sPESI ≥ 1 point(s)	6.09	2.42–15.30	< 0.001	3.37	1.27–8.98	0.015

Only variables found to significantly predict 6-month mortality by univariable analysis are displayed. These variables were entered in the multivariable model simultaneously. Hazard ratios (HR) with the respective 95% confidence intervals (CIs) for all-cause 6-month mortality were calculated by Cox regression analysis. hsTnT indicates high-sensitivity troponin T; GFR, glomerular filtration rate; RV, right ventricular; and sPESI, simplified Pulmonary Embolism Severity Index.

suggested that a hsTnT cutoff value of 14 pg/mL may be associated with a high prognostic sensitivity and NPV with regard to an adverse 30-day outcome after acute PE. These findings further indicated that the novel hsTnT assay might be helpful for identifying possible candidates for early discharge and home treatment. In the present multicenter validation cohort enrolled in collaborating sites from 3 countries, we could confirm the prognostic value of hsTnT. In fact, the area under the curve of hsTnT (0.734) in the present study was nearly identical with that (0.732) in the derivation cohort,⁵ even though the prognostic sensitivity (87%) and NPV (98%) appeared slightly lower. Notably, none of the 3 deaths that occurred in patients with a negative hsTnT test was directly related to the PE episode. This fact probably indicates that hsTnT reliably excludes even minimal myocardial injury and thus a significant hemodynamic impact of the acute PE episode, whereas it may be less capable of accounting for the patient's comorbidity. Although the sensitivity and NPV of the sPESI (94% and 99%, respectively) appeared to be slightly higher than those of the hsTnT, 2 patients with sPESI of 0 on admission still had an unfavorable clinical course. Our results with regard to sPESI are thus in accordance with previous findings.¹⁵ Importantly, at multivariable analysis, the predictive values (odds ratios) of hsTnT and the sPESI remained independent from each other in the present study. Therefore, our results appear to support the notion that hsTnT could be used as an alternative to sPESI for risk stratification of normotensive patients with acute PE, in particular, in cases in which the variables required for the calculation of the clinical score are not readily available.

Admittedly, the clinical parameters included in sPESI are easy to obtain in most cases; on the other hand, a simplified PESI of 0 may still "miss" some early adverse events. Therefore, we were particularly interested in finding out whether the combination of hsTnT with the sPESI provides additive prognostic information and, more specifically, whether it further improves the identification of low-risk patients. Overall, 127 patients (24% of the study population) had hsTnT < 14 pg/mL and a sPESI of 0; none of them had an adverse outcome within the first 30 days. Thus, the combination model was associated with an excellent prognostic sensitivity and NPV, which both reached 100%.

Patients with low-risk PE may be considered for early discharge if proper outpatient care and anticoagulant treatment can be provided. This issue may be of particular

relevance in the era of new oral anticoagulants that are expected to simplify the prophylaxis and treatment of venous thromboembolism.^{17,28} Although out-of-hospital treatment has been addressed in a few small studies, strategies and criteria for the selection of the appropriate low-risk candidates are, thus far, neither standardized nor thoroughly validated.^{29,30} In a randomized treatment trial, the rate of mortality, recurrent venous thromboembolism, and bleeding episodes did not differ significantly when low-risk patients identified with a clinical score⁹ were randomly assigned to standard hospitalization versus early discharge. However, the study was discontinued after inclusion of 132 patients because of an unexpected high rate of short-term mortality.³¹ More recently, a randomized study of 344 patients reported that low-risk patients based on the original (not the simplified) PESI can be safely treated as outpatients.³²

The consistent findings in both our derivation cohort⁵ and in the present validation study indicate that patients with hsTnT levels < 14 pg/mL on admission have a favorable short- and long-term (6-month) prognosis. They thus support the applicability of hsTnT for a careful selection of low-risk patients, in particular, when the test is combined with the sPESI. Indeed, we found that patients with a sPESI of 0 and hsTnT < 14 pg/mL had a 42% reduction in the risk of dying during the 6-month follow-up period in comparison with those with a sPESI ≥ 1 and/or hsTnT ≥ 14 pg/mL. Therefore, although our study did not directly assess the impact of hsTnT levels, alone or in combination with the sPESI, on the therapeutic management of patients with acute PE, our findings provide a firm rationale for a prospective management trial that will investigate whether thus selected low-risk patients can be discharged early and safely treated at home. Because, as already mentioned, as many as 24% of the normotensive patients included in the present study had both a sPESI of 0 and hsTnT < 14 pg/mL, outpatient treatment of this relatively large group might contribute to a significant reduction of health care costs and improvement of patient satisfaction. Interestingly, our results also indicate that echocardiographic screening might not be necessary in these particular patients, because the reported presence of signs of RV dysfunction in 15% of them had no impact on their (excellent) clinical outcome. Abnormal echocardiographic findings may often be difficult to define and standardize,^{2,24,33} whereas hsTnT and the sPESI use clearly defined easily reproducible parameters and cutoff values.

Finally, with regard to the secondary end points of our study, neither hsTnT ≥ 14 pg/mL nor a sPESI ≥ 1 point(s) appeared to predict an elevated risk of early symptomatic PE recurrence or of major bleeding. However, these results must be interpreted with caution in view of the relatively small numbers (9 and 15, respectively) of patients who reached these end points.

In conclusion, in a large multicenter validation cohort of 526 patients, we confirmed the prognostic value of both the new hsTnT assay and the sPESI. We further demonstrated that the combination of hsTnT with the sPESI yields additive prognostic information, in particular, for identification of low-risk patients. Our findings provide the basis for a prospective management trial to determine whether selected low-risk patients with pulmonary embolism can safely be treated at home.

Disclosures

None.

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CLINICAL PERSPECTIVE

Early risk stratification of patients with acute pulmonary embolism is critical for therapeutic decision-making. In patients without hemodynamic instability at presentation, laboratory markers of myocardial injury and imaging of right ventricular size and function may indicate an elevated risk, but their clinical utility remains controversial to date. In the present study, we evaluated the predictive value of a new, high-sensitivity troponin T assay (hsTnT) and compared it with a recently developed clinical prognostic score, the simplified Pulmonary Embolism Severity Index (sPESI). In a large multicenter, multinational cohort of 526 patients, the predefined hsTnT cutoff level of 14 pg/mL exhibited a high prognostic sensitivity and negative predictive value, only slightly lower than that of sPESI. Importantly, of 127 patients (24% of the study population) with hsTnT <14 pg/mL and sPESI of 0, none had an adverse 30-day outcome (negative predictive value, 100%). Thus, hsTnT may be an alternative to sPESI for exclusion of an adverse early outcome, in particular when the variables required for calculation of the clinical score are not immediately available. Moreover, in our study, combination of these 2 simple tools identified low-risk patients with an even higher degree of safety than either test alone. If confirmed by a prospective management trial, this strategy may simplify the management of a significant proportion of patients with pulmonary embolism, and possibly help to reduce treatment costs.

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