ORIGINAL ARTICLE

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Predictive value and optimal cut-off level of high-sensitivity troponin T in patients with acute pulmonary embolism

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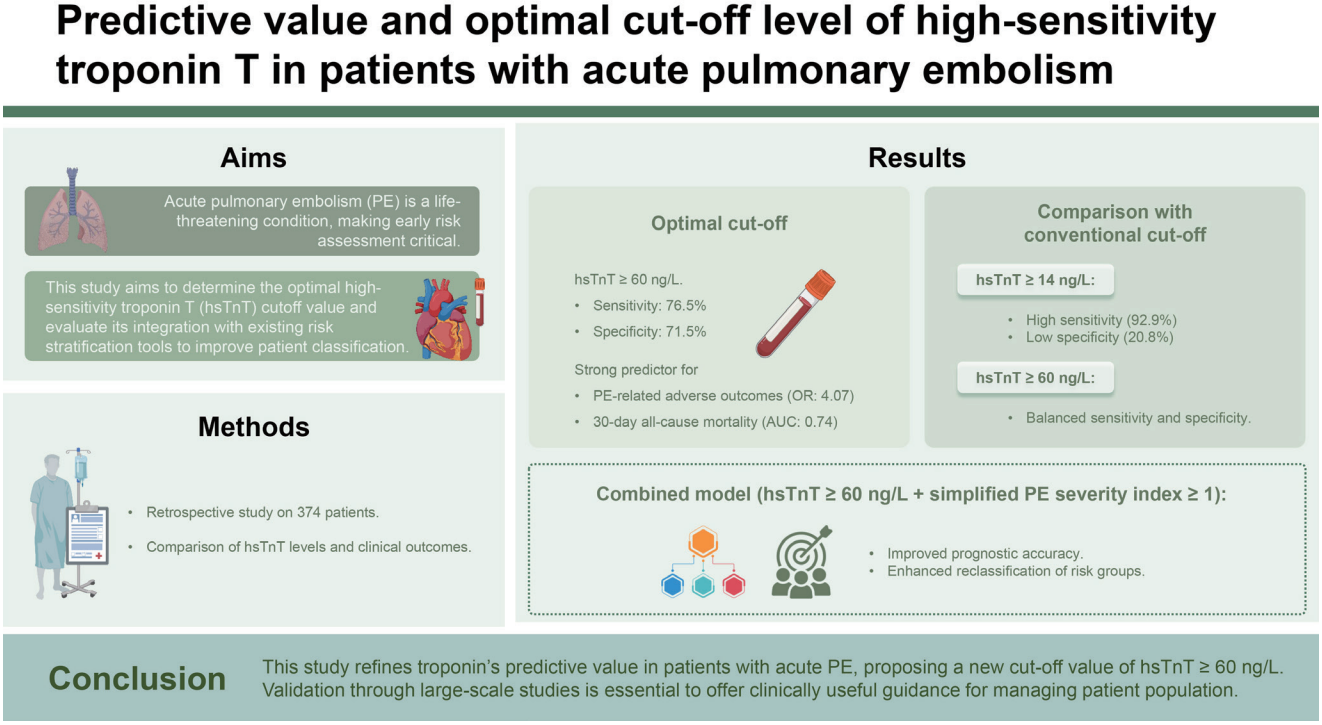

Background/Aims: Elevated troponin levels predict in-hospital mortality and influence decisions regarding thrombolytic therapy in patients with acute pulmonary embolism (PE). However, the usefulness of high-sensitivity troponin T (hsTnT) regarding PE remains uncertain. We aimed to establish the optimal cut-off level and compare its performance for precise risk stratification.

Methods: 374 patients diagnosed with acute PE were reviewed. PE-related adverse outcomes, a composite of PE-related deaths, cardiopulmonary resuscitation incidents, systolic blood pressure < 90 mmHg, and all-cause mortality within 30 days

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were evaluated. The optimal hsTnT cut-off for all-cause mortality, and the net reclassification index (NRI) was used to assess the incremental value in risk stratification.

Results: Among 343 normotensive patients, 17 (5.0%) experienced all-cause mortality, while 40 (10.7%) had PE-related adverse outcomes. An optimal hsTnT cut-off value of 60 ng/L for all-cause mortality (AUC 0.74, 95% CI 0.61–0.85, $p < 0.001$) was identified, which was significantly associated with PE-related adverse outcomes (OR 4.07, 95% CI 2.06–8.06, $p < 0.001$). Patients with hsTnT ≥ 60 ng/L were older, hypotensive, had higher creatinine levels, and right ventricular dysfunction signs. Combining hsTnT ≥ 60 ng/L with simplified pulmonary embolism severity index ≥1 provided additional prognostic information. Reclassification analysis showed a significant shift in risk categories, with an NRI of 1.016 ± 0.201 ($p < 0.001$).

Conclusions: We refined troponin's predictive value in patients with acute PE, proposing a new cut-off value of hsTnT ≥ 60 ng/L. Validation through large-scale studies is essential to offer clinically useful guidance for managing patient population.

Keywords: Troponin T; Pulmonary embolism; Risk assessment; Biomarker

INTRODUCTION

Early prognostic stratification is crucial for patients with symptomatic acute pulmonary embolism (PE) to determine appropriate therapeutic interventions and optimize clinical outcomes [1]. According to the 2019 European Society of Cardiology (ESC) guidelines for acute PE, patients presenting with clinical symptoms and signs indicative of hemodynamic instability are classified as having a high risk of early (in-hospital or 30-day) death. Subsequently, the remaining patients are further stratified into intermediate-high, intermediate-low, and low-risk groups. Risk indicators include the pulmonary embolism severity index (PESI) or simplified PESI (sPESI) score, right ventricular (RV) dysfunction through echocardiography or computed tomography pulmonary angiography (CTPA), and elevated biomarker levels [1]. While several biomarkers, such as cardiac troponin, B-type natriuretic peptide (BNP), and creatinine, have demonstrated individual or additive predictive values, only cardiac troponin has been incorporated into management guidelines based on extensive research.

Troponin elevation is thought to result from a sudden increase in pulmonary vasculature resistance, leading to RV dilatation and subsequent alteration of the contractile properties of the myocardium. The extent of troponin release appears to be dependent on the severity of PE [1-3]. However, previous validation studies did not provide separate cut-off values for troponin I or troponin T and were all conducted using their normal upper limits. In particular, the advent of the high-sensitivity troponin T (hsTnT) assay in 2009 significantly enhanced the detection of troponin levels that fell below the detection limits of conventional assays [4]. Therefore, debates surrounding whether elevated hsTnT levels, defined by the 99th percentile upper reference limit (URL) of 14 ng/L, can effectively identify patients at a heightened risk of short-term adverse outcomes and guide the administration of thrombolytic therapy.

In this study, we aimed to investigate the prognostic relevance of hsTnT, establish the optimal hsTnT cut-off level, and compare its performance in the risk stratification of patients with acute PE.

METHODS

Study participants and designs

This study retrospectively examined 394 consecutive patients diagnosed with acute PE between July 1, 2020, and September 30, 2023, at Gyeongsang National University Hospital in Jinju, Republic of Korea. Exclusions were made of patients with end-stage renal disease requiring hemodialysis (n = 2) and those with missing hsTnT levels on admission (n = 18). Consequently, 374 patients were included in the analysis. The diagnoses of all the patients were confirmed using CTPA. This study was approved by the Institutional Review Board of Gyeongsang National University Hospital (IRB No. GNUH-2023-08-015) and the requirement for informed consent was waived.

Clinical characteristics

Baseline demographic and clinical data were obtained through individual chart reviews in the institution's electron-

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ic medical record system. The following clinically relevant comorbidities were analyzed: diabetes mellitus, hypertension, dyslipidemia, chronic kidney disease, history of cancer, and history of chronic pulmonary disease. Additionally, recent immobilization and surgery within the last 4 weeks were considered. A history of cancer was defined as a known malignant disease or treatment received within the past five years. Chronic pulmonary disease encompasses various conditions, including heart failure, asthma, chronic obstructive pulmonary disease, emphysema, chronic bronchitis, and interstitial lung disease.

Laboratory parameters

Among the 374 eligible patients, 341 underwent transthoracic echocardiography (TTE) during hospitalization, and all measurements adhered to the recommendations of the American Society of Echocardiography [5]. Because of various specificity and sensitivity of the individual TTE parameter, RV dysfunction was defined as the presence of one or more of the following echocardiography findings: decreased peak systolic velocity of tricuspid annulus (< 9.5 cm/s), decreased tricuspid annular plane systolic excursion measured with M-mode (< 16 mm), and decreased fractional area contraction (< 35 %), and a right/left ventricle diameter ratio ≥ 1.0 from the apical or subcostal view.

All patients underwent an initial 12-lead electrocardiographic (ECG) assessment. RV strain was defined as the presence of one or more of the following ECG findings: incomplete or complete right bundle branch block (RBBB), T-wave inversions in leads V1–V3, and S1Q3T3 pattern. Routine laboratory parameters, including hsTnT levels, were measured directly after blood withdrawal when initial diagnostic tests for suspected PE were started, ensuring a timely and accurate assessment of the acute phase response. The concentrations of hsTnT were analyzed using the Roche Cobas® 8000 analyzer (Roche Diagnostics, Mannheim, Germany) with an analytical range of 3–10,000 ng/L. A concentration of 14 ng/L has been identified as the 99th percentile URL for a healthy reference population, with a coefficient variation of less than 10%.

Clinical outcomes

PE-related adverse outcomes and all-cause mortality within 30 days were assessed. PE-related adverse outcomes were defined as a composite of (1) PE-related death, (2) incidence of cardiopulmonary resuscitation (CPR), and (3) systolic blood pressure (SBP) < 90 mmHg. All-cause mortality encompassed deaths related to acute PE or other causes, including malignancy or septic shock, within 30 days of PE diagnosis. Specifically, PE-related death was determined in the absence of an alternative diagnosis, and all clinical outcomes were assessed within 30 days of hospitalization. For the risk assessment, the sPESI score was calculated for each patient. This index assigned one point for the presence of each of the following variables: (1) age > 80 years; (2) history of cancer; (3) history of chronic cardiopulmonary disease; (4) heart rate ≥ 110 beats per minute; (5) SBP < 100 mmHg; and (6) oxygen saturation < 90% at the time of diagnosis [6].

Statistical analysis

Categorical variables are expressed as absolute numbers with percentages and compared using the chi-squared test or Fisher's exact test, as appropriate. Continuous variables not adhering to a normal distribution are presented as medians with interquartile ranges (IQRs). The non-parametric Mann–Whitney U test was used to compare continuous variables. The Kruskal–Wallis test, a non-parametric alternative to analysis of variance (ANOVA), was used to compare

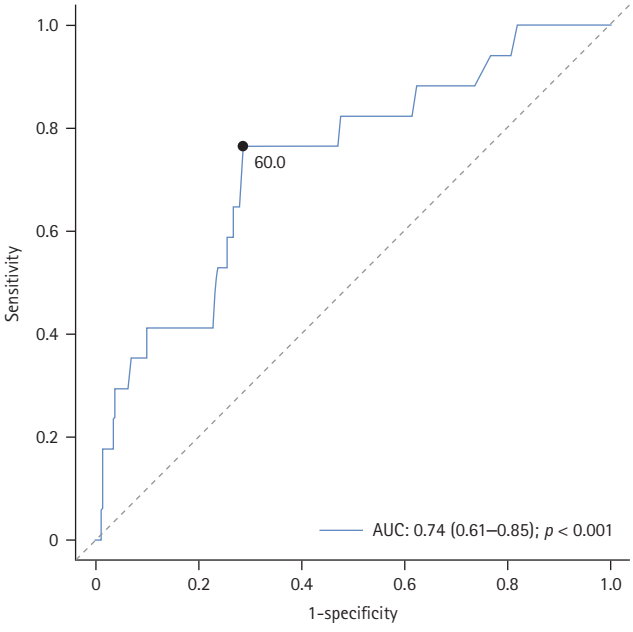

Figure 1. Receiver operating characteristic curve analysis to predict all-cause mortality in 343 normotensive patients. The dot indicates the optimal cut-off value of high-sensitivity troponin T, which was determined where the sum of specificity and specificity was the highest. AUC, area under the curve.

Table 1. Baseline characteristics of all 374 patients diagnosed with acute PE

Variable	All patients (n = 374)	Normotensive patients[a] (n = 343)		*p* value[b]	High risk patients (n = 31)	*p* value[c]
		hsTnT < 60 ng/L (n = 237)	hsTnT ≥ 60 ng/L (n = 106)			
Age (yr)	76.0 (66.0–83.0)	75.0 (64.0–82.0)	79.0 (71.0–84.0)	0.008	77.0 (71.0–83.0)	0.022
Male	162 (43.3)	106 (44.7)	44 (41.5)	0.662	12 (38.7)	0.741
BMI (kg/m^2)	23.1 (20.9–25.5)	23.2 (21.0–25.8)	22.8 (20.7–25.0)	0.297	23.4 (21.3–25.9)	0.486
Comorbidities						
Diabetes mellitus	85 (22.7)	44 (20.2)	33 (26.4)	0.233	8 (25.8)	0.612
Hypertension	194 (51.9)	103 (47.3)	75 (60.0)	0.031	16 (51.6)	0.110
Dyslipidemia	95 (25.4)	53 (24.3)	32 (25.6)	0.892	10 (32.3)	0.502
Chronic kidney disease	12 (3.2)	4 (1.8)	7 (5.6)	0.106	1 (3.2)	0.226
Malignancy	66 (17.7)	46 (21.1)	13 (10.4)	0.017	7 (22.6)	0.121
Heart failure	19 (5.1)	9 (4.1)	8 (6.4)	0.500	2 (6.5)	0.865
Chronic lung disease	95 (25.4)	57 (26.2)	32 (25.6)	> 0.999	6 (19.4)	0.666
Previous VTE	31 (8.3)	14 (6.4)	16 (12.8)	0.070	1 (3.2)	0.290
Recent immobilization or surgery	65 (17.4)	27 (12.4)	27 (21.6)	0.036	11 (35.5)	0.003
Physiologic parameters						
Systolic BP (mmHg)	130.0 (110.0–149.0)	131.0 (120.0–150.0)	122.5 (108.0–141.0)	< 0.001	79.0 (61.5–80.0)	< 0.001
Diastolic BP (mmHg)	77.0 (66.0–89.0)	80.0 (70.0–90.0)	80.0 (66.0–89.0)	0.186	46.0 (40.0–50.0)	< 0.001
Heart rate (beats/min)	90.0 (78.0–105.0)	89.0 (78.0–104.0)	92.5 (78.0–106.0)	0.359	90.0 (79.0–107.5)	0.648
SpO_2 < 90%	79 (21.1)	33 (13.9)	30 (28.3)	0.002	16 (51.6)	< 0.001
Laboratory parameters						
White blood cell (× 10^3/mm^3)	9.1 (6.7–12.3)	8.8 (6.3–11.8)	9.3 (7.7–13.7)	0.007	10.8 (8.5–13.9)	0.004
Hemoglobin (g/dL)	12.0 (10.5–13.5)	12.1 (10.6–13.5)	11.8 (10.2–13.5)	0.507	11.5 (10.1–12.4)	0.173
Platelet (× 10^3/mm^3)	200.0 (156.0–255.0)	213.0 (167.0–270.0)	188.0 (149.0–225.0)	0.001	168.0 (132.0–255.5)	< 0.001
C-reactive protein (mg/L)	23.5 (5.0–76.3)	22.4 (3.6–77.1)	23.0 (5.5–65.2)	0.738	39.2 (9.4–79.2)	0.166
Prothrombin time (s)	12.8 (11.6–14.1)	12.6 (11.6–13.9)	12.8 (11.3–13.9)	0.618	13.8 (12.6–16.1)	0.003
D-dimer (ug/mL)	6.7 (2.7–17.5)	5.5 (1.9–13.1)	14.3 (6.1–20.0)	< 0.001	19.5 (4.6–20.0)	< 0.001
Blood urea nitrogen (mg/dL)	17.4 (12.8–23.2)	15.6 (12.0–20.4)	20.6 (15.6–30.5)	< 0.001	22.0 (14.3–43.8)	< 0.001
Creatinine (mg/dL)	0.8 (0.6–1.1)	0.8 (0.6–1.0)	1.0 (0.7–1.2)	< 0.001	1.1 (0.6–2.0)	< 0.001
CKD-EPI (mL/min/1.73 m^2)	81.0 (56.0–92.0)	84.0 (66.0–94.0)	64.5 (47.0–89.0)	< 0.001	53.0 (30.5–87.5)	< 0.001
Lactic acid (mmol/L)	1.6 (1.2–2.3)	1.4 (1.1–2.2)	1.7 (1.3–2.4)	0.041	2.3 (1.6–6.8)	< 0.001

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Table 1. Continued

Variable	All patients (n = 374)	Normotensive patients[a] (n = 343)		*p* value[b]	High risk patients (n = 31)	*p* value[c]
		hsTnT < 60 ng/L (n = 237)	hsTnT ≥ 60 ng/L (n = 106)			
HbA1c (%)	5.7 (5.4–6.3)	5.8 (5.4–6.3)	5.6 (5.4–6.2)	0.304	5.8 (5.5–6.2)	0.450
hsTnT (ng/L)	34.0 (16.0–80.0)	19.0 (11.0–34.0)	115.0 (80.0–174.0)	< 0.001	62.0 (33.5–209.5)	< 0.001
NT-proBNP (pg/mL)	702.0 (178.0–2,668.0)	457.0 (129.5–1,563.5)	1,822.5 (398.0–6,685.0)	< 0.001	2,246.0 (377.0–9,063.0)	< 0.001
Initial treatment				0.013		0.004
Thrombolytic therapy	26 (7.0)	9 (3.8)	12 (11.3)		5 (16.1)	
Catheter-directed	13 (3.5)	5 (2.1)	6 (5.7)		2 (6.5)	
Systemic	13 (3.5)	4 (1.7)	6 (5.7)		3 (9.7)	
Anticoagulation alone	342 (91.4)	224 (94.5)	94 (88.7)		24 (77.4)	
Discharge medication				0.001		< 0.001
VKA	9 (2.4)	6 (2.5)	3 (3.8)		0 (0.0)	
DOAC	326 (87.2)	219 (92.4)	88 (83.0)		19 (61.3)	
Inability to maintain anticoagulants[d]	36 (9.6)	7 (3.0)	14 (13.2)		11 (35.5)	

Values are presented as median (interquartile range) or number (%).

PE, pulmonary embolism; hsTnT, high-sensitivity troponin T; BMI, body mass index; VTE, venous thromboembolism; BP, blood pressure; CKD-EPI, chronic kidney disease epidemiology collaboration; NT-proBNP, N-terminal pro-B-natriuretic peptide; VKA, vitamin K antagonist; DOAC, direct oral anticoagulant.

[a]Patients were stratified according to the cut-off value 60 ng/L of the hsTnT assay on admission.

[b]*p* value was determined using the chi-square or Mann–Whitney U test to compare groups with hsTnT levels < 60 ng/L and ≥ 60 ng/L in normotensive patients.

[c]*p* value resulted from the ANOVA test comparing three groups.

[d]Includes cases of death, active bleeding events, and high bleeding tendency.

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normotensive subgroups and high-risk patients with PE, followed by pairwise Wilcoxon post-hoc tests for detailed group comparisons. Youden's index was used to identify and select the optimal hsTnT cut-off level for predicting all-cause mortality. Receiver operating characteristic (ROC) curve analyses were performed to determine the area under the curve (AUC) with corresponding 95% confidence intervals (CIs). The efficacy of the newly defined levels was assessed by calculating the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and positive likelihood ratio. The prognostic relevance of dichotomous/dichotomized variables regarding study outcomes was assessed using univariate logistic regression analysis. After adjusting for confounders such as age, sex, history of cancer, and history of chronic pulmonary disease, a multivariable logistic regression analysis was performed. Notably, the variables used to calculate sPESI scores were not included. Harrell's C-statistic was used to assess the accuracy of correctly classifying patients into different risk categories, as outlined in the 2019 ESC guidelines, following the application of the newly defined hsTnT cut-off level. The net reclassification index (NRI) with the corresponding standard error was assessed using the incremental value when elevated cardiac troponin levels were specifically aligned with the newly defined hsTnT cut-off level. A two-sided significance level of 5% was defined as appropriate to indicate statistical significance. All statistical analyses were performed using R software (R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org/).

RESULTS

Optimal cut-off hsTnT level in normotensive patients

According to the 2019 ESC guidelines [1], patients were categorized into two groups: hemodynamically unstable patients, classified as the high-risk group, and hemodynamically stable and normotensive patients. The latter group necessitated further assessment using RV dysfunction on TTE or CTPA and cardiac troponin evaluation. Hence, only normotensive patients (n = 343) were isolated from a distinct group, and the optimal hsTnT cut-off level was determined for this study. Among normotensive patients, a total of 17 (5.0%) experienced all-cause mortality. An AUC of

Table 2. Prognostic factors and clinical outcomes

Variable	All patients (n = 374)	Normotensive patients (n = 343)		*p* value[a]	High-risk patients (n = 31)	*p* value[b]
		hsTnT < 60 ng/L (n = 237)	hsTnT ≥ 60 ng/L (n = 106)			
Prognostic factors						
Simplified PESI ≥ 1 point	261 (69.8)	151 (63.7)	80 (75.5)	0.043	30 (96.8)	< 0.001
NT-proBNP ≥ 600 pg/mL	194 (51.9)	101 (42.6)	72 (67.9)	< 0.001	21 (67.7)	< 0.001
RV dysfunction on TTE	127 (34.0)	55 (23.2)	55 (51.9)	< 0.001	17 (54.8)	< 0.001
RV strain on ECG	145 (38.8)	79 (33.3)	49 (46.2)	0.031	17 (54.8)	0.012
Outcomes						
PE-related adverse outcomes	40 (10.7)	0 (0.0)	9 (7.2)	< 0.001	31 (100.0)	< 0.001
PE-related death	16 (4.3)	0 (0.0)	7 (5.6)	0.001	9 (29.0)	< 0.001
Cardiopulmonary resuscitation	13 (3.5)	0 (0.0)	4 (3.2)	0.009	9 (29.0)	< 0.001
Systolic BP < 90 mmHg		-	-	-	31 (100.0)	
All-cause mortality	28 (7.5)	4 (1.7)	13 (12.3)	< 0.001	11 (35.5)	< 0.001

Values are presented as number (%).
hsTnT, high-sensitivity troponin T; PESI, pulmonary embolism severity index; NT-proBNP, N-terminal pro-B-natriuretic peptide; RV, right ventricle; TTE, transthoracic echocardiography; ECG, electrocardiography; PE, pulmonary embolism; BP, blood pressure.
[a]*p* value was determined using the chi-square or Mann–Whitney U test to compare groups with hsTnT levels < 60 ng/L and ≥ 60 ng/L in normotensive patients.
[b]*p* value resulted from the ANOVA test comparing three groups.

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0.74 (95% CI 0.61–0.85) was calculated using ROC analysis, demonstrating a sensitivity of 76.5% and specificity of 71.5%. The optimal cut-off for this prediction was an hsTnT level of 60 ng/L, which was subsequently used for all analyses (Fig. 1). An AUC for PE-related adverse outcomes was also 0.75 (95% CI 0.68–0.83).

Baseline clinical characteristics of the study population

The median age of the study participants was 76 years (IQR 66–83 yr), and 43.3% were male. The initial hsTnT levels ranged from 3 to 1,140 ng/L, with a median of 34.0 ng/L (IQR 16.0–80.0 ng/L). In the study population, 31 (8.3%) patients were hemodynamically unstable at the time of PE diagnosis. The majority, comprising 343 (91.7%) patients, were normotensive. Among the normotensive patients, 106 (30.9%) exhibited hsTnT levels exceeding the pre-defined cut-off level of 60 ng/L, accounting for 28.3% of all patients. When three groups were compared (normotensive patients with hsTnT < 60 ng/L and ≥ 60 ng/L and high-risk patients), significant differences were observed in age and recent immobilization or surgery rates. Among normotensive patients, those with hsTnT ≥ 60 ng/L had lower SBP and exhibited hypoxemia more frequently. The levels of creatinine, lactic acid, NT-proBNP, and hsTnT, indicative of tissue or myocardial ischemia, were significantly stratified among the three groups. Thrombolytic therapy was administered to 7.0% of the total patients and to 16.1% of high-risk patients (p = 0.004). Additionally, 21 normotensive patients who experienced deterioration during hospitalization received thrombolytic therapy. At discharge, most patients were prescribed oral anticoagulation. However, patients who died, those identified to be at increased risk of active bleeding, or those in whom thromboprophylaxis was contraindicated for other reasons were managed without anticoagulants (Table 1).

Comparison of prognostic factors, and clinical outcomes

Regarding prognostic factors, patients with hsTnT ≥ 60 ng/L exhibited a higher prevalence of adverse indicators, including sPESI ≥ 1 point (63.7% vs. 75.5%, p = 0.043), NT-proBNP ≥ 600 pg/mL (42.6% vs. 67.9%, p < 0.001), and RV dysfunction on TTE (23.2% vs. 51.9%, p < 0.001) (Table 2). The composite measure of RV strain on ECG, which included T-wave inversions in V1-V3, RBBB, and the

Table 3. Predictors of PE-related adverse outcomes and all-cause mortality

Predictors	PE-related adverse outcome				All-cause mortality			
	Univariable		Multivariable		Univariable		Multivariable	
	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
sPESI ≥ 1 point	19.68 (2.67–145.07)	0.004	24.63 (3.16–191.85)	0.002	12.92 (1.73–96.31)	0.013	12.13 (1.49–98.64)	0.020
hsTnT ≥ 60 ng/L	4.07 (2.06–8.06)	< 0.001	2.55 (1.19–5.45)	0.016	7.28 (3.00–17.65)	< 0.001	5.45 (2.08–14.29)	0.001
NT-proBNP ≥ 600 pg/mL	2.70 (1.31–5.58)	0.007	1.64 (0.73–3.69)	0.233	4.71 (1.72–12.67)	< 0.001	2.93 (1.01–8.50)	0.048
RV dysfunction on TTE	2.67 (1.37–5.18)	0.004	1.58 (0.72–3.46)	0.255	1.76 (0.81–3.83)	0.152	0.92 (0.37–2.29)	0.862
RV strain on ECG	2.10 (1.08–4.06)	0.028	1.30 (0.61–2.76	0.496	1.92 (0.88–4.16)	0.010	1.33 (0.55–3.23)	0.528

PE, pulmonary embolism; OR, odds ratio; CI, confidence interval; sPESI, simplified pulmonary embolism severity index; hsTnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-B-natriuretic peptide; RV, right ventricle; TTE, transthoracic echocardiography; ECG, electrocardiogram.

S1Q3T3 pattern, demonstrated a substantial difference as well (33.3% vs. 46.2%, $p = 0.031$). The detailed baseline TTE and ECG findings are summarized in the Supplementary Table 1 and 2. Regarding clinical outcomes, within the group of 31 high-risk patients, 9 did not recover their blood pressure and eventually died after CPR. Among the normotensive patients, the number of all-cause mortality was 17 (5.0%), showing significant differences between hsTnT < 60 ng/L and ≥ 60 ng/L, with 4 (1.7%) and 13 (12.3%) patients, respectively. Notably, all PE-related adverse outcomes occurred exclusively in the hsTnT ≥ 60 ng/L group. Specific causes of death are shown in Supplementary Table 3.

Predictors of PE-related adverse outcomes and all-cause mortality

Univariable logistic regression analysis showed that hsTnT ≥ 60 ng/L and NT-proBNP ≥ 600 pg/mL were associated with PE-related adverse outcomes and all-cause mortality. After adjusting for age, sex, history of cancer, and history of chronic pulmonary disease, only hsTnT ≥ 60 ng/L remained as an independent predictor of PE-related adverse

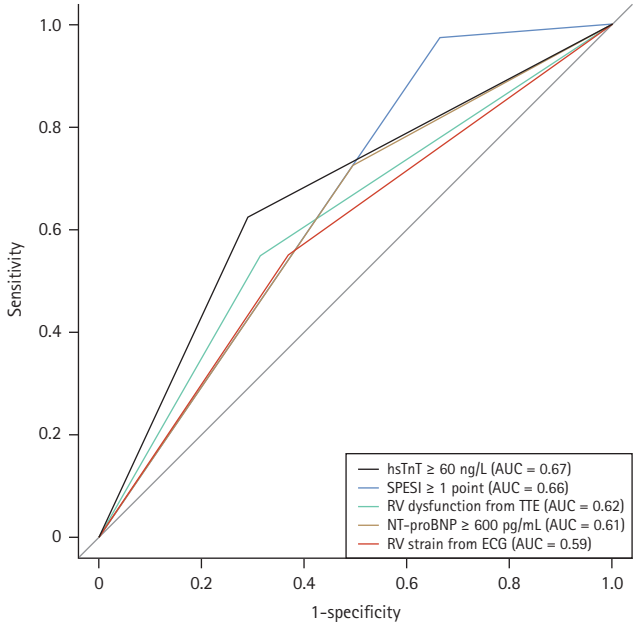

Figure 2. Receiver operating characteristic curves illustrating the binary performance of various predictors for all-cause mortality in 343 normotensive patients. hsTnT, high-sensitivity troponin T; AUC, area under the curve; sPESI, simplified pulmonary embolism severity index; RV, right ventricular; TTE, transthoracic echocardiography; NT-proBNP, N-terminal pro-B-natriuretic peptide; ECG, electrocardiogram.

Table 4. Prognostic performance of all-cause mortality according to the sPESI score and hsTnT levels

Parameters	Prevalence	All-cause mortality	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	+LR	*p* value
sPESI ≥ 1 point + hsTnT ≥ 60 ng/L	96/374 (25.7%)	21/96 (21.9%)	0.77	75.0	78.3	21.9	97.5	76.7	3.46	< 0.001
hsTnT ≥ 60 ng/L	122/374 (32.6%)	21/122 (17.2%)	0.73	75.0	70.8	17.2	97.2	71.1	2.57	< 0.001
sPESI ≥ 1 point	261/374 (69.8%)	27/261 (10.3%)	0.64	96.4	32.4	10.3	99.1	37.2	1.43	0.001
hsTnT ≥ 14 ng/L	300/374 (80.2%)	26/300 (86.7%)	0.57	92.9	20.8	8.7	97.3	26.2	1.17	0.041

sPESI, simplified pulmonary embolism severity index; hsTnT, high-sensitivity troponin T; AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio.

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outcomes. Regarding all-cause mortality, hsTnT ≥ 60 ng/L and NT-proBNP ≥ 600 pg/mL retained significance (Table 3). By the ROC curve analysis of the various predictors, hsTnT ≥ 60 ng/L was identified as the most powerful predictor, with its AUC comparable with that of sPESI score ≥ 1 (0.67 vs. 0.66, $p = 0.772$, Fig. 2).

sPESI score and hsTnT for prediction of all-cause mortality

The assessment of the prognostic performance for all-cause mortality is shown in Table 4, incorporating the sPESI score, hsTnT levels, and their combinations. sPESI ≥ 1 point was observed in 261 (69.8%) patients and demonstrated the highest sensitivity and NPV. A combined model of sPESI ≥ 1 point and hsTnT ≥ 60 ng/L was observed in 96 (25.7%) patients, representing the lowest prevalence among other parameters. However, this model exhibited the highest AUC and positive likelihood ratio for the clinical outcomes. When comparing the conventional hsTnT level of 14 ng/L with the proposed hsTnT level of 60 ng/L, sensitivity decreased from 92.9% to 75.0%, while specificity increased from 20.8% to 70.8%. A comparison of the prognostic values for PE-related adverse outcomes confirmed the additional utility of an hsTnT level of 60 ng/L on sPESI (Supplementary Table 4). The clinical outcomes according to sPESI and hsTnT levels are illustrated in Supplementary Table 5.

Risk reclassification by hsTnT ≥ 60 ng/L

If the elevated cardiac troponin levels, identified as a risk indicator in the 2019 ESC classification of PE severity [1], were specifically defined as hsTnT ≥ 60 ng/L instead of conventional hsTnT ≥ 14 ng/L, the Harrell's C-index significantly improved from 0.72 to 0.80 ($p = 0.008$). The Hosmer-Lemeshow goodness-of-fit test remained non-significant for both hsTnT ≥ 60 ng/L and ≥ 14 ng/L models ($p = 0.685$ and $p = 0.519$, respectively). Furthermore, a Sankey diagram was used to quantitatively depict patients' transition across different risk categories (Fig. 3). Among the 103 patients

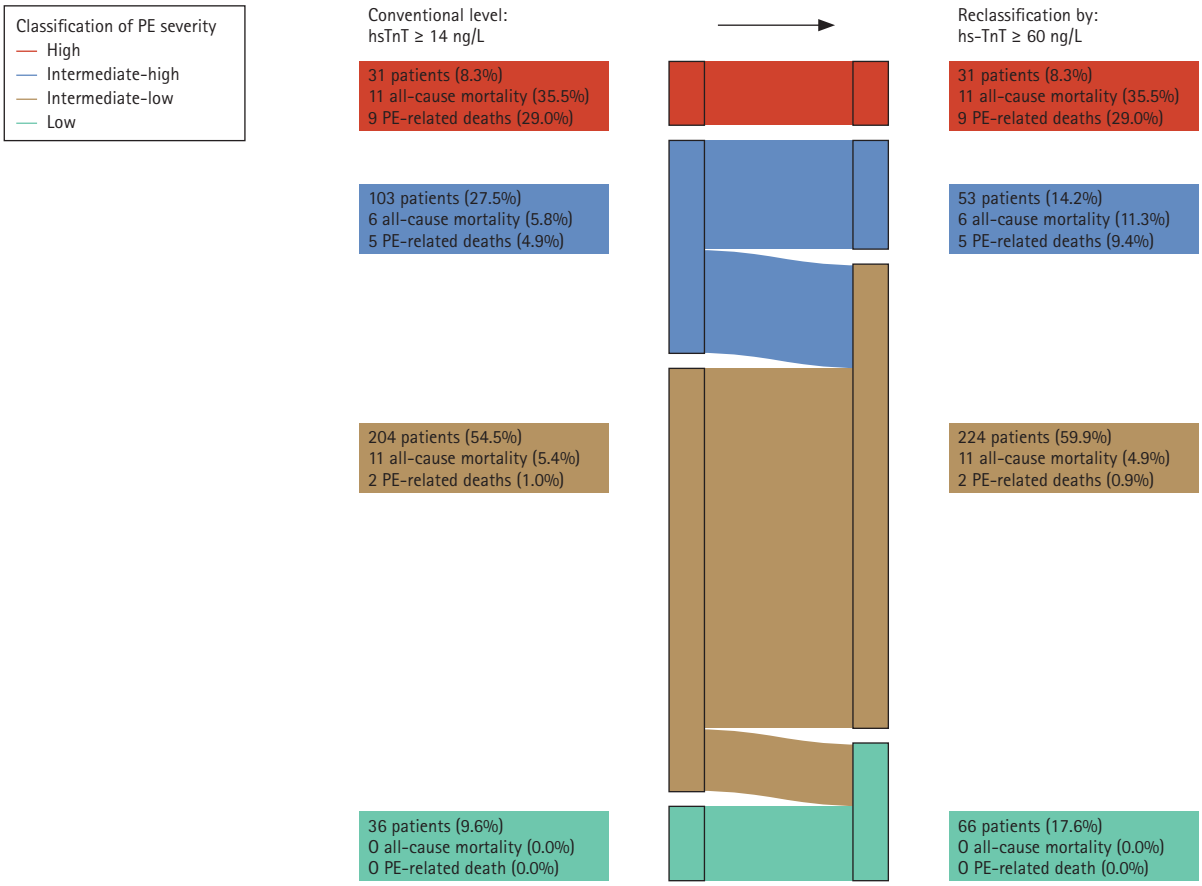

Figure 3. Sankey diagram displaying the change of risk stratification according to the newly defined hsTnT cut-off level. The width of the bars is proportional to the number of patients. PE, pulmonary embolism; hsTnT, high-sensitivity troponin T.

initially classified into the intermediate-high risk category, 50 (48.5%) underwent reclassification into the intermediate-low risk category. Similarly, among the 204 patients initially classified as intermediate-low risk, 30 (14.7%) patients were reclassified to the low-risk category. This visual representation underscores how the revised hsTnT threshold redistributes the patients into distinct risk categories. The reclassification led to a substantial increase in the mortality rate within the intermediate-high-risk group, rising from 4.9 to 9.4%, significantly improving the overall NRI analysis (1.016 ± 0.201, $p < 0.001$).

DISCUSSION

Our findings can be summarized as follows: (1) an hsTnT level of ≥ 60 ng/L was associated with an elevated risk for PE-related adverse outcomes and all-cause mortality following the diagnosis of acute PE; (2) hsTnT demonstrated additive value when integrated into a combined model with sPESI ≥ 1; and (3) in comparison to the conventional hsTnT level of 14 ng/L, an hsTnT level of 60 ng/L proved to be a more effective indicator in risk stratification.

Pitfalls and new proposals in hsTnT for risk stratification in acute PE

The prognostic significance of cardiac troponin levels in patients diagnosed with PE has been increasingly recognized. The conventional troponin I or T assay is the standard for detecting myocardial injury, which relies on elevated levels that exceed the 99th percentile URL. However, the landscape of troponin testing underwent a transformative shift with the introduction of hsTnT in 2009 [4], which significantly improved detection sensitivity, revealing troponin levels previously undetectable in earlier assays. Including hsTnT in the 2019 ESC guidelines emphasize its crucial role in risk stratification, particularly in intermediate- and low-risk patients. However, considerable uncertainty remains regarding the clinical utility of adopting the 99th URL in identifying patients who may be at an increased risk of short-term complications precisely, as the guideline does not explicitly outline the extent to which such elevations should be deemed clinically significant. Therefore, it is imperative to establish an optimal threshold instead of relying solely on the conventional hsTnT level of 14 ng/L. Jiménez et al. [6] initially validated hsTnT combined with the sPESI score to predict adverse outcomes in hemodynamically stable PE patients, using the 14 ng/L cut-off. They reported that while this cut-off level was useful for risk stratification, there was a need for more specific values tailored to PE patients to improve prognostic accuracy and clinical utility. Lankeit et al. [7,8] and others [9-13] applied an hsTnT level of 14 ng/L and demonstrated high prognostic sensitivity and NPV for the 30-day mortality risk. Although this threshold has been widely used for risk stratification and identifying patients suitable for early discharge, its initial intent was to distinguish between normal and elevated biomarker levels in coronary artery disease rather than in the specific context of PE [14]. In addition, almost two-thirds of patients presented with hsTnT ≥ 14 ng/L upon admission, leading to low specificity and PPV of the biomarker [7]. In contrast to previous studies using hsTnT, our findings indicate the clinical need for a new cut-off value. The new cut-off level of 60 ng/L exhibits remarkable performance, providing moderate specificity (71.0%) and a robust NPV (94.0%) for predicting PE-related adverse outcomes as well as all-cause mortality. This higher threshold allows for more precise risk stratification and enables targeted therapeutic interventions, potentially improving patient outcomes. While the AUC significantly increased compared to hsTnT at 14 ng/L, accompanied by a substantial change in the mortality rate within the intermediate-high risk group in the reclassification analysis, concerns may arise regarding improvement of PPV at the expense of NPV and sensitivity when adopting an hsTnT cut-off level of 60 ng/L, as opposed to the conventional 14 ng/L. This shift could lead to overlooking many at-risk patients. However, a lower hsTnT cut-off level with elevated sensitivity may result in more false positives, leading to unnecessary hospital admissions, testing, and treatments for patients not significantly at risk of adverse outcomes. While it may seem counterintuitive to sacrifice NPV to increase PPV, in the context of acute PE management, accurately identifying high-risk patients who need immediate intervention is paramount. Additionally, a combined model with sPESI ≥ 1 was identified as a particularly valuable tool for prognostic purposes. Standardized cut-off levels for different troponin assessment methods should be established in future studies involving broader patient selection.

Factors influencing hsTnT variability

Advanced age is commonly associated with chronic comorbidities that may contribute to elevated baseline hsTnT

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levels. The discussion of age-dependent troponin levels has been extensive in various studies conducted in acute and non-acute settings [15-19], with debates as to whether these increases are pathological or physiological [17,20,21]. In 2014, Kaeberich et al. [22] proposed a cut-off level of 45 ng/L for predicting adverse 30-day outcomes in patients aged ≥ 75 years while maintaining a level of 14 ng/L for patients aged < 75 years. In our study, a noteworthy elevation in the threshold level of hsTnT was observed, also set at 60 ng/L, specifically for predicting all-cause mortality in patients aged 75 years and older. However, it is important to note that, as of now, age-dependent cut-off levels are not recommended for clinical use [23].

These recommendations propose utilizing sex-specific 99th percentiles for identifying myocardial injury [4,24]. In our study, no significant difference was observed between male and female patients (33.0 ng/L [IQR 15.0–72.0 ng/L] vs. 30.0 ng/L [IQR 15.0–81.0 ng/L]; $p = 0.676$). Even after adjusting for age and sex in the multivariable model, hsTnT levels ≥ 60 ng/L remained significant in predicting clinical outcomes, underscoring the strength of their association with the observed outcomes.

A role of NT-proBNP as a biomarker in risk stratification

Like cardiac troponins, elevated NT-proBNP levels may occur because of RV strain caused by the increased pulmonary artery pressure associated with acute PE [25,26]. Meta-analyses of 12 studies conducted by Klok et al. [27] and 23 studies by Lega et al. [28] demonstrated that higher NT-proBNP levels were associated with an elevated risk of adverse outcomes, with all-cause mortality being a significant factor. However, despite its established prognostic value, the role of NT-proBNP has not yet been integrated into guiding treatment decisions in the context of randomized controlled trials as per the 2019 ESC guidelines. While an NT-proBNP cut-off level of 600 pg/mL has been recommended as the optimal concentration to distinguish low and intermediate risks of adverse outcomes and all-cause mortality within 30 days [29], our multivariable analysis demonstrated that it was only significantly associated with all-cause mortality; it did not emerge as an independent predictor of PE-specific adverse outcomes. Possible reasons for this disparity could include the dynamics of NT-proBNP release, variations in patient characteristics, comorbidities, and the presence of other clinical conditions that may not have been fully captured in the proposed cut-off. Therefore, precise evaluation of hsTnT as a prognostic factor for PE is crucial.

Limitations

This study had several limitations. First, it was a single-center retrospective study with a limited number of patients, which may affect the generalizability of the results. Further investigations with larger cohorts are necessary to validate these findings. Second, the inclusion of SBP < 90 mmHg in the PE-related adverse outcomes could potentially lead to confounding results owing to their elevated baseline risk in these patients. In high-risk patients, low SBP at admission is indeed a critical marker of hemodynamic instability and simultaneously an adverse clinical outcome in this study. The majority of PE-related adverse outcomes in high-risk patients occurred in those with low SBP at admission. reinforcing the need for immediate therapeutic interventions in this subgroup to mitigate potential adverse outcomes. This study referenced previous works [13,30] that included hypotension or "need vasopressor" as an adverse outcome. Furthermore, being retrospective in design, the reflects the results of preventing the risk of death through appropriate thrombolytic therapy in the early hemodynamic instability state; therefore, a criterion of SBP < 90 mmHg was added to the adverse outcomes. Third, the study's reliance solely on initial hsTnT levels may pose a limitation, as it remains unclear whether peak levels or serial follow-ups offer additional insights. Furthermore, excluding comorbidities may not be comprehensive, especially if some conditions are subclinical. Some study patients may have had significant coronary artery disease, which could have potentially affected the specificity of the troponin levels.

Conclusion

Our results confirmed the prognostic value of defined hsTnT level of 60 ng/L in patients with acute PE. Patients surpassing this cut-off level exhibited a heightened risk of both PE-related adverse outcomes and all-cause mortality within 30 days. With the implementation of this new threshold, patients initially classified as intermediate-high or intermediate-low risk may have a lower risk. Early identification and stratification of patients using hsTnT testing can offer valuable insights into personalized and timely management interventions.

KEY MESSAGE

1. The receiving operating characteristics analysis identified an optimal hsTnT cut-off level of 60 ng/L for predicting all-cause mortality within 30 days (AUC 0.74, 95% CI 0.61–0.85, $p < 0.001$).
2. The combined model of hsTnT ≥ 60 ng/L and sPESI ≥ 1 provided additive prognostic information.
3. Compared to the conventional hsTnT level of 14 ng/L, an hsTnT level of 60 ng/L demonstrated superior efficacy in risk stratification.

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Conflicts of interest
The authors disclose no conflicts.

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Supplementary Table 1. Echocardiography parameters

Variable	All patients (n = 341)	Normotensive patients (n = 313)		*p* value[a]	High risk patients (n = 28)	*p* value[b]
		hsTnT < 60 ng/L (n = 208)	hsTnT ≥ 60 ng/L (n = 105)			
LVEF (%)	63.0 (58.0–65.0)	63.0 (59.0–65.0)	62.0 (58.0–65.0)	0.993	62.0 (56.0–64.5)	0.399
LVEDD (mm)	45.0 (41.0–49.0)	45.0 (41.5–49.5)	44.0 (40.0–48.5)	0.039	42.0 (39.0–45.0)	0.002
LVESD (mm)	29.0 (25.0–32.0)	29.0 (26.0–32.0)	28.0 (25.0–32.5)	0.309	27.0 (24.0–30.0)	0.058
EDV (mL)	64.0 (51.0–82.0)	67.5 (53.0–86.0)	56.0 (48.0–76.5)	0.001	57.0 (42.0–74.0)	0.003
ESV (mL)	24.0 (18.0–32.0)	25.5 (19.0–33.0)	21.0 (16.0–29.0)	0.002	23.5 (18.0–34.0)	0.008
E/e'	10.0 (8.0–13.0)	10.0 (8.0–13.0)	11.0 (8.0–13.0)	0.110	10.0 (8.0–13.0)	0.286
Lateral E/e'	8.0 (6.0–10.0)	7.90 (6.0–9.0)	8.7 (7.0–11.0)	0.019	8.0 (7.0–10.0)	0.027
RVSP (mmHg)	43.0 (33.0–55.0)	39.0 (32.0–51.0)	48.0 (37.0–64.0)	< 0.001	51.5 (40.0–59.0)	< 0.001
TR Vmax (m/s)	2.9 (2.5–0.3)	2.7 (2.5–3.2)	3.1 (2.6–3.6)	0.002	3.2 (2.6–3.3)	0.006
RV S' (m/s)	0.11 (0.10–0.13)	0.12 (0.10–0.13)	0.11 (0.09–0.13)	0.029	0.11 (0.08–0.13)	0.078
TAPSE (mm)	18.0 (16.0–22.0)	20.0 (17.0–23.0)	17.0 (14.0–20.0)	< 0.001	17.0 (16.0–21.5)	< 0.001
RV FAC (%)	39.0 (30.0–45.0)	41.0 (36.0–46.0)	35.0 (24.0–43.0)	< 0.001	35.0 (23.0–41.0)	< 0.001
RV diameter (mm)	37.0 (32.0–43.0)	35.0 (31.0–41.0)	39.0 (34.5–46.0)	< 0.001	42.0 (36.5–46.5)	< 0.001
LV diameter (mm)	43.0 (39.0–48.0)	44.0 (41.0–49.0)	42.0 (36.5–47.0)	0.005	40.5 (37.0–44.0)	0.001
RV/LV diameter ratio	0.84 (0.71–1.00)	0.79 (0.69–0.92)	0.93 (0.80–1.13)	< 0.001	1.02 (0.80–1.23)	< 0.001

Values are presented as median (interquartile range).

hsTnT, high-sensitivity troponin T; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; EDV, end diastolic volume; ESV, end systolic volume; RVSP, right ventricular systolic pressure; TR, tricuspid regurgitation; S', tricuspid annulus peak systolic velocity; TAPSE, tricuspid annular plane systolic excursion; FAC, fractional area change.

[a]*p* value was determined through chi-squared or Mann–Whitney U test, comparing groups with hsTnT < 60 ng/L and ≥ 60 ng/L in normotensive patients.

[b]*p* value resulted from the ANOVA test comparing three groups.

Supplementary Table 2. Electrocardiogram parameters

Variable	All patients (n = 374)	Normotensive patients (n = 343)		*p* value[a]	High risk patients (n = 31)	*p* value[b]
		hsTnT < 60 ng/L (n = 237)	hsTnT ≥ 60 ng/L (n = 106)			
Normal electrocardiogram	158 (42.3)	120 (50.6)	29 (27.4)	< 0.001	9 (29.0)	< 0.001
Sinus tachycardia	80 (21.4)	43 (18.1)	30 (28.3)	0.048	7 (22.6)	0.104
Atrial fibrillation	24 (6.4)	11 (4.6)	9 (8.5)	0.247	4 (12.9)	0.124
T-wave inversions in lead V1–V3	91 (24.3)	51 (21.5)	31 (29.3)	0.158	9 (29.0)	0.249
Right bundle branch block (complete or incomplete)	52 (13.9)	23 (9.7)	19 (17.9)	0.049	10 (32.3)	0.001
Complete atrioventricular block	1 (0.3)	0 (0.0)	1 (0.9)	0.309	0 (0.0)	0.282

Values are presented as number (%).
hsTnT, high-sensitivity troponin T.
[a]*p* value was determined through chi-squared or Mann–Whitney U test, comparing groups with hsTnT < 60 ng/L and ≥ 60 ng/L in normotensive patients.
[b]*p* value resulted from the ANOVA test comparing three groups.

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Supplementary Table 3. Cause of death in normotensive and high-risk patients

Variable	Normotensive patients (n = 343)	High-risk patients (n = 31)
All-cause mortality	17 (5.0)	11 (35.5)
PE-related death	7 (2.0)	9 (29.0)
Non-PE-related death	10 (2.9)	2 (6.5)
Respiratory disorders	4 (1.2)	2 (6.5)
Neoplasm	4 (1.2)	0 (0.0)
Cerebrovascular disorders	1 (0.3)	0 (0.0)
Gastrointestinal disorders	1 (0.3)	0 (0.0)

Values are presented as number (%).
PE, pulmonary embolism.

Supplementary Table 4. Prognostic performance of PE-related adverse outcomes according to the sPESI score and hsTnT levels

Parameters	Prevalence	PE-related adverse outcomes	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	+LR	*p* value
sPESI ≥ 1 point + hsTnT ≥ 60 ng/L	96/374 (25.7%)	25/96 (26.0%)	0.71	62.5	78.7	26.0	94.6	77.0	2.94	< 0.001
hsTnT ≥ 60 ng/L	122/374 (32.6%)	25/122 (20.5%)	0.67	62.5	71.0	20.5	94.0	70.1	2.15	< 0.001
sPESI ≥ 1 point	261/374 (69.8%)	39/261 (14.9%)	0.66	97.5	33.5	14.9	99.1	40.4	1.47	< 0.001
hsTnT ≥ 14 ng/L	300/374 (80.2%)	39/300 (13.0%)	0.60	97.5	21.9	13.0	98.6	29.9	1.25	0.002

sPESI, simplified pulmonary embolism severity index; hsTnT, high-sensitivity troponin T; AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio.

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Supplementary Table 5. Clinical outcomes according to sPESI and hsTnT levels

Variable	sPESI 0 point (n = 113)	sPESI ≥ 1 point (n = 261)	*p* value	sPESI 0 point or hsTnT < 60 ng/L (n = 278)	sPESI ≥ 1 point and hsTnT ≥ 60 ng/L (n = 96)	*p* value	hsTnT < 14 ng/L (n = 74)	hsTnT ≥ 14 ng/L (n = 300)	*p* value
PE-related adverse outcomes	1 (0.9)	39 (14.9)	< 0.001	15 (5.4)	25 (26.0)	< 0.001	1 (1.4)	39 (13.0)	0.007
PE-related death	1 (0.9)	15 (5.7)	0.047	3 (1.1)	13 (13.5)	< 0.001	1 (1.4)	15 (5.0)	0.213
Cardiopulmonary resuscitation	1 (0.9)	12 (4.6)	0.120	4 (1.4)	9 (9.4)	0.001	0 (0.0)	13 (4.3)	0.080
Systolic BP < 90 mmHg	0 (0.0)	29 (11.1)	0.001	13 (4.7)	16 (16.7)	< 0.001	1 (1.4)	28 (9.3)	0.040
30-day all-cause mortality	1 (0.9)	27 (10.3)	0.003	7 (2.5)	21 (21.9)	< 0.001	2 (2.7)	26 (8.7)	0.134

Values are presented as number (%).

sPESI, simplified pulmonary embolism severity index; hsTnT, high-sensitivity troponin T; PE, pulmonary embolism; BP, blood pressure.

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