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Troponin I and risk stratification of patients with acute nonmassive pulmonary embolism

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ABSTRACT: The assessment of risk and appropriate treatment of patients with acute pulmonary embolism (PE) remains a challenge.

The prognostic performance of cardiac troponin I (cTnI) in predicting 30-day all-cause mortality was prospectively assessed in consecutive haemodynamically stable patients with PE.

The present study included 318 haemodynamically stable patients with PE. During the 30-day study period, 23 (7%) patients died. cTnI was elevated ($\geqslant$0.1 ng·mL^{-1}) in 102 (32%) patients. An age >65 yrs, systolic blood pressure <120 mmHg and severity of illness assessed using the PE severity index (PESI) were significantly associated with an increased risk for mortality, but no significant association was found between elevation of cTnI and 30-day mortality in a logistic regression analysis. When only fatal PE was considered, multivariate analysis showed that severity of illness using the PESI and an elevated cTnI (odds ratio 3.7, 95% confidence interval (CI) 1.1–12.8) were associated with a significant increase in the risk for death. The negative predictive value (95% CI) of a negative cTnI for mortality was 93 (90–97)%.

In conclusion, in haemodynamically stable patients with acute pulmonary embolism, cardiac troponin I was not an independent predictor of 30-day all-cause mortality, although it did predict fatal pulmonary embolism.

KEYWORDS: Prognosis, pulmonary embolism, troponin

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STATEMENT OF INTEREST
None declared.

Pulmonary embolism (PE) encompasses a wide spectrum of illnesses with diverse prognoses and management strategies [1]. Approximately 10% of patients with PE are critically ill and in cardiogenic shock. These patients warrant thrombolytic therapy unless contraindications preclude this management strategy [2]. At the other end of the spectrum are patients in whom PE has little impact on prognosis, with an average short-term mortality of <5% [3–6]. Although most of these patients remain hospitalised during initial therapy, some may be suitable for partial or complete outpatient management [7]. The risk stratification for patients with PE is important for two reasons. First, patients at high risk for complications could be treated more aggressively, *i.e.* with thrombolytic agents [8–10]. Secondly, patients estimated to be at low risk could be discharged early or managed entirely as outpatients, which could substantially reduce the use of healthcare resources.

Right ventricular dysfunction is a consequence of severe PE that is associated with poor prognosis and higher mortality rates in normotensive patients with acute PE [11]. To date, early detection of right ventricular dysfunction by bedside echocardiography has been proposed as the best established method for determining risk stratification and therapy [12]. Since echocardiography has some technical limitations, is expensive and not widely available in all medical centres, cardiac troponin testing may assist in determining the management of haemodynamically stable patients with acute PE. Although troponin elevation alone may not suffice to predict early death or major complications in patients with acute PE, prior studies suggest that normal troponin levels have a very high negative predictive value for mortality in patients with PE [13]. Thus, troponin may be potentially useful in identifying patients suitable for outpatient management.

The present study was prospectively designed to assess the prognostic significance of elevated cardiac troponin I (cTnI) in a cohort of haemodynamically stable patients with acute symptomatic PE.

METHODS

Study design

In the prospective cohort study, consecutive eligible patients were approached for enrolment between January 1, 2003 and December 31, 2005.

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Patients, setting and eligibility criteria

Outpatients presenting with symptoms of acute PE at the Emergency Dept of Ramón y Cajal Hospital (Madrid, Spain) were screened (fig. 1). Eligible patients were required to have symptomatic PE confirmed by objective testing. Exclusion criteria were: haemodynamic instability at presentation (defined as having cardiogenic shock, systolic blood pressure <90 mmHg or the need for inotropic support despite blood pressure measurements); thrombolytic therapy indicated by decision of attending physician; and troponin levels not determined within 12 h of the diagnosis of PE. The study was approved by the Institutional Review Board of Ramón y Cajal Hospital.

Diagnosis of PE

A diagnosis of PE was suggested by: a high-probability ventilation–perfusion scan according to the criteria of the prospective investigation of pulmonary embolism diagnosis [14]; an indeterminate ventilation–perfusion lung scan and confirmed lower limb deep vein thrombosis on venous ultrasound [15]; or the finding of an intraluminal filling defect on PE protocol contrast enhance helical chest computed tomography [16].

cTnI assay

Blood samples were collected from an antecubital vein at the time of hospital admission. cTnI levels were measured quantitatively using a microparticle enzyme immunoassay (Abbott Laboratories, Abbott Park, IL, USA). The analytical sensitivity for cTnI is 0.08 $ng \cdot mL^{-1}$ and represents the lowest measurable concentration of cTnI that can be distinguished from zero. Using this assay, cTnI concentrations of $\geqslant 0.1$ $ng \cdot mL^{-1}$ were regarded as indicating myocardial injury. The clinicians were unaware of the patients' troponin levels throughout the hospital stay.

Calculation of the prediction rule

Using prospectively collected baseline data at the time of PE diagnosis, PE severity index (PESI) scores were retrospectively determined and each patient was classified into one of five PESI risk classes [17].

Anticoagulant therapy

Patients were treated with therapeutic doses of parenteral anticoagulants while they were prescribed oral vitamin K antagonist therapy. After an initial overlap treatment period, patients were continued on dose-adjusted oral vitamin K antagonist therapy (acenocoumarol) with a target international normalised ratio (INR) of 2.5 (therapeutic range 2.0–3.0). INR was usually monitored daily until the therapeutic range had been achieved, twice or three times weekly for the first few weeks and then once a week to once a month, depending on the stability of the results. Thrombolytic treatment and/or inotropic support were administered in patients with haemodynamic deterioration as deemed appropriate by the attending physician.

Study end-points

The primary end-point was all-cause mortality during the first 30 days of therapy. The secondary end-point was mortality due to PE during the same period of time. Mortality was assessed using patient or proxy interviews and/or hospital chart review. Two independent experts adjudicated the cause of death as definite fatal PE or death from other causes.

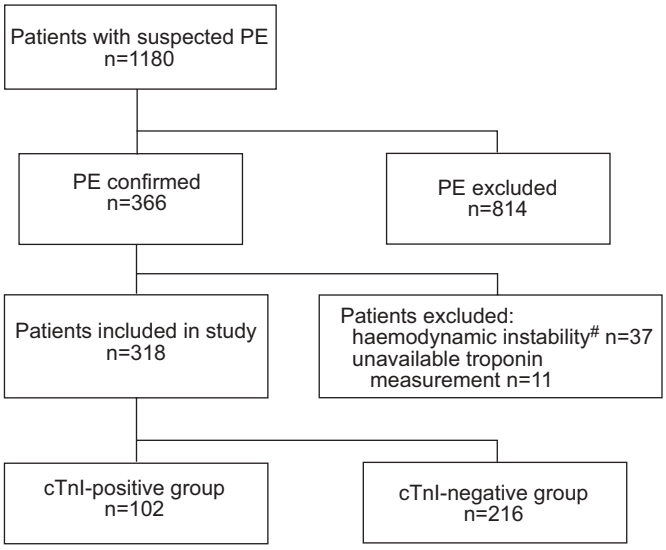

FIGURE 1. Flow diagram of patients assessed for study eligibility. PE: pulmonary embolism; cTnI: cardiac toponin I. #: defined as having cardiogenic shock, systolic blood pressure <90 mmHg or the need for inotropic support despite blood pressure measurements.

Statistical analysis

Data are expressed as mean±SD. All probability values are two-tailed and a p-value <0.05 was considered statistically significant. An unpaired t-test, Wilcoxon rank sum, Chi-squared and Fisher's exact test were used when applicable.

Logistic regression was used to examine the association between cTnI testing and 30-day all-cause mortality, adjusting for other clinical predictors previously described in the literature. Only univariate predictor variables that were significantly associated with mortality ($p<0.05$) were added to the multivariate model.

In order to assess the test and performance characteristics of the cTnI-positive *versus* cTnI-negative groups, the sensitivity, specificity, positive and negative predictive values and likelihood ratios for predicting all-cause mortality were estimated. All 95% confidence intervals (CIs) were computed from the binomial distribution.

RESULTS

A total of 366 consecutive patients with acute PE were screened. A total of 37 (10%) patients were excluded due to haemodynamic instability. Of the 329 stable patients, an additional 11 (3%) patients were excluded because troponin levels could not be determined within 12 h from the diagnosis of PE. All of the remaining eligible 318 patients (136 males and 182 females) who had a diagnosis of haemodynamically stable acute PE at the time of presentation to the emergency dept were enrolled (fig. 1).

Of the 318 enrolled patients, 102 (32%) had elevated serum cTnI levels (cTnI-positive group) and the remaining 216 patients had normal serum cTnI levels (cTnI-negative group).

TABLE 1 Baseline characteristics of 318 consecutive patients with acute pulmonary embolism

	Group		OR (95% CI)	p-value
	cTnI-positive	cTnI-negative		
Subjects n	102	216		
Clinical characteristics				
Age >65 yrs	86 (84)	154 (71)	2.2 (1.2–4.0)	0.02
Male	44 (43)	92 (43)	1.0 (0.6–1.6)	0.90
Risk factors for venous thromboembolism				
Cancer	18 (18)	30 (14)	1.3 (0.7–2.5)	0.45
Surgery	10 (10)	17 (8)	1.5 (0.6–2.9)	0.70
Immobility for ⩾4 days	19 (19)	32 (15)	1.3 (0.7–2.5)	0.46
Previous venous thromboembolism	12 (12)	25 (12)	1.0 (0.5–2.1)	0.86
Comorbid diseases				
Chronic lung disease	14 (14)	39 (18)	0.7 (0.4–1.3)	0.47
Congestive heart failure	19 (19)	26 (12)	1.7 (0.9–3.2)	0.14
Clinical presentation at admission				
Syncope	34 (34)	25 (12)	3.8 (2.1–6.9)	<0.0001
Chest pain	43 (43)	127 (59)	0.5 (0.3–0.8)	0.01
Dyspnoea	77 (77)	155 (72)	1.2 (0.7–2.1)	0.42
Cardiac frequency ⩾100 beats·min^{-1}	50 (50)	79 (37)	1.7 (1.0–2.7)	0.04
P_{O_2} <60 mmHg	52 (52)	120 (56)	0.8 (0.5–1.3)	0.59
Systolic blood pressure <120 mmHg	37 (36)	71 (33)	1.2 (0.7–1.9)	0.69
ECG				
SI-QIII pattern	16 (16)	19 (9)	1.9 (0.9–3.9)	0.09
Complete/incomplete right bundle branch block	23 (23)	24 (11)	2.3 (1.2–4.4)	0.008
Inverted T-waves in V_1 through V_3	18 (18)	25 (12)	1.6 (0.8–3.2)	0.20

Data are presented as n (%), unless otherwise stated. OR: odds ratio; CI: confidence interval; P_{O_2}: partial pressure of oxygen.

Patients in the cTnI-positive group were significantly older when compared with patients in the cTnI-negative group. Syncope on presentation was more frequent in the cTnI-positive group, whereas chest pain was more frequent in the cTnI-negative group (table 1). There was a significant association between elevated troponin levels and the presence of a right bundle branch block on the ECG (p=0.008) and sinus tachycardia (p=0.04). There was no association between

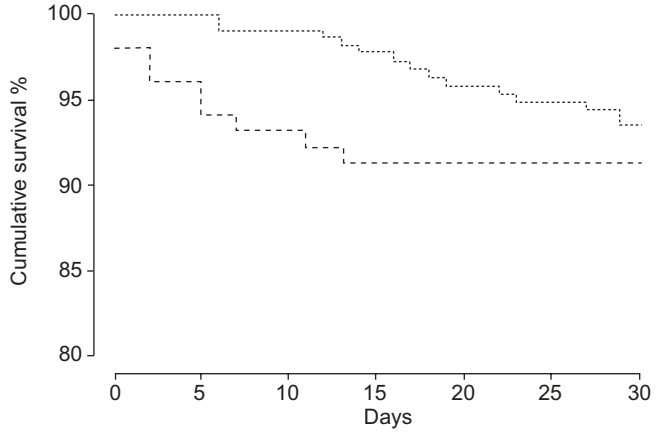

FIGURE 2. Kaplan–Meier 30-day all-cause mortality of cardiac troponin I (cTnI)-positive (----) and -negative (·····) test groups. The numbers of patients at risk in the cTnI-positive group were 102, 96, 95, 93, 93, 93 and 93, while in the cTnI-negative group they were 216, 216, 214, 211, 207, 205 and 202 for day 0, 5, 10, 15, 20, 25 and 30, respectively.

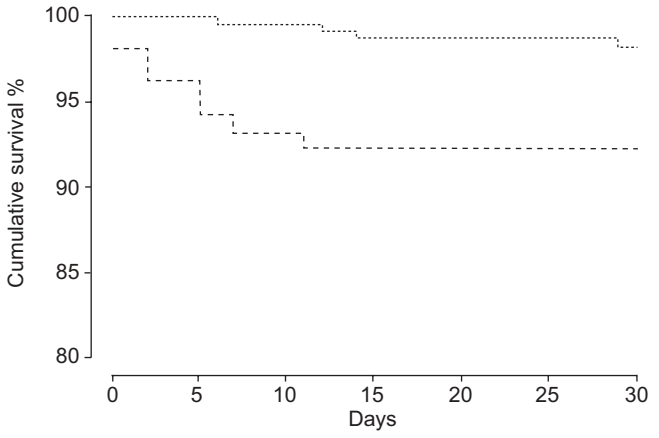

FIGURE 3. Kaplan–Meier 30-day pulmonary embolism-related mortality of cardiac troponin I (cTnI)-positive (----) and -negative (·····) test groups. The numbers of patients at risk in the cTnI-positive group were 102, 96, 95, 94, 94, 94 and 94, while in the cTnI-negative group they were 216, 216, 215, 213, 213, 213 and 212 for day 0, 5, 10, 15, 20, 25 and 30, respectively.

elevated troponin levels and the presence of an S1Q3T3 pattern or T-wave inversion on ECG.

During the 1-month follow-up period, 23 (7%) patients died. In the cTnI-positive group, 30-day all-cause mortality was 9% compared with 6% in the cTnI-negative group (odds ratio (OR) 1.4, 95% CI 0.6–3.3; p=0.46). The cTnI-positive group had a trend toward earlier death compared with the cTnI-negative group (log rank p=0.402; fig. 2). Mortality in the cTnI-positive group was the result of thromboembolic disease (eight cases) and seizures (one case). Mortality in the cTnI-negative group was the result of thromboembolic disease (four cases), heart failure (four cases), malignancy (two cases), infection (two cases), renal insufficiency (one case) and unspecified cause (one case).

For 30-day PE-related mortality, survival was lower in the cTnI-positive group compared with the cTnI-negative group (log rank p=0.008; fig. 3). Most (eight out of nine) of the early deaths (within 7–10 days after diagnosis) were due to complications of PE. Troponin test was positive in seven of the nine patients who died early. Four of the eight patients who died early from PE complications had the lowest positive troponin level.

Univariate analysis of data from the 318 patients revealed that age >65 yrs, systolic blood pressure (SBP) <120 mmHg and severity of illness assessed using the PESI were significantly associated with 30-day mortality (table 2). Upon multivariate analysis, patients with an SBP <120 mmHg (OR 4.0, 95% CI 1.6–9.7; p=0.003) and severity of illness (OR 7.8, 95% CI 1.0–60.9; p=0.05) were independently associated with an increased risk for 1-month mortality. When only fatal PE was considered, multivariate analysis showed that severity of illness using the PESI and an elevated cTnI (OR 3.7, 95% CI 1.1–12.8; p=0.03) were associated with a significant increase in the risk for 30-day all-cause mortality.

The negative predictive value of a negative cTnI (<0.1 ng·mL^{-1}) for 30-day all-cause mortality was 93% (95% CI 90–97%), while the negative likelihood ratio was 1.0% (0.9–1.1%). The negative predictive value of a negative cTnI (<0.1 ng·mL^{-1}) for 30-day PE-related mortality was 98% (96–100%), while the negative likelihood ratio was 0.5% (0.2–1.1%; table 3).

DISCUSSION

There are two principal conclusions that follow from the present results. First, an elevated cTnI was associated with a 4.5-fold increased risk of fatal PE, but it did not appear to confer an increased risk of all-cause death. Secondly, although a low cTnI level exhibited a very high negative predictive value with regard to prognosis, troponin by itself does not

TABLE 2 Risk factors for 30-day all-cause mortality

	Nonsurvivors	Survivors	OR (95%CI)	p-value
Subjects n	23	295		
Clinical characteristics				
Age >65 yrs	22 (96)	218 (74)	7.8 (1.0–58.6)	0.03
Male	10 (43)	126 (43)	1.0 (0.4–2.4)	0.83
Risk factors for venous thromboembolism				
Cancer	6 (26)	42 (14)	2.1 (0.8–5.7)	0.21
Surgery	1 (4)	26 (9)	0.5 (0.1–3.6)	0.66
Immobility for ⩾4 days	7 (30)	44 (15)	2.5 (1.0–6.4)	0.11
Previous venous thromboembolism	2 (9)	35 (12)	0.7 (0.2–3.1)	0.92
Underlying diseases				
Chronic lung disease	4 (17)	49 (17)	1.1 (0.3–3.2)	0.77
Congestive heart failure	3 (13)	42 (14)	0.9 (0.3–3.2)	0.86
Clinical presentation at admission				
Syncope	2 (9)	57 (19)	0.4 (0.1–1.7)	0.36
Chest pain	9 (39)	161 (55)	0.5 (0.2–1.3)	0.20
Dyspnoea	17 (74)	215 (73)	1.0 (0.4–2.8)	0.89
Cardiac frequency ⩾100 beats·min^{-1}	9 (39)	120 (41)	0.9 (0.4–2.2)	0.97
P_{O_2} <60 mmHg	14 (61)	158 (54)	1.3 (0.6–3.2)	0.66
Systolic blood pressure <120 mmHg	14 (61)	94 (32)	3.3 (1.4–8.0)	0.009
PESI high-risk strata[#]	22 (96)	196 (66)	11.1 (1.5–83.6)	0.006
Electrocardiogram				
SI-QIII pattern	0 (0)	35 (12)		0.16
Complete/incomplete right bundle branch block	1 (4)	46 (16)	0.2 (0–1.9)	0.21
Inverted T-waves in V_1 through V_3	3 (13)	40 (14)	1.0 (0.3–3.4)	0.86
Laboratory findings				
cTnI >0.1 ng·mL^{-1}	9 (39)	93 (32)	1.4 (0.6–3.3)	0.65

Data are presented as n (%), unless otherwise stated. OR: odds ratio; CI: confidence interval; P_{O_2}: partial pressure of oxygen; PESI: pulmonary embolism severity index; cTnI: cardiac troponin I. [#]: strata defined in [17].

TABLE 3 Risk factors for fatal pulmonary embolism (PE) during 30-days of follow-up

	Fatal PE	Non-fatal PE	OR (95% CI)	p-value
Subjects n	12	306		
Clinical characteristics				
Age >65 yrs	12 (100)	228 (74)		0.09
Male	5 (42)	131 (43)	0.9 (0.3–3.1)	0.82
Risk factors for venous thromboembolism				
Cancer	4 (33)	44 (14)	3.0 (0.9–10.3)	0.16
Surgery	1 (8)	26 (8)	1.0 (0.1–7.9)	0.58
Immobility for ⩾4 days	3 (25)	48 (16)	1.8 (0.5–6.9)	0.67
Previous venous thromboembolism	2 (17)	35 (11)	1.5 (0.3–7.4)	0.86
Underlying diseases				
Chronic lung disease	4 (33)	49 (16)	2.6 (0.8–9.0)	0.25
Congestive heart failure	3 (25)	42 (14)	2.1 (0.5–8.0)	0.52
Clinical presentation at admission				
Syncope	2 (17)	57 (19)	0.9 (0.2–4.1)	0.84
Chest pain	6 (50)	164 (54)	0.9 (0.3–2.7)	0.98
Dyspnoea	8 (67)	224 (73)	0.7 (0.2–2.5)	0.89
Cardiac frequency ⩾100 beats·min^{-1}	5 (42)	124 (40)	1.0 (0.3–3.4)	0.87
P_{O_2} <60 mmHg	7 (58)	165 (54)	1.2 (0.4–3.8)	0.98
Systolic blood pressure <120 mmHg	6 (50)	102 (33)	2.0 (0.6–6.4)	0.36
PESI high-risk strata[#]	12 (100)	206 (67)		0.03
Electrocardiogram				
SI-QIII pattern	0 (0)	35 (11)		0.46
Complete/incomplete right bundle branch block	1 (8)	46 (15)	0.5 (0.1–4.1)	0.79
Inverted T-waves in V_1 through V_3	1 (8)	42 (14)	0.6 (0.1–4.5)	0.87
Laboratory findings,				
cTnI >0.1 ng·mL^{-1}	8 (67)	94 (31)	4.5 (1.3–15.3)	0.02

Data are presented as n (%), unless otherwise stated. OR: odds ratio; CI: confidence interval; P_{O_2}: partial pressure of oxygen; PESI: PE severity index; cTnI: cardiac troponin I. [#]: strata defined in [17].

appear to clinically significantly change the pre- to post-test probability (*i.e.* positive and negative likelihood ratios are not extreme) of risk of death or PE-related complications.

PE encompasses a wide spectrum of presentations, prognoses and consequent management strategies [11]. A tool that accurately predicts adverse outcomes at the time of presentation could determine management and outcomes. cTnI may have a role for risk stratification and prognostication in patients with acute PE. cTnI may also serve as a surrogate for echocardiographic right ventricle dysfunction, and increased concentrations of cardiac troponins have been found to predict fatal outcome in patients with haemodynamically stable PE in other studies [18, 19].

The present study enrolled a large number of consecutive patients with haemodynamically stable acute PE. Elevated cTnI plasma concentrations were found in 32% of the 318 investigated cases. This detection rate was similar to that of the study by KOSTRUBIEC *et al.* [20] and lies within the range of the results of other studies that have assessed the usefulness of troponin in patients with stable PE [18, 19]. In a study of 458 patients with submassive PE, the incidence of cTnI >0.5 μg·L^{-1} was 13% [18]. The discrepancy between that study and the present findings is probably the result of differences in the cut-off value used to define an elevated cardiac troponin. Moreover, in the study by DOUKETIS *et al.* [18], patients were derived from a randomised controlled trial [21], which tends to exclude sicker patients. In another study of 106 patients with PE of unspecified severity, 41% had a cTnI >0.07 μg·L^{-1} [19]. However, although patients included in that study were normotensive, they had been referred for echocardiographic assessment of right ventricular dysfunction, thus reflecting a group of PE patients of higher severity.

A positive troponin test independently predicted fatal PE. The PE-related deaths mainly occurred within 1 week of diagnosis of PE. A positive troponin test did not predict all-cause mortality. Severity of illness, based on a validated clinical model (*i.e.* PESI), predicted both overall and specific PE mortality. The present authors, therefore, propose that an elevated cTnI is a marker of decreased cardiorespiratory reserve in patients with PE, while the PESI also underscores the prognostic significance of other important clinical factors, such as age, cancer or previous lung or cardiac disease.

The clinical benefit of cardiac troponins is foremost due to the high negative predictive value [13]. Troponin testing in normotensive patients with PE appears to be most relevant as a screening test for the identification of low-risk patients

suitable for outpatient management. The present results indicate that troponin testing does not identify patients with stable PE who are at very low risk of fatal medical outcomes. This result could be explained as a consequence of a lower performance of the troponin testing in the present series with respect to previously published studies [19, 22–24]. Since the negative likelihood ratio was not extreme, the present results may also warrant the need to combine troponin measurement with other tools (*e.g.* clinical prognostic scores, echocardiography) in order to identify low-risk patients for out-of-hospital treatment of acute PE [25].

There are several limitations to the present study that should be acknowledged. First, it has been recommended that a second biomarker test should be obtained 6–12 h after an initially negative test in a PE patient with a symptom duration of <6 h [26]. It is, however, questionable whether repeated troponin measurements represent a practical and economic approach for optimising risk stratification of PE. Secondly, coronary artery disease-related positive cTnI was excluded based on ECGs and clinical evolution of the patients. Thus, it cannot be excluded that significant coronary artery stenosis or even acute coronary syndrome may have been present in some of the study patients, limiting the specificity of troponin measurements. However, the study protocol required confirmation of PE in all cases. Therefore, additional diagnostic workup in order to exclude concomitant coronary artery disease was not deemed appropriate. Finally, it has been shown that the use of troponin measurement and echocardiography in combination can identify patients at high risk for death after PE [27, 28]. However, as echocardiography was not a protocol requirement in the present study, those results could not be confirmed.

In conclusion, the present results support the value of cardiac troponin I for the prediction of 30-day pulmonary embolism-related mortality but not all-cause mortality, in a large series of stable patients presenting to the emergency dept with acute pulmonary embolism.

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