



Troponin T predicts in-hospital and 1-year mortality in patients with pulmonary embolism

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ABSTRACT: We aimed to determine the prognostic value of troponin T (TNT) for in-hospital and 1-yr mortality in a large sample of patients with pulmonary embolism (PE).

Patients presenting at the emergency department of a tertiary care centre from January 1998 to December 2006 with PE were included. A blood sample was taken at the time of presentation. To determine in-hospital and 1-yr mortality, data from the hospital records and the national death register were used.

TNT was determined in 563 out of 737 patients with proven PE. TNT was elevated ($>0.03\text{ng}\cdot\text{mL}^{-1}$) in 27%. In-hospital survival was 79% in TNT-positive patients compared with 94% in TNT-negative patients ($p<0.001$). 1-yr survival was 71% in TNT-positive patients compared with 90% in TNT-negative patients ($p<0.001$). Elevated TNT levels meant a four-times higher risk of in-hospital death and a three-times higher risk of 1-yr mortality, even after adjustment for the other most important risk factors of death in this population.

Elevated TNT independently predicts in-hospital and 1-yr mortality in patients with acute PE.

KEYWORDS: Prognosis, pulmonary embolism, troponin

Cardiac troponins are highly specific and sensitive markers of myocardial cell injury and have been found to be elevated in acute coronary syndromes, myocarditis, acute heart failure, septic shock and after therapeutic cardiac procedures [1]. Pulmonary embolism (PE) is associated with elevated cardiac troponins in only a subset of patients. The reason for release in PE is still unclear. However, an explanation might be hypoxaemia due to perfusion-ventilation mismatch, hypoperfusion as a consequence of low output and reduced coronary blood flow, as well as cell injury caused by acute dilatation of the right ventricle, or a combination of these factors.

Currently, prognostic stratification in PE is based on blood pressure at admission, troponins as markers of right ventricular ischaemia and right ventricular dysfunction mainly assessed by echocardiography [2, 3]. However, the lack of standard criteria for right ventricular dysfunction and the need for specialised personnel limit the use of echocardiography. Troponins, which are rapidly available, have been shown to be associated with right ventricular dysfunction in PE. While their use seems to be marginal in diagnosis, troponins may significantly contribute to prognostic

stratification [4]. Due to their high negative predictive value for mortality in PE, they are particularly useful for the identification of low-risk patients [5]. Investigations are ongoing to evaluate whether troponins might qualify as a tool for the identification of a certain portion of haemodynamically stable patients who would benefit from thrombolysis. Currently, thrombolysis is only recommended in patients with massive PE causing haemodynamic instability [6].

In a recent meta-analysis [7], elevated plasma levels of troponins were associated with increased in-hospital or 3-month mortality in patients with acute PE. In the 20 included studies (eight evaluating troponin T; TNT), the longest observation period was 100 days and the average study comprised of 98 patients. However, data regarding clinical outcome is scarce and the true predictive value of elevated troponins for adverse outcome is still unclear. Thus, our study aimed to determine the relationship between TNT and survival in a much larger sample of patients diagnosed with PE. Compared to the studies included in the meta-analysis, our study clearly comprises the largest number of patients and the longest observation period.

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TABLE 1 Patient characteristics

	Total of patients with PE	Patients without TNT measurement	TNT-positive patients	TNT-negative patients	p-value [#]
Subjects n	737	174	151	412	
Age yrs	55 (54–57)	52 (49–54)	61 (59–64)	55 (53–56)	≤0.001
Body mass index	28 (27–28)	27 (26–28)	29 (27–30)	28 (27–28)	
Oxygen saturation %	92 (92–93)	92 (91–94)	90 (88–91)	94 (93–94)	≤0.001
Systolic blood pressure mmHg	128 (126–131)	131 (125–137)	110 (102–117)	134 (131–137)	≤0.001
Diastolic blood pressure mmHg	71 (69–72)	71 (68–74)	63 (59–67)	73 (72–75)	≤0.001
Heart rate beats·min⁻¹	97 (95–99)	95 (91–100)	102 (97–107)	96 (94–99)	≤0.001
Shock index beats·min⁻¹·mmHg⁻¹	0.79 (0.77–0.81)	0.75 (0.72–0.79)	0.97 (0.91–1.03)	0.74 (0.72–0.76)	≤0.001
Creatinine mg·dL⁻¹	1.17 (1.12–1.22)	1.08 (1.02–1.14)	1.46 (1.30–1.62)	1.11 (1.05–1.16)	≤0.001
Categorical data					
Male	351 (48)	74 (43)	67 (45)	210 (51)	
Positive shock index	121 (16)	22 (13)	60 (40)	39 (9)	≤0.001
Concomitant diseases					
Cancer at any time	147 (20)	36 (21)	33 (22)	78 (19)	
Chronic heart failure	71 (10)	10 (6)	24 (16)	37 (9)	≤0.05
COPD	67 (9)	13 (8)	16 (11)	38 (9)	
Coronary artery disease	93 (13)	12 (7)	24 (16)	57 (14)	
Hypertension	205 (30)	32 (22)	56 (39)	117 (29)	≤0.05
Risk factors					
Smoking	173 (24)	43 (25)	22 (15)	108 (26)	≤0.01
Immobilisation	134 (18)	43 (25)	32 (21)	59 (14)	≤0.05
Long distance travel	52 (7)	10 (6)	3 (2)	39 (9)	≤0.01
Previous VTE	215 (29)	54 (31)	33 (22)	128 (31)	≤0.05
Family history of VTE	66 (9)	20 (12)	11 (7)	35 (9)	
Surgery	105 (14)	30 (17)	32 (21)	43 (10)	≤0.01
Symptoms					
Dyspnoea on physical exercise	322 (44)	73 (42)	43 (28)	206 (50)	≤0.001
Dyspnoea while resting	223 (30)	42 (24)	88 (58)	93 (23)	≤0.001
Any of the two above	539 (73)	113 (65)	128 (85)	298 (72)	≤0.01
Pleuritic chest pain	378 (51)	111 (64)	35 (23)	232 (56)	≤0.001
Angina like chest pain	142 (19)	11 (6)	54 (36)	77 (19)	≤0.001
Any of the two above	490 (67)	117 (68)	81 (54)	292 (71)	≤0.001
Cough	131 (18)	37 (21)	16 (11)	78 (19)	≤0.05
Tachycardia	177 (24)	41 (24)	57 (38)	79 (19)	≤0.001
Syncope	88 (12)	13 (8)	47 (31)	28 (7)	≤0.001
Treatment					
Thrombolysis	132 (18)	20 (12)	66 (44)	46 (11)	≤0.001
Cardiopulmonary resuscitation	66 (9)	15 (9)	35 (23)	16 (4)	≤0.001
Catecholamine	90 (12)	21 (12)	47 (31)	22 (5)	≤0.001

Data are presented as mean (95% confidence interval) or n (%), unless otherwise stated. PE: pulmonary embolism; TNT: troponin T; COPD: chronic obstructive pulmonary disease; VTE: venous thromboembolism. #: p-values are provided for descriptive purposes only and are between TNT positive and TNT negative patients.

METHODS

Patients and measurements

All patients diagnosed with PE from January 1998 to December 2006, who had at least one blood collection for TNT measurement at the time of presentation at the emergency ward of Vienna General Hospital (Vienna, Austria), a tertiary care facility, were included. Diagnosis of PE had to be definite, either by ventilation–perfusion scintigraphy, spiral computed tomography, angiography, thrombus detection by trans-oesophageal echocardiography or autopsy. A number of patients (n=106) were included in a previously published study

evaluating in-hospital mortality [8]. The measurement of TNT was routinely performed by electrochemiluminescence immunoassay on an Elecsys 2010 analyser (Roche Diagnostics AG, Rotkreuz, Switzerland) (coefficient of variation: 5.7%) after blood sampling into evacuated tubes for clinical chemistry analysis (Vacutainer tubes; Becton Dickinson, Heidelberg, Germany). A TNT value of >0.03 ng·mL⁻¹ was interpreted as “positive”. All data except outcome were continuously entered into the database. To determine in-hospital and 1-yr mortality, a double data set of the hospital records and the Austrian death register were used. Deaths were classified by International

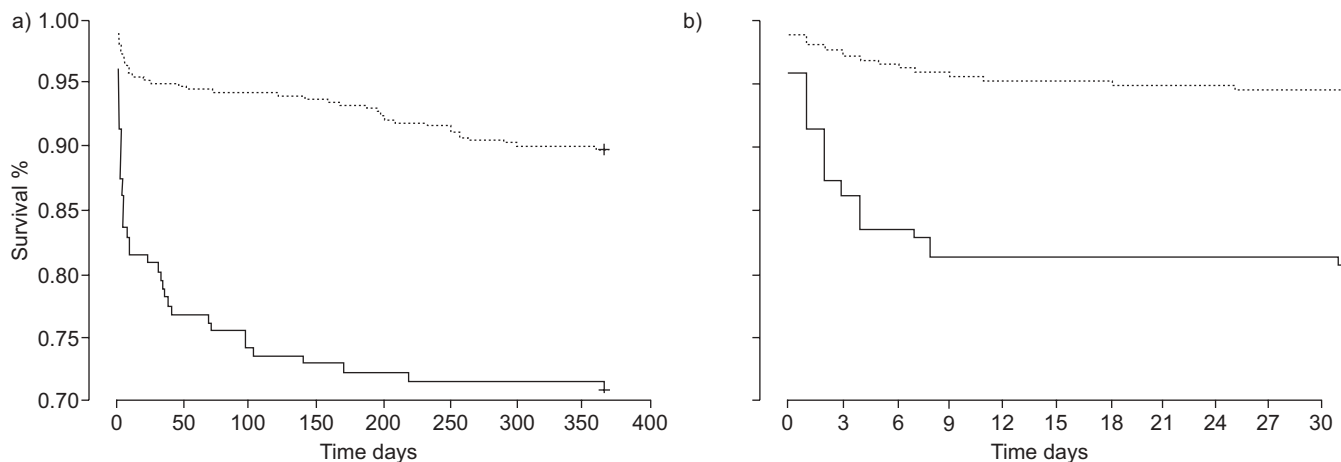


FIGURE 1. a) 1-yr and b) in-hospital survival in troponin T (TNT) positive (—) compared with TNT negative (·····) patients with pulmonary embolism. 1-yr survival was 71% in TNT positive patients compared with 90% in TNT negative patients. In-hospital survival was 79% in TNT positive patients compared with 94% in TNT negative patients.

Classification of Disease codes in both cases. In seven inconsistent classification cases a decision was made by a single investigator from the case history without regard of the TNT value. Pathologists and clinicians classifying causes of death did not know about the inclusion of the patients into the study.

Statistical analysis

Mean and 95% confidence intervals are provided for descriptive analysis and non-parametric tests were used for reasons of robustness. Survival rates are plotted according to the method of Kaplan–Meier, and log rank and Breslow tests were calculated. Multivariate analysis was performed with the Cox regression, which also included cancer, immobility and age as known risk factors [9, 10] for short-term mortality in patients suffering from PE. The level of significance was set to a two-sided probability value ($p < 0.05$). Data were analysed using SPSS Version 14.0 (SPSS Inc., Chicago, IL, USA). For generation

of the Forrest plot, Review Manager 5.0.16 (Cochrane Collaboration, Oxford, UK) was used.

RESULTS

TNT was determined in 563 out of 737 patients diagnosed with PE. In 151 (27%) patients TNT levels were $>0.03 \text{ ng}\cdot\text{mL}^{-1}$, while 412 (73%) patients were TNT negative. TNT-positive patients were older, had more comorbidities, higher serum creatinine levels and were more likely to present with severe clinical signs and symptoms of PE, including angina-like chest pain, dyspnoea while resting, tachycardia, low oxygen saturation and syncope. During the initial phase they were more likely to need cardiopulmonary resuscitation, catecholamines or to undergo thrombolysis (table 1).

During 1 yr of follow-up, 112 (15%) out of the 737 patients died. The mortality rate was similar in the 174 (15%) patients who had no TNT determined. 44 (29%) of the TNT-positive

TABLE 2 Mortality and causes of death in the study population

	Total of patients with PE	Patients without TNT measurement	TNT-positive patients	TNT-negative patients
Subjects n	737	174	151	412
Outcome				
Death in the first year	112 (15.2)	26 (14.9)	44 (29.1)	42 (10.2)
In hospital death	73 (9.9)	17 (9.8)	32 (21.2)	24 (5.8)
Causes of death				
Pulmonary embolism	48 (6.5); 43	15 (8.6); 58	23 (15.2); 52	10 (2.4); 24
Cancer	28 (3.8); 25	3 (1.7); 12	8 (5.3); 18	17 (4.1); 40
Coronary artery disease	3 (0.4); 3	0 (0.0); 0	1 (0.7); 2	2 (0.5); 5
Heart failure	4 (0.5); 4	1 (0.6); 4	2 (1.3); 5	1 (0.2); 2
Intracerebral haemorrhage	1 (0.1); 1	0 (0.0); 0	0 (0.0); 0	1 (0.2); 2
Stroke	1 (0.1); 1	1 (0.6); 4	0 (0.0); 0	0 (0.0); 0
Other	9 (1.2); 8	2 (1.1); 8	5 (3.3); 11	2 (0.5); 5
Unknown	18 (2.4); 16	4 (2.3); 15	5 (3.3); 11	9 (2.2); 21

Data are presented as n (%) or n (%); % relative, unless otherwise stated. PE: pulmonary embolism; TNT: troponin T.

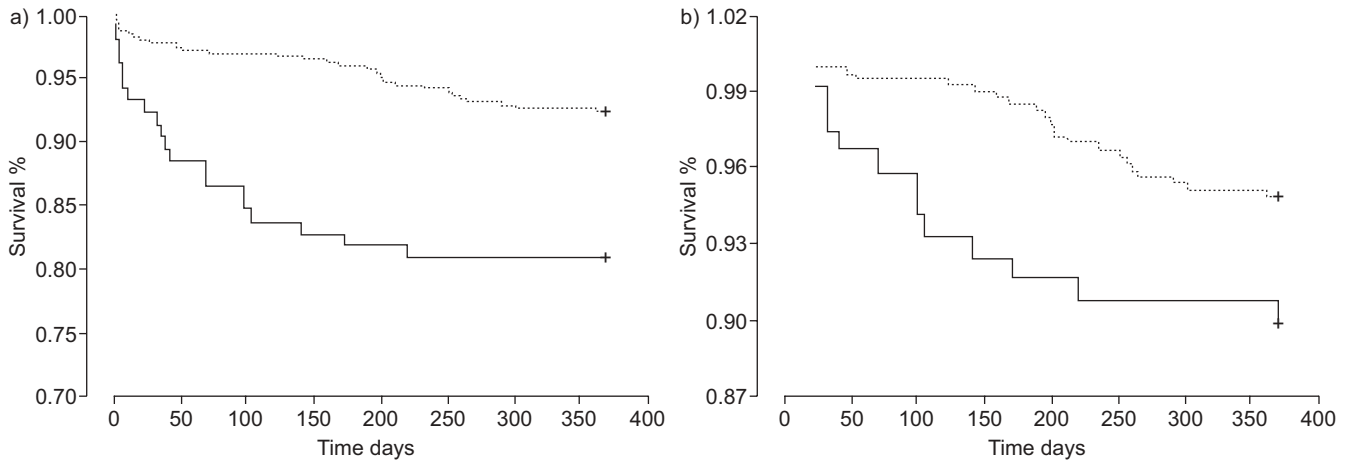


FIGURE 2. 1-yr survival after a) exclusion of initially haemodynamically unstable patients and b) exclusion of patients who died in hospital. Patients who were resuscitated prior to or at admission, who presented with a systolic blood pressure <90 mmHg, or who were treated with catecholamines in the pre-clinical phase were excluded. In the initially haemodynamically stable patients, 1-yr survival was 81% in troponin T (TNT) positive patients compared with 92% in TNT negative patients. After exclusion of patients who died in hospital, 1-yr survival was 90% in TNT positive patients compared with 95% in TNT negative patients. —: TNT positive patients;: TNT negative patients.

patients died compared to 42 (10%) of the TNT-negative patients (Rank and Breslow test: $p < 0.001$) (fig. 1a). The in-hospital death rate was 10% in the overall study population and patients without TNT measurement, 32 (21%) of the TNT-positive patients and 24 (6%) of the TNT-negative patients (Rank and Breslow test: $p < 0.001$) (table 2, fig. 1b). Exclusion of patients who were unstable at presentation resulted in 1-yr mortality rates of 19% and 8% in TNT-positive and TNT-negative patients, respectively ($p < 0.001$; fig. 2a). After exclusion of patients who died in hospital, the median duration of hospitalisation was 11 days. The median duration of hospitalisation was 14 days in TNT-positive patients compared with 10 days in TNT-negative patients. Patients who survived the hospitalisation phase had a 1-yr mortality rate of 10% and 5%, TNT-positive *versus* TNT-negative patients, respectively ($p = 0.047$; fig. 2b).

The major cause of death in the first year was PE in TNT-positive patients and in patients without TNT measurement, while in TNT-negative patients the cause of death was cancer (table 2). Of the 48 patients who died from PE, 45 died in

hospital. In contrast, of the 28 patients who died from cancer, only 11 died in hospital. Other reasons for death such as congestive heart failure, coronary artery disease, stroke and intracerebral haemorrhage were less common. In 18 (16%) patients the reason for death was not specified in the death register and was, therefore, classified as unknown.

Elevated TNT levels ($>0.03 \text{ ng}\cdot\text{mL}^{-1}$) were associated with a significant increase in the risk of all-cause death in hospital (HR 4.3, 95% CI 2.5–7.4) and death during the first year following PE (HR 3.3; 95% CI 2.2–5.0) (tables 3 and 4).

TNT remained an independent predictor of mortality after inclusion of the other most important risk factors of death (cancer, immobility and age) in the Cox model: HR 4.0 (95% CI 2.3–7.1) for in-hospital death and HR 2.8 (95% CI 1.8–4.3) for 1-yr mortality. In the multivariate analysis, cancer at any time was associated with a 3.1-fold (95% CI 2.0–4.8) increased risk for 1-yr mortality. Immobility was associated with a HR of 2.4 (95% CI 1.5–3.8), whereas age was not an independent predictor. Initial haemodynamical instability was defined by

TABLE 3 1-yr mortality

	Parametric rating	Standard error	p-value	Hazard ratio	95% CI
Univariate analysis					
Troponin T	1.19	0.22	0.0000	3.29	2.15–5.02
Age	0.02	0.01	0.0002	1.02	1.01–1.03
Cancer	1.08	0.19	0.0000	2.95	2.02–4.29
Immobility	1.18	0.20	0.0000	3.24	2.21–4.75
Multivariate analysis					
Troponin T	1.02	0.22	0.0000	2.76	1.78–4.28
Age	0.00	0.01	0.7507	1.00	0.99–1.02
Cancer	1.13	0.22	0.0000	3.11	2.00–4.82
Immobility	0.88	0.24	0.0002	2.41	1.52–3.82

TABLE 4 In-hospital mortality

	Parametric rating	Standard error	p-value	Hazard ratio	95% CI
Univariate analysis					
Troponin T	1.46	0.28	0.0000	4.32	2.51–7.44
Age	0.01	0.01	0.2968	1.01	0.99–1.02
Cancer	0.59	0.26	0.0213	1.81	1.09–2.99
Immobility	1.36	0.24	0.0000	3.88	2.42–6.22
Multivariate analysis					
Troponin T	1.39	0.29	0.0000	4.03	2.29–7.08
Age	-0.01	0.01	0.1015	0.99	0.97–1.00
Cancer	0.62	0.30	0.0397	1.87	1.03–3.39
Immobility	1.07	0.29	0.0002	2.90	1.65–5.10

TABLE 5 1-yr mortality after exclusion of patients haemodynamically instable at presentation

	Parametric rating	Standard error	p-value	Hazard ratio	95% CI
Univariate analysis					
Troponin T	1.02	0.29	0.0004	2.78	1.58–4.90
Age yrs	0.03	0.01	0.0000	1.04	1.02–1.05
Cancer	1.76	0.26	0.0000	5.81	3.49–9.69
Immobility	1.15	0.27	0.0000	3.15	1.85–5.36
Multivariate analysis					
Troponin T	0.78	0.30	0.0080	2.19	1.23–3.92
Age yrs	0.01	0.01	0.2285	1.01	0.99–1.03
Cancer	1.77	0.29	0.0000	5.90	3.32–10.46
Immobility	1.11	0.31	0.0004	3.03	1.64–5.59

TABLE 6 1-yr mortality after exclusion of in hospital deaths

	Parametric rating	Standard error	p-value	Hazard ratio	95% CI
Univariate analysis					
Troponin T	0.73	0.37	0.0466	2.07	1.01–4.23
Age yrs	0.05	0.01	0.0000	1.05	1.03–1.08
Cancer	1.88	0.32	0.0000	6.57	3.53–12.23
Immobility	0.85	0.34	0.0137	2.33	1.19–4.57
Multivariate analysis					
Troponin T	0.49	0.37	0.1848	1.63	0.79–3.35
Age yrs	0.04	0.01	0.0093	1.04	1.01–1.06
Cancer	1.92	0.37	0.0000	6.81	3.30–14.03
Immobility	0.68	0.43	0.1144	1.98	0.85–4.61

resuscitation prior to or at admission, presentation with a systolic blood pressure <90 mmHg or treatment with catecholamines in the pre-clinical phase. Even after exclusion of initially haemodynamically instable patients TNT was predictive for 1-yr mortality in the multi- and univariate analysis (HR 2.2 (95% CI 1.2–3.9) and HR 2.8 (95% CI 1.6–4.9), respectively) (table 5). After the exclusion of patients who

died in hospital, TNT only remained predictive in the univariate analysis. After discharge from the hospital, cancer was the strongest predictor for 1-yr mortality (table 6).

Replacement of the data from our prior study [8] by the results for in-hospital outcome from the meta-analysis by BECATTINI *et al.* [7] led to a shift in the overall odds ratio for death from

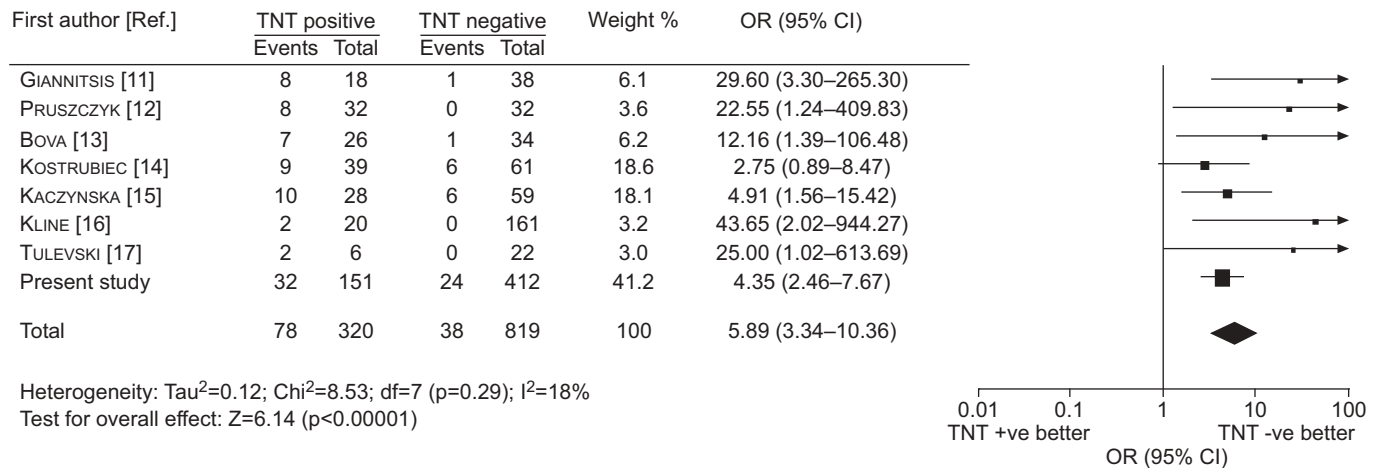


FIGURE 3. Odds ratio for in-hospital mortality based on elevated or normal plasma levels of troponin T (TNT). Levels of TNT after addition of current data to the existing meta-analysis.

7.95 to 5.89 with a reduction in the confidence interval (fig. 3). Due to the current size of the cohort this led to a weight gain from 6.0% to 41.2% in the meta-analysis without relevant impact on heterogeneity.

DISCUSSION

Our study has several interesting findings. First, the fact that elevated TNT is an independent predictor of short-term mortality in PE, as previously suggested by several small studies [8, 11–17], is confirmed in our cohort study. By including the results for in-hospital mortality from the meta-analysis of BECATTINI *et al.* [7], our study adds a lot of information on the presumed true predictive value of TNT (fig. 3), which might be slightly lower than previously assumed. The odds ratio for in-hospital mortality in the current study is 4.35 (HR 4.32), which is very similar to the odds ratio of 4.01 revealed by pooling 12 studies evaluating troponin I [7]. The best estimate is crucial when it comes to the weighting of risk factors and inclusion in prognostic scores. Such scores are considered to facilitate risk stratification in early patient management, for example, to enable outpatient care for selected low-risk patients [18].

Secondly, to our knowledge, this is the first study evaluating TNT as a predictor for 1-yr mortality in PE. Although TNT seems to be most valuable for mortality prediction in the acute phase, elevated TNT at the time of presentation was also independently predictive for 1-yr outcome (fig. 1a). We included cancer, immobility and age in the multivariate analysis because these factors have previously been reported to be the most important independent risk factors for fatality of PE [9]. LAPORTE *et al.* [10] prospectively investigated >15,000 patients with venous thromboembolism and recently confirmed these three clinical factors as being independently associated with a two to three-fold increased risk for mortality. The pronounced importance of TNT for the early phase was further reflected by a shift from TNT to cancer as a long-term mortality predictor after exclusion of patients who died in hospital (fig. 2b, table 6). However, PE was the most frequent cause of in-hospital and 1-yr mortality in the overall study population, followed by cancer. Clearly, this was not true for

TNT-negative patients, in whom cancer was the primary cause of 1-yr mortality (table 2). Therefore, the reasons for long-term mortality differed in TNT-positive and TNT-negative patients. While nearly all patients dying directly from PE died in hospital, patients dying from cancer were more likely to die after discharge following initial hospitalisation. The median duration of hospitalisation was 11 days and, therefore, longer than described for PE patients in previous studies [19, 20]. The longer hospital stay of TNT-positive patients compared with TNT-negative patients clearly reflects the higher morbidity of TNT-positive patients, who required longer in-patient care.

The epiphenomenon that TNT-positive patients had higher creatinine levels is not surprising since elevated TNT levels have been observed in patients with varying degrees of renal failure [21]. However, cardiac troponins were also shown to be predictive for general mortality in patients with chronic renal failure [22]. In contrast, creatinine levels alone were neither independently predictive for in-hospital nor for 1-yr mortality after inclusion in the Cox model with the covariates TNT, cancer, immobility and age (data not shown).

An interesting observation was that TNT-positive patients tended to experience angina-like chest pain, dyspnoea while resting, tachycardia and syncope, which are suggestive symptoms for right ventricular strain, higher clot burden or central PE. These symptoms were also reported to frequently precede cardiac arrest caused by PE [23]. TNT-negative patients more often experienced pleuritic chest pain (*i.e.* breathing dependent), dyspnoea on exercise only and cough: symptoms which might reflect pleuritic stimuli by peripheral PE (table 1). The theory of more severe PE in TNT-positive patients is strengthened by objective parameters, such as significantly lower oxygen saturation and higher shock index in these patients.

As patients with elevated troponin levels were more likely to present with severe clinical signs and symptoms of PE, this raises the question of whether TNT adds to the severity assessment, based on clinical presentation data alone. We think that the advantage of TNT is its rapid availability. As an objectively measurable parameter, TNT can be performed in patients who are not able to express themselves or adequately

describe their symptoms and comorbidities. Most of the clinical PE symptoms are rather unspecific or “soft” parameters, as they are very subjective, interindividually and intra-individually diverse, and might be influenced by social and environmental circumstances. Therefore, it makes sense to add more objective measurable markers to the established haemodynamic parameters. Future prognostic studies might include both hard and soft parameters, but evaluation of the single risk factors will be a premise for weighting. TNT as a hard, objectively measurable parameter with highly prognostic value will surely outweigh several signs and symptoms in such studies.

To date, it is still unclear if positive troponin values in haemodynamically stable patients might identify those who would benefit from thrombolysis. After exclusion of patients who were unstable at presentation we still found a two to three-fold increased risk of 1-yr mortality in TNT-positive patients compared with TNT-negative patients (table 5, fig. 2a). Therefore, although stable patients show a better overall survival, TNT seems to be a useful marker of adverse outcome also in these patients. However, randomised controlled clinical trials are necessary to evaluate the use of lysis in stable patients with elevated TNT.

Conclusion

Elevated TNT independently predicts in-hospital and 1-yr mortality in patients presenting at an emergency department with acute PE. Elevated troponin levels meant a four-times higher risk of in-hospital death and a three-times higher risk of 1-yr mortality.

STATEMENT OF INTEREST

None declared.

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