Raised troponin I in Chinese patients with acute pulmonary embolism suggests complicated clinical course and may predict intensive care unit admission

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INTRODUCTION Acute pulmonary embolism (PE) is an uncommon but potentially fatal disease. Acute right ventricular failure, which can be demonstrated by echocardiography, is known to be an adverse prognostic factor in patients with acute PE. However, this diagnostic test is not always available in emergency departments and it is also an operator-dependent investigation. This study aimed to investigate whether cardiac troponin I (cTnI) levels could predict clinical outcomes in Chinese patients with PE.

METHODS This was a retrospective cohort study performed in a tertiary regional hospital in Hong Kong. For this study, 100 patients who were diagnosed with acute PE between January 1, 2002 and December 31, 2009 were recruited. Information, including demographic data, presenting symptoms and vital signs at presentation, predisposing factors for PE, results of diagnostic procedures and clinical outcomes, was collected from the medical records of these patients.

RESULTS 71% of recruited patients had elevated cTnI levels. High cTnI levels were associated with haemodynamic instability (odds ratio [OR] 5.30, 95% confidence interval [CI] 1.32–27.71; p = 0.019) and complicated clinical course (OR 6.34, 95% CI 1.76–22.9; p = 0.002).

CONCLUSION Elevated cTnI level was associated with a complicated clinical course in patients with acute PE. We suggest that measurements of cTnI levels be used for the early risk stratification of patients with PE in the emergency departments of hospitals.

INTRODUCTION

Venous thromboembolism (VTE) is a spectrum of diseases that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). PE is a potentially fatal complication of DVT. Despite recent advances in the diagnosis and treatment of PE, the risk stratification of cardiopulmonary mortality in patients with PE remains difficult. Haemodynamic instability is associated with in-hospital mortality, which can be as high as 50% in patients with PE.[1] Among patients having acute PE with normal blood pressure at presentation, acute right ventricular (RV) failure is a poor prognostic factor.[1] RV failure can be demonstrated by echo-cardiography, which shows RV enlargement and hypokinesis.[2] However, this test is not always available in the emergency departments of hospitals, and it also depends heavily on the experience and capability of the operators. Plasma cardiac troponin I (cTnI) is a highly sensitive and specific biochemical marker for myocardial injury.[3] Elevated cTnI levels are observed in patients with acute PE, especially in those with massive PE. In addition, TnI level has prognostic implications, as it reflects myocardial injury and RV dysfunction.[4-6]

VTE is common in Caucasians, with an annual estimated incidence of 117 cases per 100,000 persons in the United States.[7] It is less common among Asians, including persons of Chinese ancestry. A local study has found that the annual incidence of VTE among Hong Kong Chinese patients was 16.6 per 100,000 population.[8] One possible explanation for the lower incidence of VTE seen among Chinese patients may be related to the prevalence of activated protein C resistance, which is extremely low in Chinese populations.[9] However, evidence of the prognostic value of cTnI in Chinese patients with PE is scarce. Therefore, this retrospective study was conducted to assess whether cTnI levels could predict clinical outcomes and complications in Chinese patients with PE.

METHODS

This was a retrospective study carried out between January 1, 2002 and December 31, 2009 at the Princess Margaret Hospital, Hong Kong, China, a tertiary regional hospital. The research complied with the Declaration of Helsinki and was approved by the local clinical research ethics committee.

The medical records of patients older than 18 years of age who were admitted for the management of acute PE were reviewed. Patients who satisfied any of the following three criteria were excluded from the study: (a) recent acute coronary syndrome within six months; (b) end-stage renal failure (creatinine clearance < 15 mL/min); and (c) no cTnI investigations performed.

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Table I. Baseline characteristics of the study population.

Variable	No. of patients (%)			p-value
	cTnI ≤ 0.04 ng/ml (n = 29)	cTnI > 0.04 ng/ml (n = 71)	Total (n = 100)	
Male	12 (41.4)	36 (50.7)	48 (48.0)	NS
Median age (IQR) [yrs]	61.0 (45.0–80.5)	75.0 (49.0–81.0)	68.5 (48.0–81.0)	NS
Risk factors of PE				
Immobilisation	15 (51.7)	25 (35.2)	40 (40.0)	NS
Malignancy	10 (34.5)	13 (18.3)	23 (23.0)	NS
Recent surgery	9 (31.0)	14 (19.7)	23 (23.0)	NS
Thrombophilia	1 (11.1)*	5 (15.2)*	6 (14.3)*	NS
Concurrent DVT	13 (59.1)†	27 (52.9)†	40 (54.8)†	NS
History				
PE	1 (3.4)	1 (1.4)	2 (2.0)	NS
DVT	3 (10.3)	4 (5.6)	7 (7.0)	NS
Hypertension	9 (31.0)	28 (39.4)	37 (37)	NS
Diabetes mellitus	3 (10.3)	13 (18.3)	16 (16.0)	NS
Ischaemic heart disease	3 (10.3)	5 (7.0)	8 (8.0)	NS
COPD	2 (6.9)	6 (8.5)	8 (8.0)	NS

*A total of 42 patients were screened for thrombophilia, of whom 9 patients had normal cTnI levels and 33 patients had elevated cTnI.
†A total of 73 patients underwent lower limb Doppler ultrasonography screening, of whom 22 patients had normal cTnI levels and 51 patients had elevated cTnI.
cTnI: cardiac troponin I; IQR: interquartile range; PE: pulmonary embolism; DVT: deep vein thrombosis; NS: not significant; COPD: chronic obstructive pulmonary disease

Data extracted from the patients' medical records included demographic information, presenting symptoms, vital signs at presentation, predisposing factors for PE, results of diagnostic procedures, including D-dimers, first cTnI level, arterial blood gas analysis, electrocardiography (ECG), transthoracic echocardiography, spiral computed tomography pulmonary angiography (CT-PA), ventilation-perfusion (V/P) scan and lower extremity duplex ultrasonography. Patients were assigned to two groups based on their observed cTnI levels (cTnI ≤ 0.04 ng/mL or cTnI > 0.04 ng/mL). Outcome parameters, including in-hospital mortality, length of hospital stay and complicated clinical course, were examined. Complicated clinical course was defined as at least one of the following: (a) use of thrombolytic therapy; (b) need for mechanical ventilation; or (c) need for inotropic support.[10]

$S_1Q_3T_3$ and right bundle branch block were taken as ECG features of RV strain. Echocardiographic findings of RV dysfunction included paradoxical interventricular septal motion, RV dilation (diastolic diameter > 15 mm/m²) and low RV systolic function (systolic excursion of the tricuspid annulus < 15 mm).[11] cTnI was determined by a specific immunoassay (Access AccuTnI Assay, Beckman Coulter, Brea, CA USA). cTnI level > 0.04 ng/mL (upper limit of the 99th percentile in the normal population) was considered to be elevated in accordance with the local laboratory normal reference ranges. The D-dimer levels were determined by an enzyme-linked immunosorbent assay using an analyser (mini VIDAS analyser, bioMérieux, Marcy l'Etoile, France). The diagnosis of PE was established based on the evidence of a filling defect on contrast-enhanced spiral CT-PA or high-probability lung scintigraphy (V/Q scan).

The five major clinical outcomes measured in our study were: (a) death; (b) haemodynamic instability (defined as systolic blood pressure [BP] < 90 mmHg, or a BP drop > 40 mmHg for ≥ 15 minutes, with signs of organ hypoperfusion not due to hypovolaemia or sepsis); (c) need of thrombolytic therapy; (d) admission to high-dependency units (intensive care units [ICUs]

or coronary care units); and (e) length of hospital stay.[12] Recurrent PE was defined as new or worsened signs and symptoms, with repeat CT-PA demonstrating a new filling defect of a different pulmonary artery.

The Statistical Package for the Social Sciences for Windows version 16.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. The data were expressed as mean ± standard deviation (SD), median with interquartile range (IQR) or proportion with 95% confidence intervals (CIs). The difference between the demographic and clinical parameters of the two patient groups was examined using Fisher's exact or chi-square tests for categorical variables. The Mann-Whitney U test and Student's t-test were used to determine the statistical significance of continuous variables. Multivariate logistic regression analysis was used to determine the association between elevated cTnI levels and mortality, after adjusting for confounders such as age, gender, malignancy, chronic lung diseases and history of arterial cardiovascular diseases. The automatic stepwise forward (likelihood ratio test) modality was used in the regression model. A p-value < 0.05 was considered to be statistically significant.

RESULTS
During the study period, 110 Chinese patients were admitted for acute PE. Of these, 10 (9.1%) patients were excluded from the study due to unavailability of cTnI investigations. Of the 100 (90.9%) patients that were finally recruited in the study, 48 (48.0%) were men. The median age of the patients at diagnosis was 68.5 (IQR 48.0–81.0) years. The diagnosis of PE was confirmed using contrast CT imaging in 98 (98.0%) patients and by high-probability lung scintigraphy in 2 (2.0%) patients. Doppler ultrasonography of the lower limbs was performed in 73 (73.0%) patients, and among these, 40 (54.8%) patients were diagnosed to have concurrent DVT.

The baseline characteristics of patients are summarised in Table I. There was no significant difference in the baseline

Table II. Clinical outcomes of patients.

Variable	No. of patients (%)			OR (95% CI)	p-value
	cTnI ≤ 0.04 (n = 29)	cTnI > 0.04 (n = 71)	Total (n = 100)		
RV strain pattern on ECG	3 (10.3)	20 (28.2)	23 (23.0)		0.055
Creatine kinase* (IU/L)	54.5 (44.3–113.8)	86.0 (60.0–134.0)	85.0 (53.0–124.5)		0.035
Complicated clinical course	3 (10.3)	30 (42.3)	33 (33.0)	6.3 (1.8–22.9)	0.005
Thrombolytic therapy	0 (0.0)	12 (16.9)	12 (12.0)	1.5 (1.3–1.7)	0.017
ICU admission	3 (10.3)	22 (31.0)	25 (25.0)	3.9 (1.1–14.2)	0.031
Death	2 (6.9)	13 (18.3)	15 (15.0)		NS
Shock	3 (10.3)	20 (28.2)	23 (23.0)	3.4 (0.9–12.5)	0.055†
Length of hospital stay (days)	11 (9.0–15.0)	15 (10.0–23.3)	13 (9.5–20.0)		0.021

*Data is presented as median (interquartile range). †p > 0.05 was not significant.
RV: right ventricular; ECG: electrocardiography; ICU: intensive care unit; CI: confidence interval; OR: odds ratio; NS: not significant

Table III. Risk factors of haemodynamic instability.

Risk factor	OR (95% CI)	p-value
Univariate analysis		
Elevated cTnI	3.4 (0.9–12.5)	0.066
Multivariate analysis*		
Elevated cTnI	5.3 (1.3–27.7)	0.019
Malignancy	5.8 (1.8–18.2)	0.003

*Logistic regression analysis; ORs were adjusted for potential confounders such as age, gender, chronic lung diseases and history of arterial cardiovascular diseases.
CI: confidence interval; cTnI: cardiac troponin I; OR: odds ratio

Table IV. Risk factors of in-hospital mortality.

Risk factor	OR (95% CI)	p-value
Univariate analysis		
Elevated cTnI	3.4 (0.9–12.5)	0.219
Haemodynamic instability at presentation	6.8 (1.2–37.8)	0.042
Malignancy	5.3 (1.7–17.0)	0.006
Multivariate analysis*		
Elevated cTnI	5.1 (0.9–28.4)	0.066

*Logistic regression analysis; ORs were adjusted for potential confounders such as age, gender, chronic lung diseases, history of arterial cardiovascular diseases and active malignancy.
CI: confidence interval; cTnI: cardiac troponin I; OR: odds ratio

characteristics of patients with cTnI ≤ 0.04 ng/mL and those with cTnI > 0.04 ng/mL. 71 (71.0%) patients were found to have elevated cTnI levels at presentation. 57 patients were diagnosed with PE at presentation – 6 (10.9%) patients were diagnosed with massive PE (haemodynamic instability), 18 (32.7%) patients with submassive PE (normal vital signs but RV dysfunction) and 31 (56.4%) patients with minor PE (normal vital signs and RV function), according to the Goldhaber classification.[13] The remaining 43 (43.0%) patients' PE status at presentation could not be determined, as echocardiography was not performed. The mortality rate and proportion of patients who had elevated cTnI levels were much higher among patients with massive PE (mortality 50.0%; elevated cTnI 100%) than among those with minor PE (mortality 16.1%; elevated cTnI 67.7%). Patients with elevated cTnI levels presented to the emergency departments sooner than those with normal cTnI (median 24 hours vs. 48 hours, p = 0.01).

A total of 30 (42.3%) patients with elevated cTnI levels had a complicated clinical course, whereas only 3 (10.3%) patients with normal cTnI had such complications. The relative risk for complicated clinical course in patients with elevated cTnI was 6.3 (95% CI 1.8–22.9; p = 0.005). The sensitivity and specificity of the cTnI test for complicated clinical course were 90.9% and 38.8%, respectively. The negative predictive and positive predictive values of high cTnI level for complicated clinical course were 89.7% and 57.7%, respectively. An elevated cTnI level was found to predict poor clinical outcome in patients who were haemodynamically stable at presentation (odds ratio [OR] 7.3, 95% CI 1.8–30.6; p = 0.006). It was also associated with a higher creatine kinase level, ECG findings of RV strain patterns, need for thrombolytic therapy, ICU admission and longer length of hospital stay (Table II).

On univariate analysis, elevated cTnI levels were associated with haemodynamic instability (Table III). Subsequent multivariate logistic regression analysis showed that the risk of developing haemodynamic instability was independently associated with elevated cTnI levels, independent of age and malignancy. The OR of elevated cTnI was 5.3 (95% CI 1.3–27.7; p = 0.019). 15 (15.0%) patients died during the hospitalisation period. Haemodynamic instability at presentation and malignancy were associated with in-hospital mortality on univariate analysis (Table IV). However, cTnI levels failed to demonstrate a statistically significant association with in-hospital mortality on univariate analysis. After adjusting for potential confounders, including haemodynamic instability at presentation and malignancy, it was found that elevated cTnI might be weakly associated with higher in-hospital mortality (OR 5.1, 95% CI 0.9–28.4; p = 0.066).

DISCUSSION

According to Goldhaber, hypotension and RV overload, which can be assessed by echocardiography, can be used to stratify patients with acute PE for the risk of death.[13] However, 24-hour echocardiography by experienced personnel is a prerequisite for accurate diagnosis, and disagreement exists regarding the criteria for RV dysfunction. Other studies have shown that cTnI is a highly sensitive marker for RV dysfunction and suggested that elevated cTnI levels are associated with mortality and adverse clinical

outcome.[14-16] The findings of our study are consistent with these earlier reports.

In the present study, cTnI was found to predict complicated clinical course and haemodynamic instability in Chinese patients with acute PE. Its prognostic value was also observed in patients who were haemodynamically stable at presentation. However, this study failed to demonstrate a statistically significant relationship between elevated cTnI levels and in-hospital mortality (p = 0.066). In our study, the time lapse between the onset of symptoms of first acute PE episode and presentation at the hospital was markedly shorter in patients with elevated cTnI (24 hours vs. 48 hours, p = 0.01). Punukollu et al, who found that no patient with a duration of symptoms > 72 hours would have raised cTnI in spite of the presence of RV dysfunction, concluded that the dynamics of cTnI release are different between patients with duration of symptoms > 72 hours and those with a shorter duration of symptoms.[17] Therefore, it is possible that a patient with acute PE who presents late to a hospital may have a normal cTnI level on admission even though RV dysfunction is present. In our study, the duration of symptoms was longer than 72 hours for 17 (17.0%) patients who presented with PE. Clinicians should bear in mind that cTnI might not predict the prognosis for these patients.

Our study also revealed that the negative predictive value of cTnI for complicated clinical course was high (89.7%). This finding is consistent with those by Konstantinides et al[6] and Kucher et al,[4] who reported slightly higher negative predictive values of 93% and 95%, respectively. Recent studies have shown that repeat cTnI measurement has additional prognostic value. According to Pruszczyk et al[18] and Müller-Bardorff et al,[19] patients with acute PE may have normal cTnI levels at presentation, but show elevated cTnI later at 6 and 12 hours. We suggest that cTnI measurement be performed for all patients presenting with acute PE whose duration of symptoms is less than 72 hours. cTnI measurements should be repeated at 6 and 12 hours for such patients, if the initial cTnI readings are normal. In our study, elevated cTnI levels were associated with complicated clinical course in patients with PE, and therefore, prompt thrombolytic therapy and intensive care are warranted for these patients.

Our study, however, was not without limitations. As this was a retrospective study, it was thus subject to selection bias and recall bias. Investigations of the association between raised cTnI and RV dysfunction were limited, as only 53% of our patients had undergone echocardiography. Our modest sample size also limited the power of the study with regard to in-hospital mortality. Furthermore, it was difficult to exclude concomitant acute coronary syndromes in patients who had raised cTnI but no acute ischaemic changes on ECG. Finally, patients with very massive PE who died in the emergency department on or before arrival, for whom autopsy was not performed, were excluded from the study.

In conclusion, we found that elevated cTnI levels were predictive for a subgroup of patients with acute PE who were prone to develop haemodynamic instability and complications in the clinical course during hospitalisation. We propose that cTnI be used as a marker for the early risk stratification of patients presenting with acute PE to the emergency departments of hospitals.

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