Implications of elevated cardiac troponin in patients presenting with acute pulmonary embolism: an observational study

Ayman El-Menyar[1,2,3], Mohammad Asim[3], Syed Nabir[4], Mohamed Nadeem Ahmed[4], Hassan Al-Thani[2]

[1]Clinical Medicine, Weill Cornell Medical College, Doha, Qatar; [2]Vascular Surgery, [3]Clinical Research, Trauma Surgery, [4]Department of Radiology, Hamad General Hospital (HGH), Doha, Qatar

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Correspondence to: Associate Professor Dr. Ayman El-Menyar. Clinical Research Trauma & Vascular Surgery, HGH, HMC, PO Box 3050, Doha, Qatar. Email: aae2001@Qatar-med.cornell.edu; aymanco65@yahoo.com.

Background: To evaluate the implications of elevated cardiac troponin (cTn) in patients presenting with pulmonary embolism (PE).

Methods: We conducted a retrospective analysis for patients with PE between 2011 and 2015 with an average of 3 years follow-up. Patients were categorized into two groups based on the cTn status on admission (negative *vs.* positive) and RV/LV ratio (≤1.2 *vs.* >1.2). PE diagnosis was made by computed tomography pulmonary angiography (CTPA) examinations.

Results: Among 220 patients with PE, 52.7% had positive cTn and 31.7% had RV dysfunction. Protein S and C deficiency were significantly higher in patients with negative cTn. Patients with positive cTn were more likely to have high-risk simplified pulmonary embolism severity index (sPESI), RV dilation, RV/LV ratio >1.2, severe inferior vena cava reflux and high Qanadli score (QS >18 points). Thrombolytic therapy was used in 15 patients; 9 (60%) of them had elevated troponin. Combined cTn and sPESI had higher sensitivity, negative predictive value and negative likelihood ratio to predict in-hospital mortality. Overall 30-day and 3 years morality were 10.0% and 22.3%; that were significantly higher in patients with positive troponin. Cox regression analysis showed that mortality increased 2.5 times with positive cTn after adjusting for age, sex, and RV dysfunction (adjusted HR 2.5; 95% CI: 1.25–5.01), P=0.009.

Conclusions: Elevated cTn is independent predictor of short and long-term mortality. The predictive power of cTn increases when combined with the clinical probability score. Further, larger prospective studies are needed to confirm the findings of the present study.

Keywords: Pulmonary embolism (PE); cardiac troponin (cTn); computed tomography; outcomes

Introduction

Despite the contemporary therapeutic advancement, acute pulmonary embolism (PE) remains a leading cause of hemodynamic instability and mortality (1). The important prognostic factors in patient presenting with PE include hemodynamic status and pre-existing comorbidities (2). Notably, the frequency of early deaths in patient with acute PE ranges from 7.9% to 14% (3). However, on initial presentation, it is difficult to distinguish PE from other acute cardiopulmonary disorders due to nonspecific signs and symptoms which might result in delayed or missed diagnosis and inappropriate management (4). Therefore, early diagnosis and risk-stratification of PE necessitate accurate tools which ensure timely and appropriate management (5).

Biomarkers, especially cardiac troponins (cTn) are highly sensitive and specific for myocardial injury which could be used for risk stratification in patients presented with acute PE as well to reflect the burden of PE on the right ventricle (RV) (6,7). Earlier studies have identified a correlation between cTn and degree of RV dysfunction (7,8). Furthermore, normotensive patients with RV dysfunction and elevated cTn are at increased risk of in-hospital mortality (9). A retrospective study from Qatar, reported 10% confirmed diagnosis of DVT among patients with clinical suspicion of venous thromboembolic event (VTE); of which 5% had PE (10). However, the association between cTn and clinical outcome in patients with acute PE is not well-defined yet. Therefore, the present study aims to evaluate the association between cTn status and outcome in patients with PE. It elucidated the prevalence of elevated cTns as well as the RV dysfunction in a relatively large cohort of patients with PE. We hypothesized that elevated troponins carried out a poor prognosis in PE.

Methods

It is a retrospective chart review of prospectively collected hospital based data for all consecutive patients with acute PE confirmed by Computed tomography pulmonary angiography (CTPA) between May 2011 and February 2015. All adult patients admitted for the management of acute PE at Hamad General Hospital and had at least one blood collection for cTn measurement during initial 24 h as well as RV assessment by CTPA were included in the study. The diagnosis of PE was made by CT scan examination in addition to clinical, laboratory and echocardiographic findings (10-14).

The collected data from the patients' medical records included demographic characteristics, body mass index, presenting symptoms, co-morbidities, predisposing factors for PE, results of diagnostic procedures including coagulation profile (protein S deficiency, protein C deficiency, hyperhomocysteinemia, anti-thrombin III deficiency, and antiphospholipid syndrome), routine laboratory findings, D-dimers, cTn [i.e., cTnI or high sensitive troponin (HsTnT)] level, echocardiography (ejection fraction, RV wall hypokinesis and pulmonary arteries dilation), and CTPA findings [RV/left ventricle ratio, bowing of interventricular septum (IVS), inferior vena cava reflux, and clot burden], management (initial and long term), hospital length of stay, and mortality. An average 3 years follow-up for all-cause mortality was obtained electronically

from the patients records. The severity of clinical presentation in patients with PE was assessed by clinical probability scores such as simplified Wells score, revised Geneva score and simplified pulmonary embolism severity index (sPESI). The sPESI includes 6 equally weighted variables: age >80 years, history of cancer, history of chronic cardiopulmonary disease, heart rate ≥110 bpm, systolic blood pressure <100 mmHg, and arterial oxyhemoglobin saturation <90%. Patients with ≥1 point(s) were classified as high-risk patients, whereas low-risk patients with a score of 0 points exhibited a mortality rate of 1% (12).

As there is no well-defined definition of RV dysfunction in prior PE studies; therefore, we have used the following parameter: RV hypokinesia/dilation by echocardiography or RV/LV ratio >1.2, bowing of IVS, or IVC reflux by CTPA (14).

Based on CTPA findings, the PE was defined as the presence of an endoluminal central filling defect partially or completely occluding the pulmonary arteries (13). The present study used CTPA based scoring system proposed by Qanadli *et al.* (15) for quantification of the vascular obstruction index; which considered the percentage of vascular obstruction of the pulmonary arterial tree developed after PE. Briefly, the Qanadli scoring system assessed the number of blocked segmental arterial branches which were adjusted by a factor of one for partial blockage or a factor of two for complete obstruction. This score has a maximum value of 40 which corresponds to the complete occlusion of pulmonary trunk. Moreover, quantitative cardiac HsTnT and cTnI tests that detected levels higher than 14 ng/L and 0.5 ng/mL, respectively were considered as positive cTn in this study. These two tests were requested according to the discretion of attending physician. We hypothesized that PE patients with elevated cTn will have poor outcomes.

The Institutional Review Board (IRB# 15139/15) of the Hamad Medical Corporation was approved and granted exempt status for this retrospective study. The study follows the STROBE checklist for observational studies (*Table S1*).

Statistical analysis

Data were reported as proportion, mean (± standard deviation), median, range or IQR, when applicable. Shapiro Wilk test was performed for normality distribution of the data. Patients were categorized into two groups based on the serum cTn status (negative *vs.* positive) and right ventricular (RV) dysfunction (RV/LV ≤1.2 *vs.* RV/LV >1.2). Comparison between the two groups was
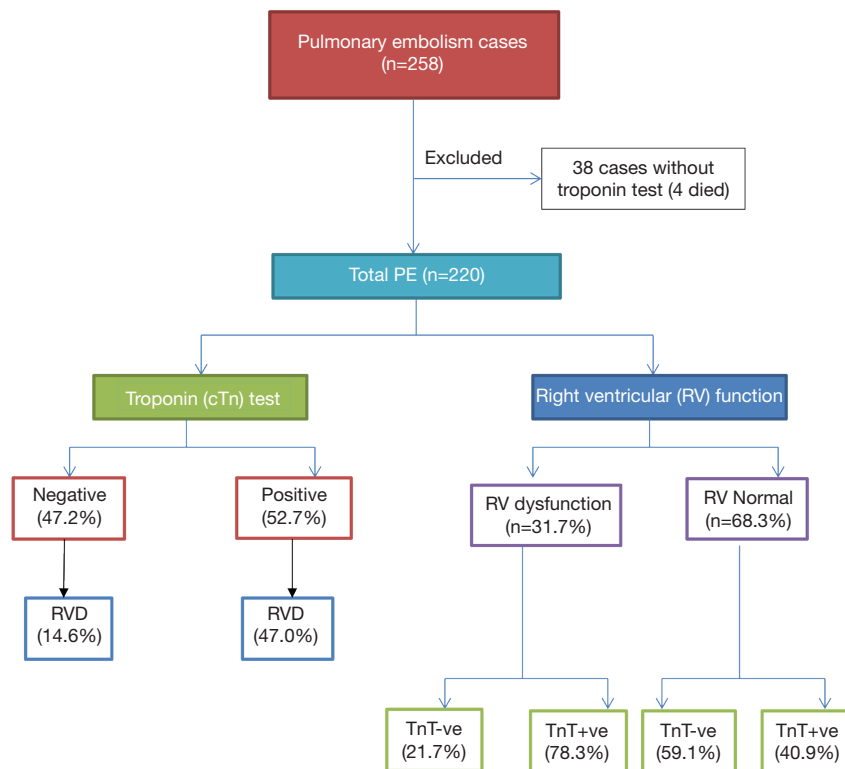
Figure 1 Chart flow of study design.

done using Pearson chi-square test for categorical variables and Students t tests or Mann-Whitney test (non-normally distributed data) for continuous variables. Yates' corrected chi-square was used for categorical variables, if the expected cell frequencies were below 5. For risk stratification, the present study attempted to combine positive cTn (hsTnT ≥0.014 ng/L or cTnI >0.5 ng/mL) as 1 plus a sPESI ≥1 point(s). The predictive value of simplified PESI, cTn result, combination of simplified PESI and cTn and clot burden was analyzed for in-hospital mortality using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+LR), negative likelihood ratio (-LR). Area under the curve (AUC) was used to compare the discriminatory power of SI with an AUC of 1.0 considered as perfect discrimination and 0.5 considered as equal to chance. A significant difference was considered when the 2-tailed P value was less than 0.05. Kaplan Meier survival curve was constructed to display survival during the 3-year clinical follow-up with respect to troponin T status and RV dysfunction. Any differences between the curves were explored using the Log-rank, Breslow and Tarone-Ware tests. Cox regression

analysis was performed after adjusting for age, sex and RV function to predict mortality in patients with and without elevated cTn; results were expressed as hazard ratio (HR) and 95% CI. Data analysis was carried out using the SPSS version 18 (SPSS Inc., Chicago, Illinois, USA).

Results

During the study period, a total of 258 consecutive patients were admitted for acute PE. Of them, cTn were not available for 38 patients and therefore they were excluded from the final analysis and 220 patients were eligible for inclusion in the study. The median follow-up was 1,097 days (1–2,065). *Figure 1* shows the study design. The mean age of patients was 52.3±16.9 yrs; 120 (54.5%) were male and 100 (45.5%) were females. Positive cTn results were found in 116 (52.7%) patients and 31.7% had RV dysfunction. *Table 1* shows the clinical characteristics, comorbidities, and risk factors of patients with PE based on cTn status. In comparison to the negative cTn group, patients with positive test were on average 7 years older and had lower BMI. No significant difference was observed between the 2

Table 1 Baseline clinical characteristics, comorbidities, and risk factors of patients with pulmonary embolism based on troponin status

Variable	Overall (n=220)	Troponin negative (n=104)	Troponin positive (n=116)	P
Age (mean ± SD)	52.3±16.9	48.4±16.2	55.8±16.9	0.001
Males	120 (54.5%)	57 (54.8%)	63 (54.3%)	0.94
Qatari	73 (33.2%)	31 (29.8%)	42 (36.2%)	0.31
Body mass index (n=125)	32.1±9.6	34.0±9.7	30.4±9.2	0.03
Frequency of admissions	1 [1–3]	1 [1–3]	1 [1–3]	0.48
Clinical presentation				
Dyspnea (n=175)	139 (79.4%)	66 (81.5%)	73 (77.7%)	0.53
Chest pain (n=171)	112 (65.5%)	57 (72.2%)	55 (59.8%)	0.09
Shortness of breath (n=209)	40 (19.1%)	24 (24.5%)	16 (14.4%)	0.06
Syncope (n=166)	25 (15.1%)	7 (9.2%)	18 (20.0%)	0.05
Cardiogenic shock (n=152)	5 (3.3%)	1 (1.4%)	4 (5.0%)	0.21
Number of CT scans	1 [1–11]	1 [1–11]	1 [1–9]	0.43
Comorbidities/risk factors				
Hypertension (n=190)	81 (42.6%)	28 (32.9%)	53 (50.5%)	0.01
Diabetes mellitus (n=192)	60 (31.3%)	16 (18.8%)	44 (41.1%)	0.001
History of DVT (n=202)	46 (22.8%)	26 (26.8%)	20 (19.0%)	0.18
History of surgery (>24 h) (n=198)	49 (24.7%)	22 (23.4%)	27 (26.0%)	0.67
Hypercholesterolemia (n=195)	46 (23.6%)	17 (19.8%)	29 (26.6%)	0.26
Coronary artery disease (n=190)	35 (18.4%)	10 (11.8%)	25 (23.8%)	0.03
History of PE (n=197)	27 (13.7%)	15 (16.0%)	12 (11.7%)	0.38
Bedridden (n=199)	22 (11.1%)	6 (6.4%)	16 (15.2%)	0.04
Trauma (n=199)	19 (9.5%)	9 (9.6%)	10 (9.5%)	0.99
Pelvic fracture (n=199)	7 (3.5%)	4 (4.3%)	3 (2.9%)	0.59
Femoral central line (n=198)	4 (2.0%)	1 (1.1%)	3 (2.9%)	0.36
History of surgery (<24 h) (n=197)	3 (1.5%)	1 (1.1%)	2 (1.9%)	0.61

groups with respect to gender and clinical presentations.

The presence of hypertension (P=0.01), diabetes mellitus (P=0.001), and coronary artery disease (P=0.03) were significantly higher among patients with positive troponin than those with negative troponin results.

Table 2 compares the coagulation profile, laboratory findings and clinical probability scores. The deficiency of protein S (63.8% *vs.* 45.0%, P=0.04), and protein C (61.3% *vs.* 42.2%, P=0.03), were significantly higher in patients with negative troponin as compared to those with positive cTn. On the other hand, patients with positive troponin were more likely to have higher median D-dimer [7.5 (3.7–16.7)

vs. 3.3 (1.9–6.3); P=0.001] than the negative cTn group.

Clinical characteristics

With respect to clinical probability scores, the majority of subjects were in low probability (82.7%) using simplified Wells score and low risk using revised Geneva score (94.1%) and simplified sPESI (69.5%). The frequency of high, moderate and low probability by simplified Wells score was comparable between the 2 groups. For revised Geneva score, patients with positive troponin were more likely to have intermediate risk of PE (9.5% *vs.* 1.9%; P=0.01) than

Table 2 Comparison of coagulation profile, laboratory findings and clinical probability scores

Abnormal coagulation	Overall (n=220)	Troponin negative (n=104)	Troponin positive (n=116)	P
Protein S deficiency (n=118)	64 (54.2%)	37 (63.8%)	27 (45.0%)	0.04
Protein C deficiency (n=126)	65 (51.6%)	38 (61.3%)	27 (42.2%)	0.03
Anti-thrombin III deficiency (n=106)	45 (42.5%)	25 (49.0%)	20 (36.4%)	0.19
Hyperhomocysteine (n=110)	46 (41.8%)	26 (48.1%)	20 (35.7%)	0.18
Abnormal lupus anticoagulation (n=107)	22 (20.6%)	14 (25.9%)	8 (15.1%)	0.16
Antiphospholipid syndrome (n=92)	8 (8.7%)	4 (9.5%)	4 (8.0%)	0.79
Factor V Leiden (n=69)	5 (7.2%)	2 (7.4%)	3 (7.1%)	0.96
Systemic lupus erythematosus (n=93)	3 (3.2%)	0 (0.0%)	3 (6.0%)	0.10
D-Dimer (mg/L FEU) median, IQR (n=199)	4.3 (2.4–11.4)	3.3 (1.9–6.3)	7.5 (3.7–16.7)	0.001
Positive (>0.55 mg/L)	169 (84.9%)	79 (86.8%)	90 (83.3%)	0.49
Routine laboratory				
WBC count (4×10^3–10×10^3/μL)	10.6±5.3	9.8±4.5	11.8±5.7	0.004
Hemoglobin (mean ± SD) (g/dL)	12.5±2.5	12.5±2.6	12.2±2.5	0.33
Platelet count (150×10^3–400×10^3/μL)	258±140	264±149	254±134	0.59
Hematocrit (40–50%)	38.1±8.2	38.1±8.2	38.2±8.3	0.96
Clinical probability scores				
Simplified Wells score	1 (0–3)	1 (0–2)	1 (0–3)	0.71
High probability (>6)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.29 for all
Moderate probability (score 2–6)	38 (17.3%)	15 (14.4%)	23 (19.8%)	
Low probability (<2)	182 (82.7%)	89 (85.6%)	93 (80.2%)	
Revised Geneva score	2 (0–5)	2 (0–4)	2 (0–5)	0.17
Low risk (score 0–3)	207 (94.1%)	102 (98.1%)	105 (90.5%)	0.01 for all
Intermediate risk (score 4–10)	13 (5.9%)	2 (1.9%)	11 (9.5%)	
High risk (score ≥11)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
sPESI	0 (0–2)	0 (0–2)	0 (0–2)	0.003
Low risk (0 point)	153 (69.5%)	82 (78.8%)	71 (61.2%)	0.005 for all
High risk (≥1 point)	67 (30.5%)	22 (21.2%)	45 (38.8%)	

sPESI, simplified pulmonary embolism severity index.

the negative group. The sPESI classified 67 patients (30.5%) in the high-risk group (≥1 point). The frequency of high-risk patients by sPESI was more in the troponin positive group (P=0.005) than those who had negative cTn.

Imaging modalities

Transthoracic echocardiography findings were available in 184 cases, of which 29 patients had RV dilatation and 18 had RV hypokinesis. The left ventricular ejection fraction (LVEF), RV wall hypokinesis, pulmonary arteries dilation and inferior vena cava dilatation were comparable between the 2 groups (*Table 3*). The group of patients with positive troponin was more likely to have RV dilation (29.3% *vs.* 9.1%; P=0.005).

The parameters of the RV dysfunction by the CTPA

Table 3 Echocardiography and CTPA findings of right ventricular dysfunction parameters

Variable	Overall (n=220)	Troponin negative (n=104)	Troponin positive (n=116)	P
Echocardiography (n=184)	147 (79.9%)	57 (71.3%)	90 (86.5%)	0.01
LV ejection fraction (%)	54.1±8.5	54.2±9.2	54.0±8.1	0.88
Mobile thrombi at right-heart chambers (n=134)	2 (1.5%)	1 (1.9%)	1 (1.3%)	0.77
Right ventricular (RV) dilation (n=137)	29 (21.2%)	5 (9.1%)	24 (29.3%)	0.005
RV wall hypokinesis (n=137)	18 (13.1%)	6 (11.1%)	12 (14.5%)	0.57
Pulmonary arteries dilation (n=131)	7 (5.3%)	3 (5.6%)	4 (5.2%)	0.92
Inferior vena cava dilatation (n=51)	8 (15.7%)	2 (8.7%)	6 (21.4%)	0.21
CTPA findings (n=210)				
Right ventricle/left ventricle ratio (n=210)	1.07±0.4	0.95±0.2	1.19±0.4	0.001
>1.2	50 (23.8%)	12 (12.0%)	38 (34.5%)	0.001 for all
≤1.2	160 (76.2%)	88 (88.0%)	72 (65.5%)	
Bowing of interventricular septum	61 (29.0%)	13 (13.0%)	48 (43.6%)	0.001
Pulmonary artery diameter (PA)	29.4±4.6	29.1±4.6	29.7±4.5	0.34
Aorta diameter (AO)	30.9±4.1	30.8±3.8	30.9±4.4	0.89
PA/AO ratio	0.96±0.17	0.95±0.16	0.97±0.17	0.40
>1.0	73 (34.8%)	33 (33.0%)	40 (36.4%)	0.60 for all
≤1.0	137 (65.2%)	67 (67.0%)	70 (63.6%)	
Superior vena cava diameter	21.3±3.7	21.5±3.7	21.1±3.6	0.42
Azygous vein diameter	9.9±2.4	9.9±2.4	9.8±2.4	0.79
Inferior vena cava reflux	2.0±1.3	1.6±1.1	2.4±1.4	0.001
Mild–moderate (grades 1–3)	170 (81.0%)	91 (90.1%)	79 (72.5%)	0.001 for all
Severe (grades 4–6)	40 (19.0%)	10 (9.9%)	30 (27.5%)	
Clot burden (Qanadli score) (n=204)	16.8±11.7	13.3±9.7	20.1±12.5	0.001
QS ≤18 points	114 (55.9%)	68 (69.4%)	46 (43.4%)	0.001 for all
QS >18 points	90 (44.1%)	30 (30.6%)	60 (56.6%)	
Clot burden (%)	40.7±29.8	32.2±24.7	48.4±32.0	0.001
Right pleural effusion	6 (2.7%)	2 (1.9%)	4 (3.4%)	0.48
Bilateral pleural effusion	10 (4.5%)	4 (3.8%)	6 (5.2%)	0.63
Bilateral infiltrates	3 (1.4%)	2 (1.9%)	1 (0.9%)	0.49
Right pulmonary infarction	3 (1.4%)	3 (2.9%)	0 (0.0%)	0.06
Left pulmonary infarction	1 (0.5%)	0 (0.0%)	1 (0.9%)	0.34
Bilateral infarcts	1 (0.5%)	0 (0.0%)	1 (0.9%)	0.34

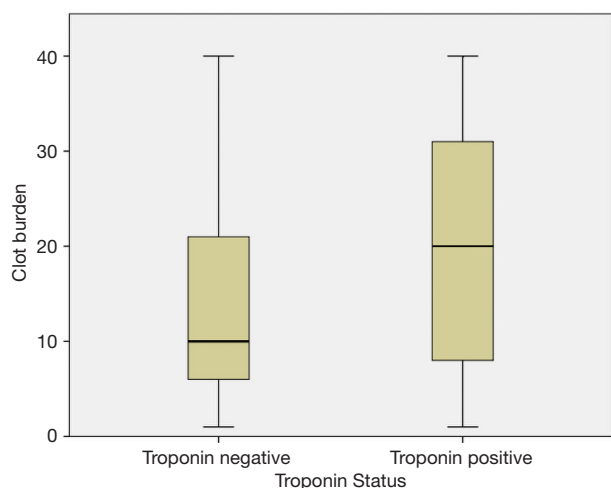CTPA, computed tomography pulmonary angiography.

Figure 2 Comparison of clot burden (Qanadli score) based on troponin status; (P=0.001).

showed that 23.8% of patients had RV/LV ratio >1.2 and 34.8% cases had higher PA/AO ratio (>1.0).

The mean clot burden (QS) was 16.8±11.7 points and 44.1% of patients had QS >18 points. In 81.0% of the patients, inferior vena cava reflux was identified to have mild-to-moderate (I–III) grades and 19.0% had severe (IV–VI) grades. Bowing of IVS was found in 61 (29.0%) patients. Higher proportion of positive troponin patients had abnormal CTPA findings in terms of higher RV/LV ratio >1.2 (34.5% *vs.* 12.0%; P=0.001), bowing of IVS (43.6% *vs.* 13.0%; P=0.001), severe grades [4–6] of inferior vena cava reflux (27.5% *vs.* 9.9%; P=0.001) and Qanadli score >18 points (56.6% *vs.* 30.6%; P=0.001).

Figure 2 shows comparison of clot burden based on cTn status. The median clot burden was significantly higher in patients with positive troponin results {20 [1–40] *vs.* 10 [1–40]; P=0.001} as compared to those with negative troponin.

Treatment

The frequently used medications were enoxaparin (72.5%), warfarin (71.5%), heparin (59.5%) and aspirin (44.1%) (*Table 4*). Patients with positive troponin were frequently treated with heparin (71.7% *vs.* 45.4%, P=0.001) and aspirin (53.2% *vs.* 33.7%, P=0.005) when compared to negative troponin group. Thrombolytic therapy of pulmonary clots was used in 15 patients; 9 of them had elevated troponin.

Outcomes

Patients with elevation troponin were found to have prolonged hospital length of stay as compared to those without troponin elevation. *Figure 3* represents the ROC curves of HsTnT for predicting the risk of in-hospital mortality. According to the ROC curve analysis, the cutoff points of HsTnT for predicting the in-hospital mortality was 31.5 with sensitivity, 72.2%; specificity, 50.0%; and AUC 0.67 (0.52–0.81); P=0.02.

Table 5 shows the predictive value of different potential prognostic parameters with respect to in-hospital mortality. For instance, to predict the risk of in-hospital mortality; cTn test showed sensitivity 75% and NPV 94.7% , whereas the combination of sPESI with cTn troponin test showed sensitivity 90% and NPV 97.3%.

Clinico-radiological characteristics and RV dysfunction

Demographics, preexisting comorbidities/risk factors and findings of echocardiography were comparable among the two groups. However, cTn (76.0% *vs.* 45.0%; P=0.001), median D-dimer level [9.0 (0.2–290) *vs.* 3.9 (0.2–36.1); P=0.002], high-risk sPESI (54.0% *vs.* 25.0%; P=0.001) were significantly higher in patients with RV dysfunction. Based on radiological findings, patients with RV dysfunction were more likely to have bowing of IVS (86.0% *vs.* 11.3%; P=0.001), PA/AO ratio >1.0 (52.0% *vs.* 29.4%; P=0.003), severe inferior vena cava reflux (50.0% *vs.* 9.4%; P=0.001) and higher QS >18 points (84.0% *vs.* 31.4%; P=0.001). Also, the mean SVC diameter (22.4±3.2 *vs.* 20.9±3.7; P=0.01), azygos vein diameter (10.5±2.6 *vs.* 9.7±2.3; P=0.04) and clot burden (26.7±8.2 *vs.* 13.6±10.9; P=0.001) were significantly higher in patients with RV dysfunction. The mortality rate did not differ significantly among the two groups (8.0% *vs.* 10.1%, P=0.65).

Survival analysis

Overall mortality was 10.0% (n=21) that was significantly higher in patients with positive troponin (14% *vs.* 5.2%; P=0.03) in comparison to those with negative troponin. The 3-year mortality was 22.3% (+ve cTn 32.5% *vs.* –ve cTn12.5%, P=0.001).

Figure 4 shows the Kaplan-Meier survival curves with significantly higher mortality in the positive troponin

Table 4 Management, complications and outcomes

| Variable	Overall (n=220)	Troponin negative (n=104)	Troponin positive (n=116)	P
Treatment				
Enoxaparin (n=207)	150 (72.5%)	74 (77.9%)	76 (67.9%)	0.10
Warfarin (n=207)	148 (71.5%)	74 (77.9%)	74 (66.1%)	0.06
Aspirin (n=207)	90 (44.1%)	32 (33.7%)	58 (53.2%)	0.005
Dalteparin (n=208)	41 (19.7%)	19 (19.8%)	22 (19.6%)	0.97
Heparin (n=210)	125 (59.5%)	44 (45.4%)	81 (71.7%)	0.001
Warfarin for life (n=215)	40 (18.6%)	19 (19.2%)	21 (18.1%)	0.83
Warfarin (<2 years)	77 (35.0%)	41 (39.4%)	36 (31.0%)	0.19
Warfarin (>2 years)	33 (15.0%)	15 (14.4%)	18 (15.5%)	0.82
Plavix (n=208)	22 (10.6%)	8 (8.3%)	14 (12.5%)	0.33
Thrombolytic therapy (n=214)	15 (7.0%)	6 (6.1%)	9 (7.8%)	0.61
Complications				
Leg edema (n=212)	38 (17.9%)	23 (23.5%)	15 (13.2%)	0.05
Pulmonary hypertension (n=211)	35 (16.6%)	13 (13.3%)	22 (19.5%)	0.22
Pain (n=211)	30 (14.2%)	18 (18.6%)	12 (10.5%)	0.09
Leg ulcer (n=212)	6 (2.8%)	3 (3.1%)	3 (2.6%)	0.85
Hospital stay (days)	8.5 [1–240]	7 [1–180]	11 [1–240]	0.002
In-hospital mortality (n=210)	21 (10.0%)	5 (5.2%)	16 (14.0%)	0.04
3 years mortality (n=210)	49 (22.3%)	12 (12.5%)	37 (32.5%)	0.001
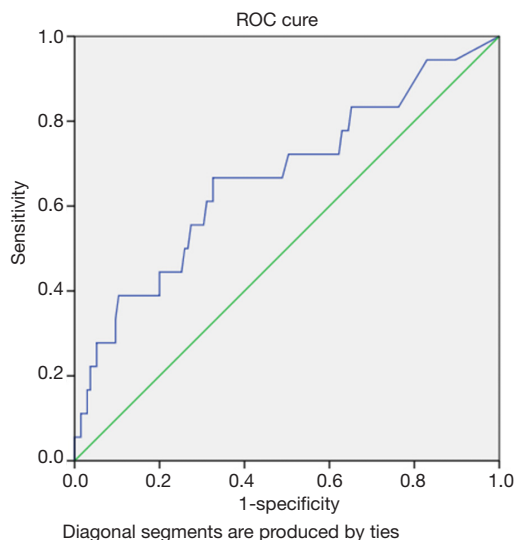
Figure 3 Receiver operating characteristic curve of cardiac high sensitive troponin T and mortality [HsTnT =31.5; sensitivity =72.2%, specificity =50.0%; AUC 0.67 (0.52–0.81)].

group than negative group (Log-rank: X^2=11.3, P=0.001, Breslow: X^2=11.0, P=0.001 and Tarone-Ware: X^2=11.2, P=0.001). However, no significant difference was observed for mortality with respect to RV dysfunction Log-rank: X^2=0.45, P=0.49, Breslow: X^2=0.29, P=0.58 and Tarone-Ware: X^2=0.37, P=0.54).

Cox regression analysis showed that mortality increased 3 times with positive cTn after adjusting for age and RV dysfunction (adjusted HR 2.5; 95% CI: 1.25–5.01), P=0.009) (*Figure 5*).

Discussion

This is a large cohort study that analyzes the association between elevated cTn and acute PE from an Arab Middle Eastern country. Interestingly, a number of studies have identified an association of elevated cTn levels in patients with acute PE with an incidence of 30% to 40% (6,16,17). In this study, more than a half of PE patients had elevated

Table 5 Test characteristics for predicting in-hospital mortality

Variable	sPESI	+ ve cTn	sPESI plus cTn	RVD + cTn
Sensitivity	60%	75%	90.0%	11.1%
Specificity	72.2%	48.1%	38.5%	93.7%
Positive predictive value	18.7%	13.4%	13.5%	73.7%
Negative predictive value	94.4%	94.7%	97.3%	39.8%
Positive likelihood ratio	2.16	1.45	1.46	1.76
Negative likelihood ratio	0.55	0.52	0.26	0.95

sPESI, simplified pulmonary embolism severity index; cTn, cardiac troponin.
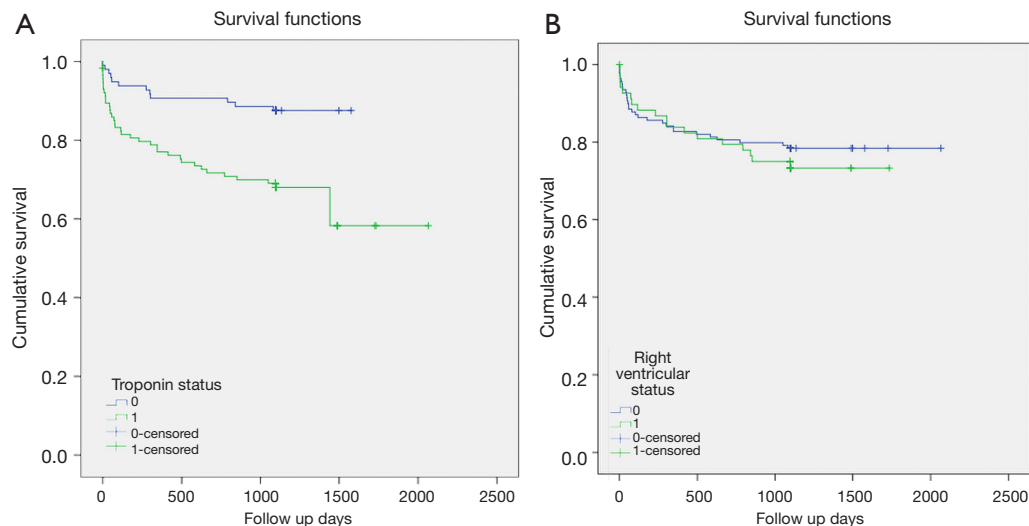
Figure 4 Kaplan Meier survival curves. (A) Shows a significant difference between troponin positive and negative groups (Log-rank: X^2=11.3, P=0.001, Breslow: X^2=11.0, P=0.001 and Tarone-Ware: X^2=11.2, P=0.001); (B) shows no significant difference between RV dysfunction and RV normal groups (Log-rank: X^2=0.45, P=0.49, Breslow: X^2=0.29, P=0.58 and Tarone-Ware: X^2=0.37, P=0.54).

cTn and such patients were more likely to be elderly with more comorbidities. Cox regression analysis showed that regardless of the age, sex and RV dysfunction, an elevated cTn is associated with 2.5-fold increase at the risk of long-term mortality. Consistent with our findings, a study from Austria reported an association between advanced age, higher comorbidities, presentation with severe clinical manifestations of PE and elevated cTn (11). The possible explanation for the release of cTn is attributed to acute RV strain, decreased coronary blood flow, and hypoxemia secondary to PE (18). The RV is integral to normal cardiac function; however, the crescent-shaped geometry of the RV makes the chamber poorly tolerant of acute elevations in pulmonary circulation which can cause acute RV dilation, damaging the contractile sarcomere apparatus (19) with

resultant RV dysfunction and troponin and BNP release.

cTn has a prognostic relevance for risk stratification and outcome of PE due to its high negative predictive value (11,12). Moreover, in patients with acute PE, increased levels of cTn indicate a significant RV strain which might be related to the higher risk of severe PE as well as a higher overall mortality (6,20,21). Therefore, detection of negative troponin might be useful for identifying low-risk patients that could be managed without even hospitalization (22). In the current study, elevated cTn showed a higher association with sPESI scores, RV dilation on echocardiography, CTPA parameters, prolonged hospital course and higher rate of mortality. Early assessment of the severity for acute PE is crucial for accurate decision making and initiation of the first line treatment (23). Among various prognostic scoring,
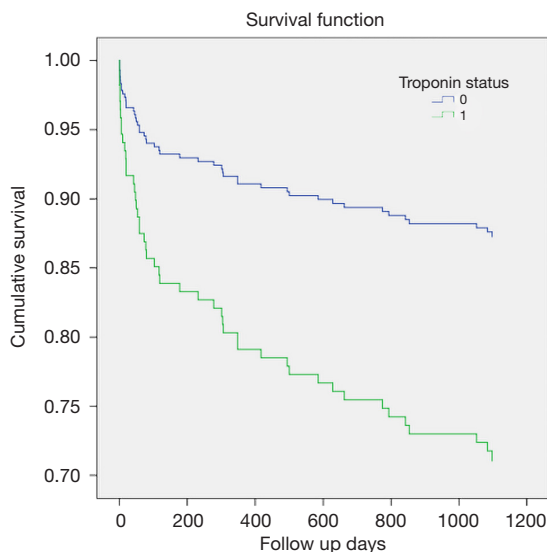
Figure 5 Cox regression analysis: hazard ratio adjusted for age, sex and right ventricular dysfunction (HR 2.5; 95% CI: 1.25–5.01), P=0.009), 0= negative, 1= positive cTn. cTn, cardiac troponin.

sPESI was considered as the most useful and validated tool to predict mortality in patients with PE (24). In the present study, based on sPESI score, one-third of patients were identified to have high-risk. Importantly, hemodynamically unstable patients who were considered as high-risk patients , were found to have more than 15% chance of early death; while, patients categorized as low-risk showed a better prognosis (25). However, the calculation of PESI is complex involving 11 different parameters. In our study, high risk sPESI was more in patients with positive cTn in comparison to the negative cTn group (38.8% *vs.* 21.2%).

In our study, deficiencies of protein S, protein C and anti-thrombin III were the most common hereditary risk factors of PE which is consistent with an earlier study (26). Earlier reports have demonstrated the utility of D-dimer testing for risk assessment in patients with acute PE (27,28). There was a relationship between elevated D-dimer levels with the severity of acute PE, RV dysfunction, clot burden, and mortality in acute PE cases (29). In the current study, median D-dimer values in the troponin positive group were found to be higher when compared to negative cTn group.

Furthermore, some investigators found a significant relationship between NT-proBNP, troponin levels, and RV dysfunction in PE and recommended their measurement at the earliest for better risk stratification (30). Several studies have demonstrated a significant correlation between RV dysfunction on echocardiography and elevated troponin

levels (31,32). Notably, echocardiographic RV dysfunction was found to be an independent predictor of mortality in patients with acute PE, regardless of the hemodynamic status (30).

In our series, we have observed a significant correlation between cTn status and clot burden which is in agreement with an earlier study (32). Studies using CTPA findings to diagnose RV dysfunction were more reliable and many of them have assessed its association with troponin levels (33). In the present study, 24% of the patients had a RV/LV ratio of >1.2 which was also significantly higher in patients with positive troponin as described by Jeebun *et al.* (32). The authors reported that in patients with elevated troponin levels, 90% had a RV/LV ratio of >0.9 which is higher as compared to our study (34.5%) which is attributed to the lower RV/LV ratio (>0.9) used in Jeebun study.

The present study also observed a significant association between positive cTn and CTPA findings. Similar to our findings, an earlier report identified an association of leftward bowing of IVS with elevated cTn levels (32). The present study re-confirms findings of our previous finding that patients with RV dysfunction (RV/LV ratio >1.2) were more likely to have greater clot burden, and septal bowing (34).

Arram *et al.* (35) suggested that troponin and myoglobin testing can be integrated with risk assessment of acute PE to guide treatment. The authors concluded that PE patients with normal troponin and myoglobin values could be successfully managed with anticoagulation therapy alone.

The overall in-hospital mortality in our cohort was 10.0% and the 3-year mortality was 22.3%. Patients with positive troponin were found to have two to three-fold increased risk of early or long-term mortality. Similar to our findings, Giannitsis *et al.* (18) reported a higher rate of in-hospital mortality in patients with positive cTnT (44%) compared to those with negative cTnT (3%). Another study by Pruszczyk *et al.* (36) included 64 normotensive patients with acute PE. The authors reported that all eight patients who died in the hospital had elevated troponin; whereas, all the survivors had no signs of myocardial injury. A recent meta-analysis included 22 studies of low-risk PE patients to assess the prognostic implications of RV dysfunction and elevated cardiac biomarkers (37). The authors concluded that RV dysfunction on initial presentation is associated with early mortality among low-risk PE patients. Also, imaging based diagnosis of RV dysfunction seems to have similar prognostic implications as that of the elevation of cardiac biomarkers. We noticed that the sensitivity, NPV and -LR have been strengthened significantly when we

combined troponin status with the sPESI for prediction of mortality (*Table 5*). Similarly, Singanayaga *et al.* (23) suggested that addition of cTn to PESI score have better predictive value for 30-day mortality in patients with acute PE. Therefore, it can be used to guide initial management of normotensive PE patients.

Timely identification of imaging based RV dysfunction can provide indirect clue of imminent hemodynamic failure in normotensive PE patients which may lead to PE-related shock (25). Earlier investigators considered RV dysfunction in PE based on RV/LV ratio (ranges 1 to 1.5) and degree of obstruction which also has potential to predict of PE-related mortality (37,38). Moreover, the assessment of circulatory collapse and severity of PE could be more precisely made by RV dysfunction rather than the clot burden (39). In the present study, patients with RV dysfunction were more likely to have elevated cTn, D-dimer level, and had high-risk sPESI. Consistent with our findings, an earlier study revealed that two-third of the PE patients had elevated cTnI which was significantly associated with RV dysfunction (34). Similarly, Rydman *et al.* (40) reported that patients with high-risk sPESI had higher association with RV dysfunction.

Limitations

The present study has certain limitations owing to the retrospective design which might influence the generalizability of the findings. Selection bias cannot be ruled out as all patients with PE who underwent CTPA and cTn testing were included in the analysis. We missed cTn measurement in 14.7% of cases, of them 4 cases died. Also echocardiography was missed in 16% of cases whereas all cases underwent CTPA scanning.

Another limitation is that we did not consider the predictive value of other cardiac biomarkers such as BNP, which had association with adverse clinical outcomes in earlier studies (37).

In addition, 2 assays of troponin were used; however, the timing and indication, and the choice between 2 assays were not explained. Myoglobin and BNP were not measured in our cohort. The exact cause of death during the 3 years follow-up was not reported.

Conclusions

Measurement of cTn is a useful additional prognostic indicator for risk stratification and long term outcome

in patients with acute PE event. cTn, if combined with clinical probability score has higher predictive power to identify PE patients at increased risk of mortality. Moreover, radiological findings of RV dysfunction also have clinical implications in PE patients. Therefore, the association between cTn and RV dysfunction indicates a link between acute elevation of RV pressure and severity of PE. Furthermore, larger prospective studies are needed to confirm the findings of the present study. Also, we need to know whether the clinicians have realized the importance of measuring cTn in PE and changed their routine management approach based on the cTn status.

Acknowledgments

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study has been performed in accordance with the ethical standards. The study obtained ethical approval from Research Ethics Committee, at Medical Research Center, Hamad Medical Corporation (HMC), Doha, Qatar (IRB#15139/15). A waiver of consent was granted as no direct contact with patients and data were anonymous.

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Table S1 STROBE statement—checklist of items that should be included in reports of observational studies

Checklist	Item No.	Recommendation
Title and abstract	1	(I) Indicate the study's design with a commonly used term in the title or the abstract. Page 1,2
		(II) Provide in the abstract an informative and balanced summary of what was done and what was found. Page 2,3
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported. Pages 3 and 4
Objectives	3	State specific objectives, including any prespecified hypotheses. Page 4
Methods		
Study design	4	Present key elements of study design early in the paper. Page 4-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection. Page 4-6
Participants	6	(I) Cohort study—give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up; case-control study—give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls; cross-sectional study—give the eligibility criteria, and the sources and methods of selection of participants. Page 4-6
		(II) Cohort study—for matched studies, give matching criteria and number of exposed and unexposed; case-control study—for matched studies, give matching criteria and the number of controls per case. Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. Page 4-6, tables, figures
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Page 4-6
Bias	9	Describe any efforts to address potential sources of bias. Page 6-7
Study size	10	Explain how the study size was arrived at Page 6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why. Page 6,7
Statistical methods	12	(I) Describe all statistical methods, including those used to control for confounding. Page 6,7
		(II) Describe any methods used to examine subgroups and interactions. Tables &figures
		(III) Explain how missing data were addressed. Page 7
		(IV) Cohort study—if applicable, explain how loss to follow-up was addressed; case-control study—if applicable, explain how matching of cases and controls was addressed; cross-sectional study—if applicable, describe analytical methods taking account of sampling strategy
		(V) Describe any sensitivity analyses. Tables &figures
Results		
Participants	13*	(I) Report numbers of individuals at each stage of study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(II) Give reasons for non-participation at each stage
		(III) Consider use of a flow diagram. Page 7,8, figures
Descriptive data	14*	(I) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders
		(II) Indicate number of participants with missing data for each variable of interest
		(III) Cohort study—summarise follow-up time (e.g., average and total amount). Page 7,8
Outcome data	15*	Cohort study—report numbers of outcome events or summary measures over time
		Case-control study—report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—report numbers of outcome events or summary measures. Page 8-11
Main results	16	(I) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(II) Report category boundaries when continuous variables were categorized
		(III) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period. Page 8-11
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives. Page 11-15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias. Page 15,16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. Page 11-15
Generalisability	21	Discuss the generalisability (external validity) of the study results. Page 12-15
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based. Not applicable

An explanation and elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org. *, give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.