ORIGINAL ARTICLE

Value of cardiac biomarkers in patients with acute pulmonary embolism

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Abstract *Background:* Prognostic stratification of patients with PE is important in management and potentially improve clinical outcome. Cardiac biomarkers are used as an adjunct to clinical and echocardiographic risk stratification in a variety of circumstances, (Creatine-kinase-MB "CK-MB") and cardiac troponin I (cTnI) are most widely used because of their high sensitivities, and very high specificity of troponin for heart muscle injury. Evidence is mounting that myoglobin's sensitivity for myocardial necrosis combined with its unique release and clearance properties may render it particularly attractive as a risk marker either alone or in combination with other markers.

Objectives: The aim of the current study is to assess the levels of cardiac specific biomarkers in relation to different clinical, ECG and echocardiogrphic findings in patients with acute PE, as well as evaluating the prognostic value of these biomarkers for inhospital mortality and adverse clinical events.

Patients and methods: This study comprised 40 patients with proved PE (22 males and 18 females), their mean age was 50.05 ± 13.09 years (range 22–70 years). The following investigations were performed for all patients; 12-leads ECG, Full echo Doppler study, spiral CT of the chest, and laboratory testing: arterial blood gas, serum myoglobin, serum troponin, total CK and CK-MB, kidney and liver function tests.

Result: Significant elevation of CK-MB ($>10\ \mu/L$) was noted only in 7.5% of patients, while cardiac cTnI was elevated ($\geqslant 0.07\ ng/ml$) in 45% of patients and elevated serum myoglobin was found very early after symptoms ($<4\ h$) in 55% of patients. Elevated serum cTnI and myoglobin were significantly associated with ECG signs of right ventricular strain and echocardiographic evidence of right ventricular dysfunction.

Conclusion: The results of the present study demonstrate the prognostic value of cardiac specific biomarkers, cardiac troponin I & myoglobin in acute pulmonary embolism. Thus, the current data combined with the results of previous studies strongly support the integration of troponin and myoglobin testing into the risk stratification and management of patients with established acute PE.

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Introduction

Acute pulmonary embolism (PE) has a wide spectrum of clinical presentations. The short-term clinical outcome of patients with PE varies from early recovery of symptoms to hemodynamic deterioration and death [1]. Echocardiography has emerged as the principal tool for risk stratification in acute PE. From a prognostic point of view, echocardiography helps to classify patients with PE, right ventricular dysfunction on the echocardiogram is an independent and powerful predictor of early death in patients with acute PE [2].

Among patients with normal blood pressure on admission, right ventricular (RV) dysfunction at echocardiography (Echo) identifies those at high risk for in- hospital mortality. In those patients, elevated levels of cardiac biomarkers have been associated with RV dysfunction at Echo [3].

Severe dyspnea, cyanosis, and syncope indicate life-threatening PE. The clinical examination may reveal signs of acute right ventricular dysfunction, including tachycardia, a low arterial blood pressure, distended neck veins, an accentuated P 2, or a tricuspid regurgitation murmur. On the ECG, T-wave inversion or a pseudoinfarction pattern (Qr) in the anterior precordial leads indicates right ventricular dilation and dysfunction [4].

Myoglobin is a heme protein found in all striated muscles. Although the sensitivity of myoglobin for cardiac necrosis is similar to that of cardiac troponin (Tn) and creatine-kinase myocardial band (CK-MB), its diagnostic use is limited by concerns about its lack of specificity [5]. However, evidence is mounting that myoglobin sensitivity for myocardial necrosis combined with its unique release and clearance properties may render it particularly attractive as a risk marker either alone or in combination with other markers. Myoglobin may be detectable above the upper limits of normal in the serum within 1–3 h of the onset of myocardial injury, but becomes no longer detectable within 12–18 h. This unique profile offers special opportunities for using myoglobin in diagnostic and risk stratification purposes [6]. The relationship between serum levels of myoglobin and clinical outcomes in patients with PE has been assessed in a limited number of studies, but – however – remains unclear [2].

Cardiac troponins are the most sensitive and specific biomarkers of myocardial cell damage, reflecting microscopic myocardial necrosis [7]. Elevated Tn levels predict adverse outcomes in patients with acute myocardial infarction (MI) and in critically ill patients without acute coronary syndromes [8]. Troponin is a regulatory protein of the thin filament of striated muscle and consists of 3 subunits: TnC at 18 kDa, cTnI at 21 kDa, and TnT at 37 kDa. The serum levels of TnT and cTnI are increased for many days after MI, but less elevation occurs with PE; being of short duration [9].

The current study aimed at assessing the levels of these cardiac biomarkers in relation to the different clinical, ECG, and Echo findings in patients with acute PE; as well as evaluating the prognostic value of these biomarkers for in-hospital mortality and adverse clinical events in this category of patients.

Patients and methods

This study comprised 40 consecutive patients (22 male and 18 female) aged 50.1 ± 13.1 years. These patients were proved to have acute PE by spiral contrast-enhanced computed tomography (CT) of the chest. Only the patients referred within 12 h of the onset of symptoms were included in this study.

Exclusion criteria included delayed presentation after the onset of symptoms, patients with ischemic, valvular, or congenital heart diseases, renal or hepatic failure, connective tissue disorders, endocrine disorders, and recent trauma or surgery.

All patients were subjected to thorough history taking (with stress on the analysis of chest pain, dyspnea, hemoptysis, and cardiovascular collapse) and complete general and local examination. All patients underwent the following investigations: standard transthoracic 12-leads ECG, full Echo-Doppler study (to evaluate left ventricular size and function, cardiac valves, pericardium, RV size and function, pulmonary artery diameter and pressure), spiral chest CT, and laboratory tests (arterial blood gases, serum myoglobin, serum troponin, total CK and CK-MB, kidney and liver function tests).

Clinical end points of the study included overall mortality and complicated in-hospital course; which is defined as one or more of the following: need for thrombolytic therapy, catecholamine support of blood pressure, endotracheal intubation or cardiopulmonary resuscitation. Other in-hospital adverse clinical events include: ischemic stroke (confirmed by CT brain) and major bleeding (defined according to standardized criteria). Recurrent PE was confirmed by spiral chest CT. The mean duration of in-hospital stay was 25.2 ± 9.6 days. The cutoff levels of both cTnI and myoglobin in cases of acute pulmonary embolism (> 0.07 ng/ml, > 70 ng/ml), respectively, were applied in the current study as mentioned according to European guidelines on the diagnosis and management of pulmonary embolism [10].

Laboratory methods

Venous blood sample (5 ml) was drawn from each patient through antecubital vein and the separated sera were aliquoted and preserved at -70 °C till the time of Tn, CK-MB, and myoglobin assay.

cTnI assay: this was estimated using chemiluminscence autoanalyzer (Imnulite 1000, USA).

Myoglobin assay: this was done through the immunoturbidimetry method using automated Cobas Integra instrument (Roche, Germany).

CK-MB assay: this was done through the immunoinhibition method.

Statistical methods

Data were analyzed using SPSS program version 16. Qualitative data were presented as number of patients (percentage). Quantitative data were tested for normality by Kolmogrov–Smirnov test. Normally distributed data were presented as mean ± SD. Independent-samples t-test was used to compare between two groups. Pearson correlation co-efficient was used to correlate between variables. A two-tailed p-value < 0.05 was regarded as significant.

Results

The clinical and other characteristics of the study population are shown in Table 1. As shown in the table, almost all patients

Table 1 Clinical and other characteristics of the study population of patients with acute pulmonary embolism on the time of presentation.

Variables	Number ($n = 40$)	Percentage (%)
I – Acute symptoms		
Dyspnea	38	95
Chest pain	32	80
Hemoptysis	22	55
Lower limb pain and tenderness	20	50
Syncope	18	45
II – Predisposing factors for pulmonary embolism		
Reduced mobility	24	60
Lowe limb problems	22	55
-Deep vein thrombosis	16	40
-Varicose veins	4	10
-Bone fracture(s)	2	5
Obesity	10	25
Hormonal contraception	2	5
III – ECG changes suggestive of pulmonary embolism		
Recent $S_I Q_{III} T_{III}$	10	25
Inverted T-wave (V_1 through V_3)	8	20
Complete/incomplete RBBB	4	10
IV – Echocardiographic evidence of RV dysfunction		
RV enlargement	20	50
Significant tricuspid regurge ($\geqslant$ grade III/IV)	18	45
Paradoxical septal motion	16	40
V – Laboratory data		
Myoglobin $\geqslant 70$ ng/ml	22	55
Troponin-I $\geqslant 0.07$ ng/ml	18	45
CK-MB $\geqslant 10$ U/L	3	7.5

CK-MB, creatine-kinase myocardial band; ECG, electrocardiographic; RBBB, right bundle branch block; RV, right ventricular.

(95%) had dyspnea on presentation followed by chest pain (80%); while 60% of the patients had reduced mobility as the commonest predisposing factor for acute PE. The commonest ECG change which existed in these patients was recent $S_I Q_{III} T_{III}$ (25%); while the commonest Echo finding was RV enlargement (half the cases).

Elevated levels of cardiac tissue-specific biomarkers were detected in high percentage of patients: elevated ($\geqslant 70$ ng/ml) serum myoglobin levels existed in 55% of patients; while elevated serum cTnI levels ($\geqslant 0.07$ ng/ml) existed in 45% of them.

However, elevated serum CK-MB levels ($\geqslant 10$ U/L) existed only in 7.5% of patients with acute PE. The cut-off values used in this study to define elevated levels of cardiac tissue-specific biomarkers are derived from the European Guidelines [10].

Significant and strong positive correlations existed between myoglobin serum levels and respiratory rate; while the same variable correlated negatively and strongly with the values of systolic, diastolic, and mean arterial blood pressure. cTnI levels correlated positively with respiratory rate, but showed no significant correlation with the values of systolic, diastolic, or mean arterial blood pressure as shown in Table 2.

As shown in Table 3, significantly higher mean values of all cardiac biomarkers existed in relation to the presence of ECG signs of RV strain; namely recent $S_I Q_{III} T_{III}$, right bundle branch block, and inverted T-waves (in V_1 through V_3).

As shown in Table 4, statistically significant positive correlations existed between RV diastolic diameter (indicator of RV enlargement) and the levels of all cardiac biomarkers; but this correlation was particularly strong in the case of myoglobin followed by cTnI then CK-MB. Significant tricuspid regurge correlated positively and strongly with cTnI levels; and moderately with CK-MB then myoglobin levels in this order of strength. The values of fractional shortening and pulmonary artery pressure correlated negatively with CK-MB levels; but had no significant correlation with myoglobin or cTnI levels.

Table 5 and Fig. 1 show the incidence of in-hospital adverse clinical events in the studied population. As shown in the table, the commonest event was the administration of thrombolytic therapy (44% of patients) followed by hemodynamic support by catecholamine (10% of patients); while the least common events were recurrent PE and death (5% for each).

Multiple step-wise logistic regression analysis model was constructed to extract the variables independently associated with in-hospital mortality and adverse clinical events. As shown in Table 6, elevated levels of cTnI and myoglobin were significantly and independently associated with very high odds (14–17 times) of in-hospital mortality and adverse clinical events.

Discussion

The rapid evaluation and risk stratification of patients presenting with symptoms suggestive of acute PE are of great clinical relevance. Biomarkers have become increasingly important in this setting, especially cardiac troponin, which is still the main routinely used marker due to its myocardial tissue-specificity and sensitivity. Although myoglobin serum level increases after myocardial injury (even before detectable rise of cardiac troponin levels), myoglobin was not adequately evaluated in acute PE [11]. Considering the latter fact, this study was

Table 2 Correlation between the values of different clinical variables and the levels of serum myoglobin and troponin-I.

	Myoglobin (ng/ml)		Troponin-I (ng/ml)	
	R	p	R	p
Respiratory rate (cycle/minute)	0.528	$<0.001^{**}$	0.410	$<0.001^{**}$
Systolic blood pressure (mmHg)	−0.647	$<0.001^{**}$	−0.142	0.383
Diastolic blood pressure (mmHg)	−0.659	$<0.001^{**}$	−0.053	0.744
Mean blood pressure (mmHg)	−0.660	$<0.001^{**}$	−0.089	0.584

** $p < 0.01$.

Table 3 Comparison of mean values of cardiac biomarkers in patients with acute pulmonary embolism with and without suggestive ECG findings.

Variables	Recent S_I Q_{III} T_{III}			Complete/incomplete RBBB			Inverted T (V_1 through V_3)		
	+ve (n = 10)	−ve (n = 30)	p	+ve (n = 4)	−ve (n = 36)	p	+ve (n = 8)	−ve (n = 32)	p
Myoglobin (ng/ml)	87.0 ± 8.8	65.0 ± 7.5	<0.001**	91.0 ± 8.67	81 ± 6.67	<0.001**	84 ± 7.98	79 ± 6.12	<0.001**
Troponin-I (ng/ml)	0.089 ± 0.0092	0.062 ± 0.0057	<0.001**	0.096 ± 0.011	0.081 ± 0.0091	0.004**	0.11 ± 0.0085	0.095 ± 0.0076	<0.001**
CK-MB (U/L)	24.5 ± 3.5	17.4 ± 2.2	<0.001**	28.9 ± 4.4	19.8 ± 3.1	<0.001**	34.5 ± 2.8	19.1 ± 2.6	<0.001**

CK-MB, creatine-kinase myocardial band; RBBB, right bundle branch block.
** $p < 0.01$.

Table 4 Correlations between the levels of cardiac biomarkers and the values of different Echo variables in patients with acute pulmonary embolism.

Variable	Myoglobin (ng/ml)		Troponin-I (ng/ml)		CK-MB (U/L)	
	R	p	R	p	R	p
RVEDD (cm)	0.534	<0.001**	0.475	0.002**	0.376	0.017*
LVESD (cm)	−0.051	0.754	0.190	0.241	0.193	0.232
LVEDD (cm)	−0.063	0.698	0.121	0.458	−0.091	0.576
LAD (cm)	−0.141	0.384	0.112	0.490	0.063	0.698
EF (%)	−0.255	0.112	−0.215	0.182	−0.283	0.077
FS (%)	−0.301	0.059	−0.255	0.112	−0.352	0.026*
PAP (mmHg)	0.035	0.830	−0.055	0.734	−0.320	0.044*
TR#	0.349	0.027*	0.545	<0.001**	0.379	0.016*

CK-MB, creatine-kinase myocardial band; EF, ejection fraction; FS, fractional shortening; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; PAP, pulmonary artery pressure; RVEDD, right ventricular end-diastolic diameter; TR, significant tricuspid regurge (⩾grade III/IV).
* $p < 0.05$.
** $p < 0.01$.
# Spearman rank correlation.

Table 5 Incidence of in-hospital adverse clinical events in studied group of patients with acute pulmonary embolism.

Events	Number (n = 40)	Percentage (%)
Thrombolytic therapy	22	55
Hemodynamic support by catecholamine	4	10
Cardiopulmonary resuscitation	3	7.5
Recurrent pulmonary embolism	2	5
Death	2	5

designed to evaluate the levels and prognostic significance of myoglobin and other tissue-specific cardiac biomarkers (cTnI and CK-MB) in patients with acute PE.

Cardiac troponins are widely established in clinical practice, but their detection in the circulation may require several hours after the onset of symptoms. Therefore, the troponin levels measured on admission may not suffice to assess the prognosis and guide early therapeutic decisions, pointing to the need for novel biomarkers and algorithms that guarantee more efficient and (particularly) faster risk assessment of acute PE [12,13].

Our results demonstrate that nearly half (45%) the patients diagnosed with PE have elevated cTnI level, so that testing this biomarker could help to identify patients with RV dysfunction who had higher risk of adverse clinical outcome. Thus, cTnI assay is useful to detect minor myocardial damage in PE

patients as previously confirmed by Meyer et al. [14]. Elevated cTnI serum levels were also correlated with ECG and Echo criteria of RV dysfunction, indicating irreversible myocardial cell damage. In this respect, it is known that the release of cTnI is related to acute RV shear stress, with ensuing microinjury and microinfarctions [15]. Besides, a dilated overloaded RV increases oxygen demand and diminishes perfusion of the right coronary artery, even in the absence of atherosclerosis [16]. The observed cTnI release in patients with acute PE in this study is quantitatively small far less than typically observed in an ST-elevation MI [15,17]. However, cTnI level correlated well with RV dysfunction in this study, a result confirmed in a previous report [15].

Elevated cTnI serum levels were independently associated with mortality and adverse in-hospital clinical events. Both patients who died during hospitalization had elevated cTnI level
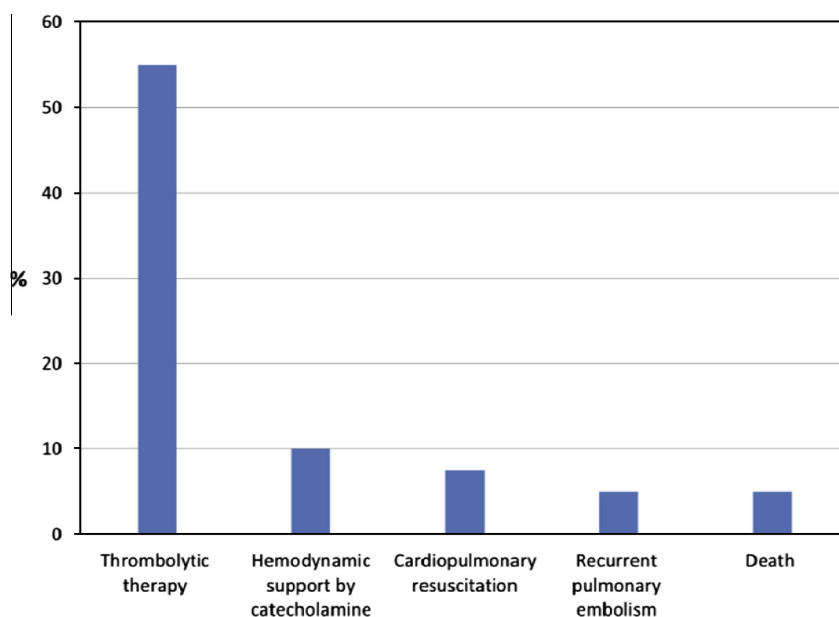
Figure 1 The incidence of in-hospital clinical events in patients with acute pulmonary embolism.

Table 6 The final results of the multiple step-wise logistic regression analysis model used to extract the variables independently associated with in-hospital mortality and adverse clinical events. As shown, elevated levels of troponin-I and myoglobin were significantly and independently associated with very high odds (14–17 times) of in-hospital mortality and adverse clinical events.

Variables	Overall in-hospital mortality (odds ratio)	In-hospital adverse clinical events (odds ratio)
Troponin-I (ng/ml)		
< 0.07 ng/ml	6.1 [0.6–62.0] $p = 0.085$	2.2 [0.8–10.3] $p = 0.069$
> 0.07 ng/ml	15.8 [1.5–166.7] $p = 0.018^*$	14.4 [2.8–51.6] $p < 0.001^{**}$
Myoglobin (ng/ml)		
< 70 ng/ml	5.1 [0.6–59.0] $p = 0.076$	2.1 [0.7–4.2] $p = 0.059$
> 70 ng/ml	16.7 [1.6–165.6] $p = 0.002^*$	17.2 [2.6–49.6] $p < 0.001^{**}$

> 0.07 ng/ml (a finding similar to the other studies [15–17]), elevated myoglobin levels > 70 ng/ml, as well as echocardiographic evidence of RV dysfunction; and all these findings are supported by other investigators [9,18].

Elevated serum levels of myoglobin occurred very early after the onset of symptoms (< 4 h) in 55% of patients, and were strongly associated with ECG and Echo findings suggestive of RV dysfunction, in line with the previous finding of Bochowicz et al. [19].

We found a strong positive correlation between elevated serum myoglobin levels and respiratory distress (indicated by tachypnea), while there was a strong negative correlation between serum myoglobin levels and hemodynamic status (indicated by systolic, diastolic, and mean arterial blood pressure). These findings could be translated as follows: the patients with more respiratory distress and/or hemodynamic instability may have higher serum levels of myoglobin, which in turn reflect more RV dysfunction, a finding that favors early thrombolytic therapy. These results are similar to the report of Pruszczyk et al. [20]. Myoglobin sensitivity for myocardial necrosis combined with its unique release and clearance properties may render it particularly attractive as a risk marker, either alone or in combination with other markers [6,11].

The observed myoglobin release is quantitatively small far less than typically observed in MI (> 239 ng/ml) [21]. However, mildly elevated myoglobin (> 70 ng/ml) in acute PE correlated well with RV dysfunction by Echo and was independently associated with very high odds of in-hospital mortality and adverse clinical events using multivariately-adjusted logistic regression analysis model. These findings are almost similar to those reported by Pruszczyk et al. [20] who found elevated myoglobin levels in almost half the patients with acute PE on admission. Thus, myoglobin – this instantly elevated marker – is a very useful tool for early risk stratification of patients with acute PE, facilitating the choice of an appropriate therapeutic strategy that could in turn positively affect the patient's prognosis.

As in the case of myoglobin, the risk for in-hospital adverse clinical events and mortality was significantly higher in patients with high cTnI but not CK-MB levels using the same multivariate logistic regression analysis. Thus, CK-MB was not found to be an independent predictor of a complicated in-hospital course in this study; because it was elevated in just 3 patients (7.5%). These results are in accordance with the reports of other studies [15,16,19].

Although the results obtained with both troponin and myoglobin were directionally similar, the major superiority

of myoglobin compared with cTnI is related to the unique instant release dynamics of myoglobin (within 4 h of the onset of PE) that may favorably affect risk stratification of patients and hence planning the suitable therapeutic strategy. In other words, it can be proposed that cardiac troponin and myoglobin levels should be obtained in normotensive patients with acute PE to assist clinicians in management. Those patients with normal troponin and myoglobin can almost certainly be treated with anticoagulation therapy alone. If concern persists about the prognosis in individual patients, the prediction of benign clinical course can be confirmed with Echo, showing normal or near normal RV function. On the other hand, patients with acute PE and elevated troponin and myoglobin levels should undergo further testing of RV function with Echo. If the echocardiogram shows moderate or severe RV dysfunction in the presence of elevated troponin and myoglobin levels, this may portend a lethal combination. This last category of patients should be emergently assessed to determine whether thrombolysis or embolectomy is the appropriate strategy in this setting.

Conclusion

The results of this study strongly support the integration of troponin and myoglobin testing in management algorithms of patients with established acute PE, particularly myoglobin, owing to on its unique instant release in acute PE which makes it a valuable cardiac biomarker for early planning of instant therapeutic strategies. Additional therapeutic trials are needed to determine whether troponin and myoglobin (alone or in combination with clinical and/or Echo findings) suggestive of RV dysfunction can be used to guide the treatment of patients with acute PE and particularly improve the prognosis of high-risk patients.

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