Cardiac Troponin I as a Marker of Sepsis Severity and Mortality Prediction

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Abstract

Background: Cardiac troponins I (cTnI) are biomarkers that are currently used for diagnosis and risk stratification in patients with myocardial infarction and congestive heart failure, however, their prognostic and diagnostic impact in patients with sepsis syndrome need more clarification.

Aim: To study the prognostic value of cTnI on mortality and adverse complications in patients with sepsis and septic shock, and to study the relation of cTnI with ICU scoring systems.

Methods: A prospective comparative study was conducted on forty five patients admitted to the ICU with sepsis or septic shock. Then patients were divided into 2 groups; group 1: included 20 patients with positive cTnI (mean age 58 ± 18.9yrs, 40% males) and group 2: included 25 patients with negative cTnI (mean age 52 ± 19.3yrs, 64% males), comparisons between 2 groups were done according to all demographic, scoring systems, medications used and adverse outcome.

Results: Seventeen patients 85% of cTnI positive group vs. 36% of patients in cTnI negative group had severe sepsis or septic shock (p-value=0.001). There were statistically significant relations between the 2 groups as regards APACHE II (34.6 ± 10.9 vs. 17.8 ± 5.4, p-value=0.001), SOFA on admission (14.9 ± 4.2 vs. 6.9 ± 4.5, p-value=0.000 1) and SOFA at 2nd day (15.8 ± 5.4 vs. 5.5 ± 4.4, p-value=0.0001). The need for vaso-pressors was significantly higher in cTnI positive group than cTnI negative group (85% vs. 24%, p-value=0.0001). Mortality was significantly higher in group 1 than group 2 (90% vs. 60%, p-value=0.024). Cardiac troponins I was highly correlated with APACHE score on admission (r=0.71, p-value=0.0001), and with SOFA score both on admission and 2nd day (r=0.69, r=0.64 respectively p-value=0.0001). Only APACHE II and SOFA scores were found to be predictors of mortality in the study groups (p-value=0.0001), while Cardiac troponins I was not found to be predictor of mortality (p-value=0.29) by logistic regression analysis.

Conclusions: Sepsis patients with high cTnI levels are usually more critically ill and more prone to adverse outcome and mortality but cTnI level is not a predicator of mortality.

Key Words: Cardiac troponin I – Sepsis – APACHE II – SOFA and mortality.

Introduction

SEVERE sepsis is the leading cause of death in the non-coronary intensive care unit (ICU) and the 10th leading cause of death overall [1-3].

Cardiac troponin I (cTnI) has been shown to be an indicator of myocardial injury and is an accepted prognostic factor of myocardial infarction (MI) [4,5]. Although cTnI is cardiac-specific, its release seems not to be limited to cardiac-related events, but is also detectable in other critical clinical conditions, such as trauma, pulmonary embolism, and severe sepsis.

The elevation of cardiac troponins in patients with sepsis, severe sepsis and septic shock has been shown to indicate a poor prognosis. Troponin release in this population occurs in the absence of flow-limiting coronary artery disease, suggesting the presence of mechanisms other than thrombotic coronary artery occlusion, probably a transient loss in membrane integrity with subsequent troponin release or microvascular thrombotic injury [6].

The aim of the study was to assess if cardiac troponin cTnI can be used as a marker of sepsis severity and predictor for mortality and outcome in relation to ICU scoring systems (APACHE II, SOFA).

Patients and Methods

Forty five patients diagnosed to have various degrees of systemic sepsis admitted to the critical care department at Cairo University and internal medicine department (critical care unit) at Beni-Suef University were included in a prospective comparative study, from the period of July 2011...
to November 2011. The study was approved by the local ethical committee, where patients included in our study.

Included patients fulfilled the following criteria on admission:

A- In the presence of a source of Sepsis, Two or more of the following parameters:
- Temperature >38°C or <36°C.
- HR >90bpm.
- RR >20/min with PaCO2 <32mmHg.
- TLC >12000/dL or <4000/dL or >10% staff cells.

B- and/or (Severe sepsis or septic shock):
Sepsis with organ dysfunction, hypoperfusion (defined as lactic acidosis, oliguria or acute alteration in mental status) or hypotension defined as (systolic pressure <90mmHg or reduced from baseline by >40mmHg), with or without response to fluid resuscitation.

All included patients were followed-up until discharge or death. Hospitalization outcome was defined as mortality or discharged when improved.

Excluded from the study were patients with any disease that may be associated with an elevation of cardiac troponins as follows: Ischemic heart disease (IHD) by history or ECG findings, cardiothoracic trauma or surgery, dilated cardiomyopathy or LV dysfunction, chronic renal failure, Known advanced metastatic malignancy or neuromuscular disease. Severe trauma or known exposure to burns or toxic chemicals.

All patients were subjected to full medical history, complete clinical examination, ECG, CXR, TTE and full lab, including Cardiac troponin I. Both SOFA and APACHE II were calculated for patients on admission and 2nd day only for SOFA.

I- Full medical history taking: Especially history of ischemic heart diseases, hypertension, diabetes, liver diseases, smoking, renal diseases.

II- Complete general examination.

III- Sequential Organ Failure Assessment score (SOFA) score (Table 1): Was evaluated on admission and on the 2nd day, It is one of several ICU scoring systems. It is a six-organ dysfunction/failure score, one each for the respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems, measuring multiple organ dysfunction/failure to track a patient's status during the stay in an ICU, and used to determine the extent of a person's organ function or rate of failure. Each organ is graded from 0 (normal) to 4 (the most abnormal), providing a daily score of 0 to 24 points.

IV- Acute Physiologic Assessment and Chronic Health Evaluation (APACHE II) score (Table 2): Was done to all patients within the first 24 hours from admission to assess disease severity and predict prognosis of the patients. APACHE II scoring system is the most common system used in assessment of critically ill patients in ICU, it was introduced in 1985. It generates a point score ranging from 0 to 71 based on 12 physiologic variables, age, and underlying health, the less the score the better the prognosis and vice versa.

V- Base line 12-lead ECG: To exclude acute ischemic event.

VI- Baseline arterial blood pressure and monitoring continuously.

VII- Full blood chemistry including:
- Complete blood picture on admission.
- Liver function test to detect the presence of liver dysfunction.
- Coagulation profile (Prothrombin time, Prothrombin concentration and platelets count)
- Kidney function test including urea and creatinine.
- Arterial blood gases on admission and daily follow-up.
- Cardiac troponin I on admission: Troponin I was measured using Troponin I kit used for IMMULITE/IMMULITE 1000 Siemens system. It was a solid-phase, enzyme-labeled, chemiluminescent immunometric assay. The solid phase (beads) are covered with monoclonal murine anti-troponin I antibody. The liquid phase consisted of alkaline phosphatase conjugated to polyclonal goat anti-troponin I antibody.

According to the IMMULITE/IMMULITE 1000, values below 0.4mcg/l were considered negative for troponin I, it was measured once only on admission.

According to the level of cTnI patients were divided into 2 groups: Group 1: Included patients with positive cTnI (≥0.4mcg/l) and group 2: Included patients with negative cTnI (<0.4mcg/l), both groups were compared to each other in relation to all demographic, risk factors, scoring systems, mortality and other adverse outcomes including
the requirements for mechanical ventilation and need for vasopressors, and the length of ICU stay (LOS).

Statistical analysis: Patients’ data were tabulated and processed using SPSS (15.0) statistical package for Windows XP.

Quantitative variables were expressed as means and standard deviation.

Descriptive statistics for parametric data of both groups and frequency tables was used for categorical data, t-test when comparison between parametric data of both groups was needed, Pearson correlation coefficients when examining the strength between two parametric variables.

Spearman correlation co-efficient test: Was used to rank different variables against each other's positively or inversely.

$p$-value >0.05 = insignificant, $p$-value <0.05 = significant, $p$-value <0.01 = highly significant.

Results

Forty five patients admitted to the critical care unit with various severity of sepsis (19 patients 42% had sepsis and 26 patients 58% had severe sepsis or septic shock) were enrolled in this study and they were divided into 2 groups according to the level of cTnI, group 1: Included 20 patients with positive cTnI (mean age 58±18.9yrs, 40% male) and group 2: Included 25 patients with negative cTnI (mean age 52±19.3yrs, 64% male).

Patient characteristics and hemodynamic data:

There were no statistically significant differences between 2 groups regarding demographic data and comorbid diseases, but HR, MAP and SBP were significantly different between 2 groups, while patient temperature and central venous pressure CVP were not statistically different between 2 groups Table (1).

Severity of sepsis and scoring system:

Seventeen patients (85%) of cTnI positive group were in severe sepsis or septic shock versus 36% in cTnI negative group ($p$-value 0.001).

Patients with elevated cTnI were more critically ill as reflected by higher APACHE II scores at study entry and SOFA score on admission and on 2nd day: APACHE II was (34.6±10.9 vs. 17.8±5.4, $p$-value=0.001), SOFA on admission (14.9±4.2 vs. 6.9±4.5, $p$-value=0.0001) and SOFA at 2 nd day (15.8±5.4 vs. 5.5±4.4, $p$-value=0.0001) Table (2).

Vasopressors, clinical course and outcome:

The need for vasopressors was significantly higher in cTnI positive group than the cTnI negative group (85% vs. 24%, $p$-value=0.0001).

In cTnI positive group more than one vasoactive drug was needed to maintain hemodynamics in 41% of them, while the dose of nor-adrenaline more than 0.66 mic/Kg/min was needed in 29.4% of patients in this group).

As regard the need for mechanical ventilation, its duration and length of stay (LOS) in ICU; no significant differences were found between 2 groups.

Mortality was significantly high in group 1 than group 2 (90% vs. 60%, $p$-value=0.024) Table (3).

Table (1): Baseline characteristic and hemodynamic data of both groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1: Positive cTnI</th>
<th>Group 2: Negative cTnI</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>58±18.9</td>
<td>52±19.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>40%</td>
<td>64%</td>
<td>0.14</td>
</tr>
<tr>
<td>DM</td>
<td>65%</td>
<td>44%</td>
<td>0.23</td>
</tr>
<tr>
<td>HTN</td>
<td>45%</td>
<td>40%</td>
<td>0.7</td>
</tr>
<tr>
<td>HR</td>
<td>126±25</td>
<td>107±18.3</td>
<td>0.005</td>
</tr>
<tr>
<td>SBP</td>
<td>80±13.3</td>
<td>118.8±30.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>MAP</td>
<td>63.9±16.45</td>
<td>85.5±20</td>
<td>0.0001</td>
</tr>
<tr>
<td>Temp</td>
<td>38.1±1.4</td>
<td>37.80.7</td>
<td>0.49</td>
</tr>
<tr>
<td>CVP</td>
<td>9.1±5.3</td>
<td>9.6±6.2</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Table (2): Troponin level, of severity of sepsis and score systems of each group.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1: Positive cTnI</th>
<th>Group 2: Negative cTnI</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troponin level</td>
<td>2.04±1.5</td>
<td>0.2±0.14</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sepsis (Severe sepsis or shock)</td>
<td>15%</td>
<td>64%</td>
<td>0.0001</td>
</tr>
<tr>
<td>APACHE</td>
<td>34.6±10.9</td>
<td>17.8±5.4</td>
<td>0.0001</td>
</tr>
<tr>
<td>SOFA (0)</td>
<td>14.9±4.2</td>
<td>6.9±4.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>SOFA (2)</td>
<td>15.8±5.4</td>
<td>5.5±4.4</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Table (3): Need for vasopressors and outcome in both groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1: Positive cTnI</th>
<th>Group 2: Negative cTnI</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasopressors</td>
<td>85%</td>
<td>24%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Need for MV</td>
<td>75%</td>
<td>60%</td>
<td>0.35</td>
</tr>
<tr>
<td>MV duration</td>
<td>4.6±3.5</td>
<td>9.6±8.7</td>
<td>0.09</td>
</tr>
<tr>
<td>LOS in ICU</td>
<td>14.2±13.4</td>
<td>23.6±25.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Mortality</td>
<td>90%</td>
<td>60%</td>
<td>0.04</td>
</tr>
</tbody>
</table>

MV: Mechanical ventilation. LOS: Length of stay.
Correlative results:

Cardiac troponin I level was found to be significantly correlated with HR, SBP and MAP (r=0.37, 0.68 and 0.61 respectively, p-value=0.001) in all patients. CTn I levels was also correlated with APACHE, SOFA 1st and 2nd day (r=0.71, –0.64 and –0.69 respectively, p-value=0.0001) in the study groups.

Relation to mortality:

Patients were subdivided again according to mortality where scoring systems values and cTn I levels were compared between survivals (12 patients) and dead (33 patients). Only APACHE II and SOFA scores were found to be significantly high in group of mortality than survivals; (p-value =0.0001), while cardiac troponins I was not found to be statistically different between 2 groups (p-value=0.44) Table (4).

Table (4): Relation of CTn I and scoring systems to mortality.

<table>
<thead>
<tr>
<th></th>
<th>Survivals (N=12)</th>
<th>Mortality (N=33)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE II</td>
<td>16.6±5.3</td>
<td>28.5±12</td>
<td>0.001</td>
</tr>
<tr>
<td>SOFA (0)</td>
<td>4.6±2.6</td>
<td>12.6±5.2</td>
<td>0.001</td>
</tr>
<tr>
<td>SOFA (2)</td>
<td>3.1±2.16</td>
<td>12.6±6.5</td>
<td>0.001</td>
</tr>
<tr>
<td>cTn I</td>
<td>0.63±1.04</td>
<td>1.15±1.4</td>
<td>0.44</td>
</tr>
</tbody>
</table>

Discussion

In this study serum cTnI level was positive in 44.4% of the patients with sepsis, severe sepsis, or septic shock, this incidence is consistent with previous studies of severe septic patients where incidence of elevated troponin was 43% to 85% of patients [7-10].

Some of These studies were retrospective analyses as in Moghadam et al., [10]; others were small prospective observational studies as in Ammann et al., where cardiac troponin I was elevated in 85% of patients with sepsis, septic shock or SIRS [7].

In Scott et al., the incidence of elevated troponin I in severely sepsis and septic shocked patients at study entrance was (64%), which is much higher than our results and this can be explained by that our study group was including 19 patients with sepsis 42% and 26 patients 58% with severe sepsis or septic shock while the previous study included only severe sepsis or septic shock patients [8].

In our study patients with elevated cTnI were more critically ill which appear by higher APACHE II (34.6±10.9 vs. 17.8±5.4, p-value=0.001), SOFA scores at 1st and 2nd day of admission (15.8±5.4 vs. 5.5±4.4, p-value=0.0001), as well 85% of patients of this group had either severe sepsis or septic shock vs 36% in group 2 patients which manifested by significantly higher heart rate (HR) and lower SBP and MAP in cTnI positive group. These results are similar to Mehta et al., results, where cTnI positive patients showed significantly higher APACHE II score and higher mortality (56% vs. 24%, p=0.04) [6], also Aziz et al., demonstrated that Troponin I-positive group had higher APACHE II score (30±6 vs. 22±4.7) on admission [11].

In the present study, need for vasopressor support was significantly higher in cTnI positive group exactly to those of severe sepsis and septic shock and 23.5% of them needed dose of noradrenaline >0.66 while none of the other group required such dose; this can be explained by the severity of illness in the 1st group. This result is consistent with Mannam et al., result where cTnI positive required increase dose of vasopressors (9.9 vs. 1, p=0.006) [12].

This result also found by Mehta et al., in their study where cTnI+ patients showed higher need for inotropic/vasopressor support (94% vs. 53%, p=0.018), Serum cTnI, APACHE II score, anion gap and serum lactate were independent predictor of need for inotropic/vasopressor support [6].

The results of the present study found no significant difference in need for mechanical ventilation and its duration or length of ICU stay (LOS) in both group, similar to those demonstrated by Moghadam et al., who found no significant statistical difference between the 3 groups cTnI+, gray zone, cTnI- in duration of MV (p=0.17) [10]. This is against what Mannam et al., demonstrated as cTnI+ experienced longer duration of mechanical ventilation (12 vs. 2 days, p=0.002) but they take a lower point for positive troponin >0.1ng/ml and non significant statistically trend toward longer ICU stay (16.3 vs. 5.3 days, p=0.082) [12]. Regarding LOS; Tiruvoipati et al., showed no statistical difference in intensive care or hospital duration of stay in his study [13].

Our results regarding mortality showed that it was significantly high in group 1 than group 2 (90% vs. 60%, p-value=0.024). The previous results are consistent with different studies showed that sepsis patients with elevated troponin levels had
higher APACHE II scores and higher mortality [12, 14,15,16]. One of those studies Mannam et al., who found that mortality was significantly higher in cTn positive septic patients (45.4% vs. 7.7%, p <0.04) [12].

Kang et al., showed that elevated cTnI levels were significantly associated with short- and long-term mortality in ESRD patients with sepsis. Therefore, elevated cTnI levels in these patients should not be overlooked and be followed for adverse outcomes [17].

Despite mortality was significantly higher in cTnI positive group but cTnI level was not found to be an independent predictor of mortality and still APACHE II, SOFA scores were found to be predictor of mortality; these results are similar to the study done by Smith et al., for higher mortality in cTnI positive group but didn’t prove its prediction of mortality [18].

Moghadam et al., also demonstrated that elevated cTn I levels measured upon admission were not associated with increased morbidity or mortality rates. Cardiac troponin does not independently predict mortality beyond that provided by APACHE II [10].

Tiruvoipati et al., results also showed significantly higher mortality either in hospital (15% vs 36.1%; p <0.01) or intensive care (11% vs 25%; p<0.01), but Logistic regression analysis revealed temperature, simplified acute physiology score II and serum lactate to be independent predictors of hospital mortality [13]. In addition, Oliveira et al., demonstrated that severity of septic disease was the only variable significantly associated with the death [19].

Contrary to our results cardiac troponin I found to be an independent predictor of hospital mortality in Mehta et al., study who found that serum cTnI and APACHE II score were independent predictor of death and length of stay in intensive care unit [6].

John et al., also found that Elevated cTnI was an independent prognosticator of mortality (odds ratio, 2.020; 95% confidence interval, 1.153-3.541) after adjusting for other significant variables [15].

Conclusions: Sepsis patients with high cTnI levels are usually more critically ill and more prone to adverse outcome and mortality but cTnI level is not a predictor of mortality.

References

