Original Article

Prognostic Value of Serum Troponin I in Sepsis Patients

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Abstract

Background: *Sepsis is one of the leading causes of admission in ICU with high mortality and morbidity. Intensivists face challenges to manage sepsis in their practices particularly in a limited resource setting. The diagnosis of sepsis and its evaluation of severity are not easy because of its complex pathophysiology and variable nature of presentation. So, researchers identified biomarkers including troponin I for potential use in sepsis. Of them troponin I is a useful biomarker with prognostic significance.*

Materials and methods: *This prospective observational study was conducted among purposively selected 110 patients diagnosed as sepsis at intensive care unit (ICU) in Dhaka Medical College & Hospital. After fulfilling the inclusion and exclusion criteria, ECG was done to exclude MI. Then troponin I was measured with a cut of value of 0.6 ng/ml. the patients were followed up for a period upto 30 days. Statistical associations between categorical variables were tested using chi-square test and mean difference of continuous variables by independent t-test. Correlation between troponin I value length of ICU stays and ventilator days were calculated.*

Results:*Among 110 patients diagnosed as sepsis 56.4% had normal troponin I and 43.6% had elevated troponin I. Distribution of elevated troponin I was higher among male patients (77.1% vs 64.5%) than female. Mean duration of ICU stay was prolonged in elevated troponin I group as like ventilator support. Positive relationship was found between troponin level I and duration of ventilator support as well as length of ICU stay (r=0.225, 0.279). There was significantly increased mortality rate in elevated troponin group of patients compared to normal troponin group (72.9% vs 35.5%) in sepsis patients (p<0.001) followed by in severe sepsis 67.5% vs 35.48% (p=0.001) and 92.9% vs 57.1%) in septic shock (p<0.029).*

Conclusion: *This study showed that mortality and morbidity increases when troponin I value elevated in sepsis.*

Key words: *prognostic value, troponin I, sepsis*

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Introduction

Troponins are present in cardiac, skeletal and smooth muscle which primary function is to take part in muscle contraction. It has three components: troponin I, troponin C and troponin T. Among them troponin I is well accepted as a biomarker of acute coronary syndrome (ACS). The measurement of troponin I in blood has been accepted by the Joint Committee of the European Society of Cardiology and the American College of Cardiology as the standard biomarker for the diagnosis of acute myocardial infarction and by the American College of Cardiology and the American Heart Association for the diagnosis and management of unstable angina[1]. In acute coronary syndrome high rise of troponin I is associated with increased mortality[2].

Besides the enthusiasm for troponin I measurement in ACS, critically ill patients admitted in ICU have elevated troponin I that are

notalways explained by coronary artery disease. In critically ill patients, cardiac troponins are detectable in the plasma in up to 60% of cases[3]. There have been several reports demonstrating a high incidence of elevated troponin levels in patients with sepsis and septic shock. In different studies the troponin I level in sepsis was raised ranging from 43% to 56% and hospital mortality was raised in higher troponin groups[4, 5, 6].

Troponins are not normally present in the peripheral blood of healthy persons. Majority of them are bound with microfilaments and a small portion of them are present in cytosol. When the membrane integrity is lost first the cytosolic portion of troponin I first appear in blood. When major damage of cell occur the bound portion of troponin I also release in the blood. For this reason besides extensive literature on troponin release in acute coronary syndrome, there is evidence that troponin release can occur by other mechanism like trauma, toxins and inflammation. In sepsis widespread inflammation can damage integrity myocardial cell membrane. Moreover, activation of coagulation cascade causes microthombiformation which is also responsible for leakage of troponin I in blood. In sepsis, tissue hypoperfusion may cause further insult to myocytes with subsequent leakage of troponins in blood.

Sepsis is among the leading causes of admission to intensive care units (ICUs). The incidence of sepsis in different studies ranges from 8.4% to 11.4% of all patients admitted to the ICU[7,8,9]. Care for patients with sepsis represents a great economic burden as extraordinary resources are devoted to developing and evaluating potential treatments as well as to studying the systemic inflammatory response and multiple organ failure that are characteristic of severe sepsis. Published mortality rates for sepsis were up to 56%[7, 8, 9]. Researchers are exploring new ways to diagnose, reverse, or prevent this serious and costly condition. Clinical and standard laboratory tests are not very helpful because most critically ill patients develop some degree of inflammatory response, whether or not they have sepsis. Even microbiological assessment is unreliable because many culture samples do not yield microorganisms in these patients. So, some researchers studied on different biomarkers including troponin I, which have been assessed for their potential use in sepsis. Among them troponin I may be a promising tool in low resource countries because it is widely available as well as less costly than other biomarkers commonly used in sepsis.

The aim of the study was to determine the prognostic value of S. troponin I in sepsis patients admitted in ICU.

Materials and Methods

A prospective observational study was conducted at intensive care unit of Dhaka Medical College Hospital, Bangladesh from January 2014 to December 2015. Total 110 patients with sepsis were purposively selected as per inclusion and exclusion criteria as follows:

Inclusion criteria:

- Patients admitted in ICU of Dhaka Medical College Hospital during the study period
- Patients diagnosed as sepsis as per operational definition
- Willing to participate with informed written consent.

Exclusion criteria:

- Patients who had history of previous IHD
- Patients who had previous cardiac surgery
- Patient who had recent chest injury, DC cardioversion or CPR
- Patient or attendant's refusal at any time of study period.
- Accidental or unexplained death during study.

Permission was taken from hospital authorities and ethical review committee of Dhaka medical college for data collection. Then the study was conducted in the intensive care unit (ICU) of Dhaka Medical College Hospital. Patients admitted and clinically diagnosed as sepsis were primarily selected. Sepsis was diagnosed as per definition of accp/sccm consensus conference guidelines (Bone *et al*, 1992) as infection plus two or more of the followings

Core temperature $>38^0$ C or $<36^0$C

Heart rate >90beats/min

Respiratory rate >20/min or PCO_2>32 mm Hg

WBC count >12000/cmm or <4000/cmm or >10% immature band form

Clinically diagnosed sepsis patients who will fulfill the inclusion and exclusion criteria were included in the study. Informed written consent was taken from patients/relatives. Then a 12 lead ECG was done. Patient who have ST elevation or depression >2mm in chest leads and /or >1mm in limb leads were excluded as acute coronary syndrome. In the remaining patients data were collected using a checklist from the hospital records. A sample of blood was sent for troponin I measurements. troponin I was measured by using **Siemens DPC IMMULITE® 2000 Immunoassay Analyzer**. Cut off value was selected above 99th percentile value of normal population as e"0.60 ng/ml.

A checklist was used to collect patients' information using medical records. With all aseptic precaution 5 ml of venous blood was collected in a test tube containing EDTA will be sent immediately for S. troponin I measurement.

Finally these patients were followed up for a period of 30 days. Those who died during this follow up period were recorded. Those who survived, discharged, referred, dropped out were also recorded.

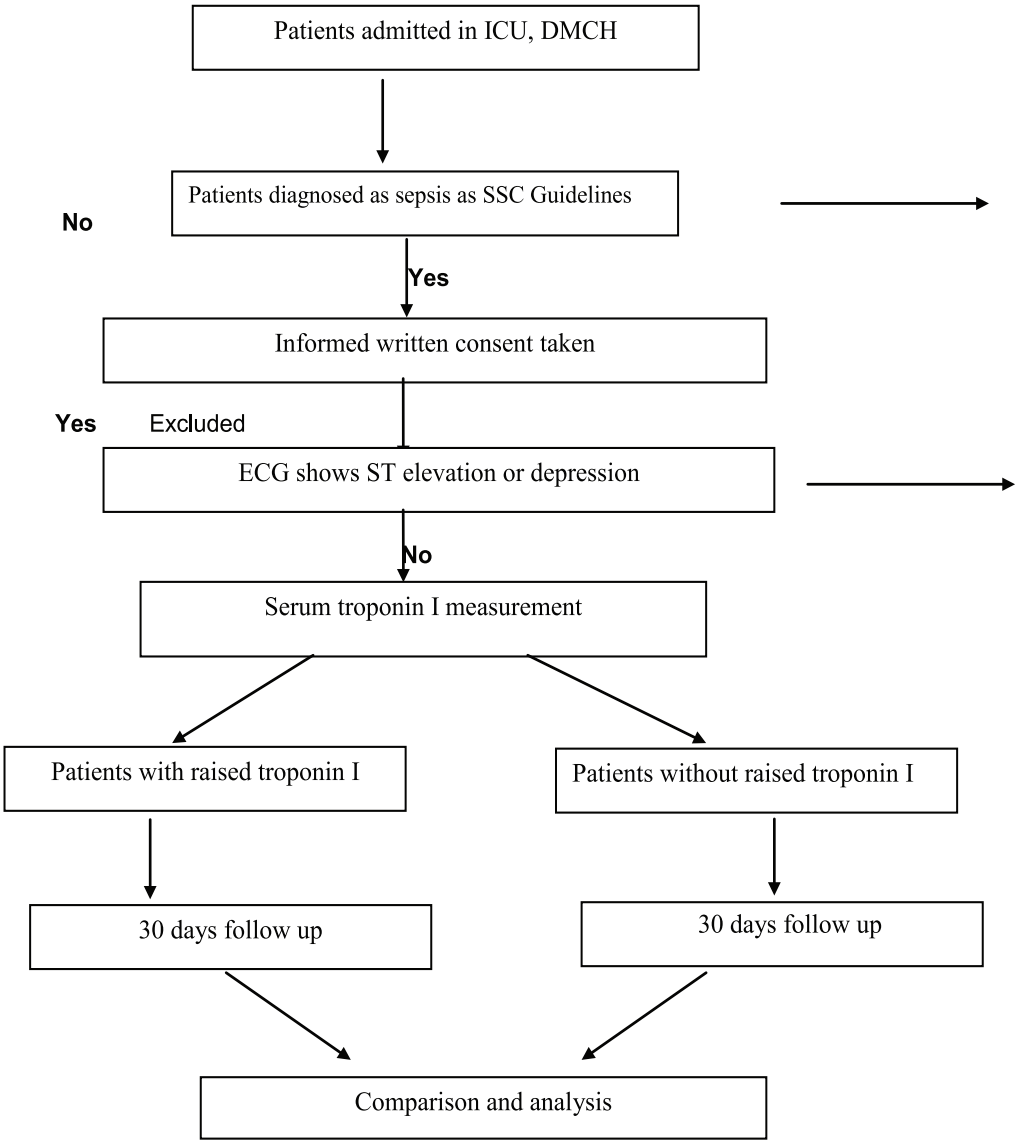

Fig 1 *Algorithm for methods of data collection*

Statistical analysis

To analyze the data Statistical Package for Social Science (SPSS) version 18.0 was used. After entry, range and consistency were checked. Descriptive statistics were computed for background characteristics of the study subjects. Statistical associations between categorical variables were tested using chi-square test and mean difference of continuous variables by independent t-test.

All *p* values presented were two tailed. The statistical tests were considered significant at a level of 5 %(0.05). Data were presented by table and graphs.

Results

Table I *Distribution of patients by sepsis, severe sepsis and septic shock (n=110)*

Variables		N	%
Sepsis	39	35.5	
Severe sepsis	Septic shock (n=28) Without shock (n=43)	71	64.5
Total	110	100	

Total 110 patients with sepsis were included in the study. Among them 71(64.5%) were diagnosed as severe sepsis. Among 71(100%) severe sepsis 28(39.43%) were found septic shock.

Table II *Distribution of patients by level of troponin I (n=110)*

Variables	f	%
Normal troponin group[a]	62	56.4
Elevated troponin group[a]	48	43.6
Total	110	100

a= cut of value of troponin I was 0.60 ng/mL
f=frequency

43.6% sepsis patients had elevated troponin I and 56.4% sepsis patients had normal tropon in I.

Table III *Distribution of patients by age between normal and elevated troponin group (n=110)*

Age group in	Normal troponin I	Elevated troponin I	Total	p value
years	f(%)	f(%)	f(%)	
d”21-40	27(24.5)	14(12.7)	41(37.3)	0.164[ns]
41-e”60	35(31.8)	34(30.9)	69(62.7)	
Total	62(56.4)	48(43.6)	110(100)	

ns=nonsignificant, p value extracted from $\eth^2$ test
f= frequency

There was no significant association between age group and troponin I group (p=0.164>0.05)

Table IV *Distribution of patients by sex between normal and elevated troponin group (n=110)*

Sex group	Normal troponin I	Elevated troponin I	Total	p value
	f(%)	f(%)	f(%)	
Female	22(20.0)	11(10.0)	33(30.0)	0.208[ns]
Male	40(36.4)	37(33.6)	77(70.0)	
Total	62(56.4)	48(43.6)	110(100)	

ns= not significant, p value extracted from $\eth^2$ test
f= frequency

Elevated troponin I was higher among male patients than female but it is not statistically significant (p=0.208>0.05)

Table V *Comparison of mean duration of ventilator support and length of stay (in days) in ICU in sepsis, severe sepsis and septic shock patients (n=110)*

Variables	Normal troponin I Mean(±SD)	Elevated troponin I Mean(±SD)	p value
	Sepsis		
Duration of ventilator support (n=94)	9.57(±4.41)	12.91(±6.25)	0.002[s]
Length of stay in ICU (n=110)	10.31(±4.34)	14.18(±5.89)	0.004[s]
	Severe sepsis		
Duration of ventilator support (n=71)	8.23±3.97	11±6.19	0.025[s]
Length of stay in ICU (n=71)	8.75±4.13	12.48±5.63	0.002[s]
	Septic shock		
Duration of ventilator support (n=28)	8.79(±2.94)	14.43(±7.86)	0.03[s]
Length of stay in ICU (n=28)	9.79(±3.66)	16.14(±6.46)	0.07[ns]

s=significant, p value extracted from independent two sample t test

ICU stay of sepsis, severe sepsis and septic patients was prolonged in elevated troponin group and it is statistically significant except septic shock (p=0.07>0.05). Mean duration of mechanical ventilation was also significantly higher in elevated troponin group.

Table VI *Correlation between Troponin I and ventilator support and length of stay (in days) in ICU in sepsis, severe sepsis and septic shock patients (n=110)*

Troponin I	Sepsis	R	P
	Duration of ventilator support	0.225	0.018
	Length of ICU stay	0.279	0.003
	Severe sepsis		
	Duration of ventilator support	-0.012	0.922
	Length of ICU stay	-0.100	0.405
	Septic shock		
	Duration of ventilator support	-0.504	0.012
	Length of ICU stay	-0.477	0.019

Pearson's correlation coefficient is performed for the analysis; p<0.01 are considered as statistically significant

Positive relationship was found between troponin level I and duration of ventilator support as well as length of ICU stay (r=0.225, 0.279) and it was statistically significant at 1% level of significance among sepsis patients. On the other hand negative relationship was found in case of severe sepsis and septic shock.

Table VII *Comparison of mortality in sepsis, severe sepsis and septic shock patients (n=110)*

Mortality	Normal troponin I f(%)	Elevated troponin I f(%)	Total f(%)	p value
	Sepsis			
Not survived	22(35.5)	35(72.9)	57(51.8)	0.001[s]
Survived	40(64.5)	13(27.1)	53(48.2)	
	Severe sepsis			
Not survived	11(35.48)	27(67.5)	38(53.52)	0.001[s]
Survived	20(64.45)	13(32.5)	33(46.47)	
	Septic shock			
Not survived	8(57.1)	13(92.9)	21(75.0)	0.029[s]
Survived	6(42.9)	1(7.1)	7(25.0)	

s=significant, p value extracted from $\eth^2$ test f= frequency

There was significantly increased mortality in elevated troponin group of patients compared to normal troponin group (72.9% vs 35.5%), (67.5% vs 35.48%) and (92.9% vs 57.1%) in sepsis, severe sepsis and septic shock patients respectively.

Discussion

Primary objective of the study was to find out the prognostic value of troponin I in sepsis patients. Total 110 patients with sepsis were included in the study. Among them 62 (56.4%) patients had normal troponin I and 48 (43.6%) patients had elevated troponin I. The cut off value of troponin was 0.60 ng/ml. In this study, among 110 patients with sepsis 64.5% patients was diagnosed as severe sepsis. Among them, 39.43% patients had septic shock.

There was no statistical significant association between age group and troponin I group (p=0.164>0.05). Occurrence of elevated troponin I was higher among male patients than female (30.9% vs 13.6%) in sepsis, although the result was not statistically significant (p=0.208>0.05). The study found no significant association of troponin I value with clinical diagnosis of sepsis patients.

The study found that the mean duration of ICU stay was prolonged in elevated troponin I group. In overall sepsis, mean duration of ICU stay was 10.31(±4.34) days in normal troponin I group and it was prolonged 14.18(±5.89) days in elevated troponin I group (p=0.004). The mean duration ICU stay was 12.48±5.63 days elevated troponin I group and 8.75±4.13 days in normal troponin I group in severe sepsis (p=0.002). In case of septic shock mean duration of ICU stay was 9.79(±3.66) and 16.14(±6.46) days in normal and elevated troponin I group respectively (p=0.07). Mean duration of ICU stay was one of the important variables that studied in previous literatures. Guest *et al*[10]in 1995 and Quenot *et al*[11]in 2005 showed that length of ICU stay increases as troponin level elevated.

Mean duration of ventilator support was also significantly prolonged in elevated troponin I group. In sepsis, mean duration of ventilator support of normal troponin group was 9.57(±4.41) days and in elevated troponin I group it was 12.91(±6.25) days (p=0.002). In severe sepsis, mean duration of ventilator support of normal troponin group was 8.23±3.97 days and in elevated troponin I group it was 8.75±4.13 days (p=0.025). In case of septic shock, mean duration of ventilator support were 8.79(±2.94) days and 14.43(±7.86) days respectively in normal and elevated troponin I group (p=0.03). Mean duration of ventilator support was also prolonged in different studies. Mannamet al[12] in 2004 demonstrated as cTn+ experienced longer duration of mechanical ventilation (12 vs. 2 days, p=0.002).

This study showed positive relationship between troponin level I and duration of ventilator support as well as length of ICU stay (r=0.225, 0.279) and it was statistically significant at 1% level of significance among sepsis patients. On the other hand negative relationship was found in case of severe sepsis and septic shock.

There was significantly increased mortality in elevated troponin group of patients compared to normal troponin group (72.9% vs 35.5%, p<0.001). In severe sepsis mortality of elevated troponin I group was 67.5% and mortality of normal troponin I group was 35.48% (p=0.001). There was also significantly increased mortality in elevated troponin group of patients compared to normal troponin group (92.9% vs 57.1%, p<0.029) in septic shock. In most literatures mortality of septic patients was higher in elevated troponin group in ICU. John *et al*[13]in 2010 studied a 28-day mortality and found significantly higher mortality in the TnI+patients as compared with the TnI"patients (32.2% vs 13.6%, p=-0.001). Ammann*et al*[14]in 2004 showed out of 58 critically ill patients, 32(55%) without evidence of ACS were troponin-positive. Positive troponin levels were associated with higher mortality (22.4% vs. 5.2%, p=-0.018). Spies *et al* [15]*in 1998*, in a prospective study of 26 patients in a surgical ICU with early sepsis showed that mortality is higher in troponin positive than troponin negative (83%vs37%, p=-0.02). Mehta *et al*[4] in 2004 showed in a prospective MICU that among 37 patients with septic shock mortality was higher in elevated troponin (56%) than normal troponin group (24%), p=-0.04. Scott *et al*[16] in 2004 showed that in a prospective study of 66 patients with severe sepsis and septic shock, mortality in elevated troponin group was 29% and troponin normal group was 21%, p=-0.69. Tiruvoipati*et al*[5] in 2012 in a retrospectrive study of 293 patients with severe sepsis showed that 36% patients died

in troponin positive group and 15% patients died in troponin negative group, p=-<0.01. Francis et al[17] in a meta-analysis of Thirteen studies encompassing 1,227 patients were showed that elevated troponin was significantly associated with all-cause mortality (RR 1.91; CI 1.63–2.24), with homogeneity across studies.

Conclusion

Significant number of sepsis patients had elevated troponin I and troponin I elevation had significant adverse outcome of these patients. In this study, the mortality of sepsis increased as troponin I value was raised. Length of ICU stay and length of ventilator support were prolonged in elevated troponin I group. Positive relationship was found between troponin I level and duration of ventilator support as well as length of ICU stay and it was statistically significant.

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