*Original Article*

# Troponin I, A Biomarker of Diagnosis of SIRS, Sepsis and Septic Shock

**Shahnaz Afroza[1], Muslema Begum[2], Iqbal Hossain Chowdhury[3], Md. Mozaffer Hossain[4]**

[1]Consultant – Intensives, Apollo Hospitals Dhaka, [2]Assistant Professor, Department of Anesthesia, Analgesia, Palliative & Intensive Care Medicine, DMCH, [3]Asso.Prof. Department of Anesthesia , Analgesia and Intensive Care Medicine, BSMMU, [4]Professor & Head, Department of Anesthesia, Analgesia, Palliative & Intensive Care Medicine, DMCH, Dhaka

**Corresponding Author:** Email: pushpopp74@yahoo.com

**Abstract:**

***Background:*** *Sepsis related troponin elevation (SRTE) has always been the demand and supply mismatch theory. In the setting of sepsis, the cardiac metabolic requirements are high and in order to meet these requirements an increase in the coronary blood flow is needed. Patients with underlying anemia and preexisting subclinical CAD may develop a mismatch ischemia in this setting. It was always thought that sepsis-related hypotension causes a decrease in coronary perfusion pressure thus leading to a decreased blood flow to cardiac myocytes and thereby leading to SRTE.*

***Objectives:*** *To establish Troponin-I as a useful diagnostic marker for sepsis.*

***Settings and Study Design:*** *This prospective study was carried out in the department of Anesthesia, pain, palliative and intensive care medicine, Dhaka Medical College, Dhaka during July 2013 to June 2015.*

***Methods:*** *This study was carried out in the department of Anesthesia, pain, palliative and intensive care medicine, Dhaka Medical College, Dhaka during July 2013 to June 2015. According to Troponin-I value patients were divided into Troponin-I positive and negative for sepsis. Three cut off values of Troponin-I (0.05, 0.035, 0.015) were used for this study. By using Receiver operating characteristic (ROC) curve the best sensitively, specificity, negative predictive value and positive predictive values of Troponin-I were determined.*

***Results:*** *The validity of troponin I (>0.05 ng/dl) evaluation for blood culture positive were sensitivity 45.0%, specificity 53.8%, accuracy 48.5%, positive predictive values 60.0% and negative predictive values 38.9%. The validity of troponin I (>0.035 ng/dl) evaluation for blood culture positive were sensitivity 57.5%, specificity 23.1%, accuracy 43.9%, positive predictive values 53.5% and negative predictive values 26.1%. The validity of troponin I (>0.015 ng/dl) evaluation for blood culture positive were sensitivity 72.5%, specificity 15.4%, accuracy 50.0%, positive predictive values 56.9% and negative predictive values 26.7%.*

***Conclusion:*** *The cutoff values of troponin-I (>0.035 ng/dl) observed more sensitivity of blood culture.*

***Keywords:*** *SIRS, sepsis, septic shock, ICU, Troponin-I*

*(JBSA 2018; 31(1): 3-11)*

## Introduction:

Sepsis historically has been a condition that is difficult to identify and diagnose. As far back as 100 BC, Marcus Terentius Varro, the ancient Roman scholar and writer (116 BC–27 BC), was quoted as noting that "small creatures, invisible to the eye, fill the atmosphere, and breathed through the nose cause dangerous diseases." Perhaps the most prescient description of sepsis was by the historian, philosopher, humanist and Renaissance author Niccolo Machiavelli (1469–1527), as reported in his treatise, *The Prince*, in 1513.

Among the earliest concepts was to consider sepsis as a systemic host response to an infection[1]. In fact, it was classically described by the eminent American physician William Osler (1849–1919) in his seminal observation that the patient appears to die from the body's response to an infection rather than from the infection itself. Closer to the modern era, in 1972 this concept was reinforced in a medical review, noting that "it is our response that makes the disease"[2].

It was the failure of these medical definitions[3], and myriad attempts at developing diagnostic tools and assays to identify sepsis[4], that led to a consensus conference focusing on a way to clinically define sepsis. In 1992, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) jointly published the consensus definitions of sepsis [5].

Troponin is a complex of three regulatory proteins (troponin I, TnI, troponin C, TnC, troponin T, TnT) and TnT binds to tropomyosin that lies in between the groves of actin TnI binds to actin whereas TnC binds to calcium [6]. Troponin is integral to contractile mechanism of cardiac and skeletal muscles. Binding of calcium on TnC leads to a conformational change in TnI and thereby in tropomyosin which exposes myosin binding sites on actin leading to actin and myosin interaction and muscle contraction. TnI and TnT of skeletal and cardiac muscles have different amino acid sequences; the same is not true for Tnc. TnI is much more specific for detection of any damage to cardiac myocytes as compared to TnT, and TnI levels do not increase in setting of renal failure [7].

Elevation of cardiac troponins and creatinine kinase (CK) is observed in 31%–80% of patients in setting of systemic inflammatory response syndrome (SIRS), sepsis, or septic shock (SIRS, sepsis, or septic shock related troponin elevations (SRTE). Skeletal muscle ischemia due to sepsis-related hypotension explains the elevated CK. Majority of SRTE patients without any prior history of coronary artery disease (CAD) on testing are found not to have any significant CADs[8,9]. Troponin elevation in setting of sepsis has been proposed as a biomarker for underlying myocardial dysfunction. Sepsis-related mortality has been reported to equal the mortality due to myocardial infarction and myocardial dysfunction has been shown to be a common complication in the setting of sepsis[10,11].

A hypothesis is that, in a setting of stress, cytosolic troponins may leak and lead to a rise in blood levels even in the absence of any damage to myofibril[8]. Bacterial myocarditis leading to release of troponins in absence of CAD has also been suggested as a possible pathogenic mechanism for SRTE. Release of cytokines (IL1â, IL-6, and TNFá), nitric oxide, endotoxins, and activation of caspases (caspases 3)[12] in setting of a gram negative bacteremia and sepsis leading to myocardial depression and ventricular dilatation is another theory to explain SRTE.

SRTE has been proposed as a biomarker of underlying myocardial dysfunction (a major contributor to the worse outcomes in the setting of SRTE) in setting of sepsis. Sepsis-mediated myocardial dysfunction results in reduced stroke volume either by systolic or diastolic dysfunction [13] or combination of both.

Many studies in sepsis have shown that continuous ECG monitoring and transthoracic echocardio-graphy examination at diagnosis do not disclose developing ischemia nor exclude myocardial infarction[14,15]. In troponin-positive septic shock patients, the presence of myocardial ischemia has been excluded based upon results of stress echocardiography[16,14]. It should be pointed out; however, that stress echocardiography cannot definitely exclude micro embolization from non-flow limiting unstable plaques as well as local wall motion abnormalities as a cause of elevated troponins. In this specific context, even very small episodes of myocardial necrosis (< 1 g) may be associated with significant troponin increases[7].

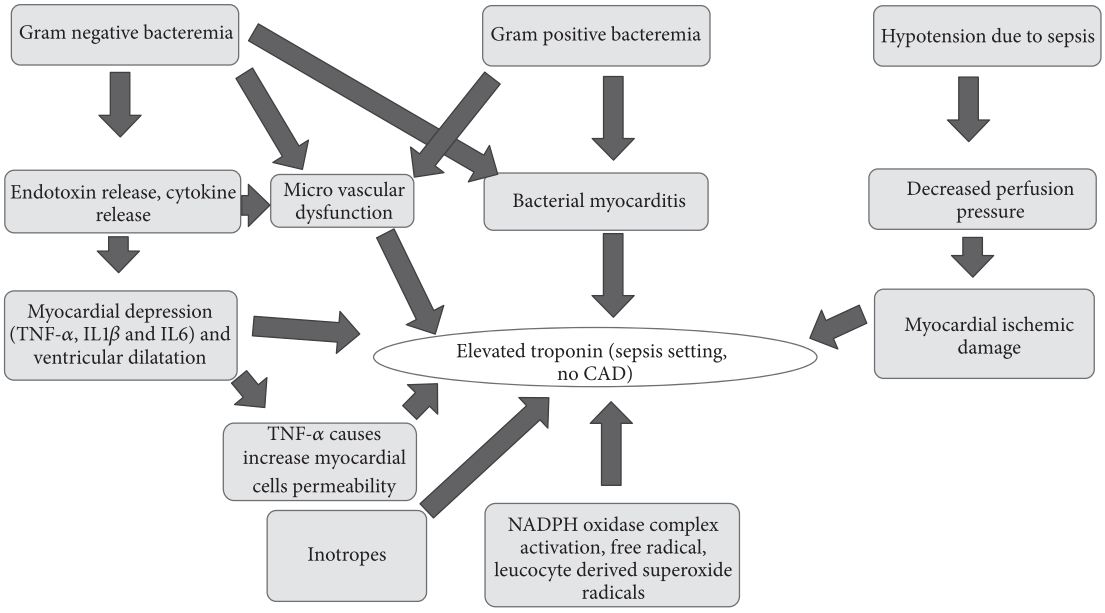


Figure 1: Pathogenic mechanisms of SRTE.

-SIRS, sepsis and consequent septic shock charge a heavy toll upon the patients admitted in ICU in respect to mortality and morbidity. It is an utmost necessity to diagnose these deadly conditions and if possible the potential consequence in each patient better be predicted. For this purpose different biomarkers have been intensely investigated to find out their efficacy in diagnosis of sepsis and septic shock as well as their accuracy in predictability of the disease course that is likely to be adopted in each patient. Troponin I, a biomarker widely used to determine the burden of irreversible myocardial damage, has been proposed as a biomarker in such conditions. Troponin I was found to be a definite bad prognostic factor in sepsis and septic shock. This study intends to evaluate whether troponin I without subtle injury to myocardial ischaemia is distributed differently accross the spectrum of sepsis and septic shock. The result of the study would enable the physicians to understand the role of elevated troponin I in all medical sectors.

**Materials:**

This prospective cohort study was carried out in 66 adult (>18 yrs old) patients admitted due to suspected as sepsis or septic shock in the Intensive Care Unit of Dhaka Medical Collage, Dhaka, during July' 2013 to June' 2015were included. Patients with suspected or diagnosed as sepsis and those who had no ECG finding of acute coronary syndrome were included in this study. Patients with known cardiac disease and patients with renal failure were excluded from the study. Informed written consent was taken from the patient or patient's guardian after duly informing the procedure of treatment, anticipated result, possible advantages, disadvantages and complications' considering all ethical issues and the protocol was approved by ethical committee of Dhaka Medical College & Hospital. Purposive sampling according to availability of the patients and strictly considering the inclusion and exclusion criteria's.

The American College of Chest Physicians/Society of Critical Care Medicine consensus classification was used for the diagnosis of SIRS, sepsis and septic shock [5]. Patients those who were diagnosed as suspected sepsis had undergone evaluation for the presence of ACS (Acute cornorary syndrome). ECG was used for the evaluation of ACS. Presence of ST elevation or depression was considered as ACS. After enrollment blood was collected to see the troponin I level and blood was sent to see the organism growth. Other sources of infection like respiratory tract, urinary tract, intra-abdominal infection etc. were also assessed according to the features. Blood samples for troponin I was collected in heparinised tube and refrigeration was avoided. It was sent for immediate assessment to a single institute equipped with analysis of troponin I

according to internationally recommended standard. Troponin I was assessed by Architect plus i1000-SR/ ADVIA Centaur XP Random Access Multi batch Immunoassay Analyzer in which 99th percentile is considered as 0.04 ng/dl, above which it was considered as abnormal. Blood sample for culture was send in specific blood collecting bottle and was done by automated Bactec machine in DMCH. On admission, the patient's age, sex, height and approximate weight was recorded by using a prescribed data sheet.

**Operational definition:**

**Systemic Inflammatory Response Syndrome (SIRS) [18]**

The systemic inflammatory response to a wide variety of severe clinical insults, manifested by two or more of the following conditions:

- Temperature > 38°C or < 36°C (>98.8°F or <96.5°F)
- Heart rate > 90 beats/min
- Respiratory rate > 20 breaths/min or $PaCO_2$ < 32 mm Hg
- WBC count >12,000/$mm^3$, <4000/$mm^3$, or > 10% immature (band) forms.

**Sepsis:**

Sepsis was defined as SIRS criteria plus suspected infection.

**Severe sepsis/SIRS:**

Severe sepsis was defined as sepsis criteria plus dysfunction of one or more vital organs.

**Refractory (septic) shock/SIRS shock:**

Septic shock was defined as severe sepsis plus hypotension even after fluid resuscitation.

**Multiple Organ Dysfunction Syndrome (MODS)**

It cane be defined as septic shock plus abnormal function in more than one vital organ plus hypotension.

**Elevated troponin I (Van Bockel et al. 2005)[19]:**

If the troponin I level is > 0.05 ng/dl then it was taken as raised troponin I.

For this study troponin I were > 0.015 and > 0.035 ng/dl were also considered as raised troponin I for better prediction of sepsis.

**The coronary syndromes[20]:**

Acute coronary syndromes (ACS) are characterized by the sudden onset of coronary insufficiency as a result of thrombotic occlusion of one and more coronary arteries. The following conditions are identified:

1. ST-segment elevation myocardial infarction (STEMI), caused by complete and sustained coronary occlusion.
2. Non-ST-segment myocardial infarction (non-STEMI) and unstable angina (UA), which are caused by partial coronary occlusion with spontaneous revascularization.

**The S-T segment[21]**

The S-T segment elevation ranges from 0.5 mm to 5 mm but is usually less than 2 mm in the precordial leads and not more than 0.5 mm in the limb leads.

**Statistical analysis:**

Statistical analyses were carried out by using the Statistical Package for Social Sciences version 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The mean values were calculated for continuous variables. The quantitative observations were indicated by frequencies and percentages. Receiver operating characteristic (ROC) curves was generated to determine the cutoff value for the best sensitivity, specificity negative and positive predictive values of Troponin I with regard to diagnosis of sepsis. A model with a cutoff value of Troponin-I above 0.05 ng/dl was considered as positive. A P-value was considered to be statistically non significant if >0.05 and statistically significant if ≤ 0.05.

**Results:**

The mean age was found 51.2±20.3 years with range from 18.0 to 80.0 years. Male female ratio was 1.5:1. Positive blood culture was found in 40(60.6%) patients, positive urine culture was in 40(60.6%) patients and tracheal aspirate culture positive was in 23(34.8%) patients. Troponin I >0.05 ng/dl was considered as significant for identification of blood culture positive, true positive 18 cases, false positive 12 cases, false negative 22 cases and true negative 14 cases in identification by blood culture positive. Troponin I >0.035 ng/dl was considered as significant for identification of blood culture positive, true positive 23 cases, false positive 20 cases, false negative 17 cases and true negative 6 cases in identification by blood culture positive. Troponin I >0.015 ng/dl was considered as significant for identification of blood culture positive, true positive 29 cases, false positive 22 cases, false negative 11 cases and true negative 4 cases in identification by blood culture positive.

**Table I** *Receiver-operator characteristic (ROC) curve of troponin I and blood culture for identification of blood culture positive.*

| Blood culture | Cut of value | Sensitivity | Specificity | Area under the ROC curve | 95% Confidence interval (CI) | |
|---|---|---|---|---|---|---|
| | | | | | Lower bound | Upper bound |
| positive | >0.05 | 41.0 | 48.1 | 0.397 | 0.259 | 0.536 |
| positive | >0.035 | 56.4 | 22.2 | 0.397 | 0.259 | 0.536 |
| positive | >0.015 | 71.8 | 14.8 | 0.397 | 0.259 | 0.536 |

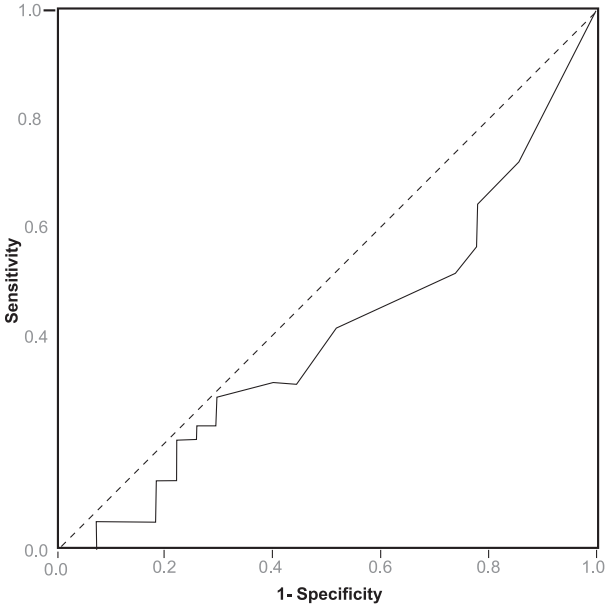


**Figure 2:** *Receiver-operator characteristic (ROC) curve of troponin I and blood culture for identification of blood culture positive.*

**Discussion:**

Altmann et al. [11] and Ammann et al. [22] observed mean age of their patients were 66±14 years and 55±21 years respectively, which is higher with the present study. It could be due to geographical variations, racial and ethnic differences, genetic causes, different lifestyle and increased life expectancy in their studied patients may have significant impacts on Systemic Inflammatory Response Syndrome. Although the incidence of sepsis is higher in men than in women, it is controversial whether there are sex-based differences in sepsis-associated mortality. Ammann et al. [8] also found male predominant where they observed male to female ratio was 3:1 suffered from septic shock, 2:1 from sepsis without shock and 3:0 from SIRS, which are closely resembled with the present study. In another study Altmann et al. [11] observed male to female ratio was 1:1.

Detection of bacteraemia or fungaemia by blood culture is critical in managing patients with infection, and directs the appropriate selection of antimicrobials. Blood culture is a common laboratory investigation where blood is inoculated into culture medium and incubated. SIRS is an important and predictive factor for UTI, especially in urinary sepsis. However, traditional urinary tests could not efficiently reflect the progression of SIRS that had originated from the urinary tract. In Hou et al. [23] study, bacterial culture positive rates in the SIRS group were only 20.5%. Mariappan et al. [24] found that 42.0% of patients had a positive urine culture. According to the study of Margel et al. [25] positive detection of urine culture is accepted as a relative risk for SIRS. In addition, their study and that of others emphasize the use of microbiological methods for diagnosing SIRS is poorly sensitive and nonspecific. Altmann et al. [11] and Turner et al. [7] found that majority of patients with Systemic inflammatory response syndrome (SIRS), sepsis, and septic shock-related deaths had positive cardiac troponins at time of death.

In a study by Kristien et al. [26] transesophageal echocardiogram demonstrated left ventricular dysfunction in 78% of TnI positive patients but only in 2% of TnI negative patients. Results from previously described studies suggest that, in setting of sepsis, TnI may act as a better and sensitive biomarker for detection of myocardial dysfunction and associated worse prognosis as compared to echocardiogram.

A study by Spies et al. [27] done on 26 patients with sepsis, the group of patients with troponin I values ≥0.2μ/l had an increased mortality rate (83% *v* 38%, p =0.02) compared to the group with troponin I values below this value.

Favory & Neviere [6] reported in their study that it should be pointed out, however, that the relative expected and documented ranges of troponin that can be seen in sepsis are rather difficult to depict because there is huge variability in the sensitivity of assays. Arlati et al. [28] showed cutoff value of troponin I > 0.5 varied from 0.5-11.2 μg/l, Kristien et al. [26] obtained cutoff value of troponin I > 0.4 varied from 0.8-6.8 μg/l, Ammann et al. [8] observed cutoff value of troponin I >0.1 varied from 0.2-15.4 μg/l and Mehta et al. [29] showed cutoff value of troponin I >0.1 varied from0.1-10.8 μg/l.

Among the other biomarkers, procalcitonin (PCT) has been widely investigated for its prognostic value in septic patients. Liu et al. [30] done a meta-analysis is to explore the diagnostic accuracy of a single PCT concentration and PCT non-clearance in predicting sepsis. An elevated PCT level was associated with a higher risk of death. The pooled relative risk (RR) was 2.60 (95% confidence interval (CI), 2.05–3.30) using a random-effects model. The overall area under the receiver operator characteristic (ROC) curve was 0.77 (95% CI, 0.73–0.80), with a sensitivity and specificity of 0.76 (95% CI, 0.67–0.82) and 0.64 (95% CI, 0.52–0.74), respectively. There was significant evidence of heterogeneity for the PCT testing time (*P<0.05*). Initial PCT values were of limited prognostic value in patients with sepsis. PCT non-clearance was a prognostic factor of death in patients with sepsis. The pooled *relative risk* (RR) was 3.05 (95% CI, 2.35–3.95) using a fixed-effects model. The overall area under the ROC curve was 0.79 (95% CI, 0.75–0.83), with a sensitivity and specificity of 0.72 (95% CI, 0.58–0.82) and 0.77 (95% CI, 0.55–0.90), respectively. Elevated PCT concentrations and PCT non-clearance are strongly associated in septic patients.

Again the prognostic value of isolated lactate measurements and serial measurements has been investigated in various settings by Howell et al. [31], Jansen et al. [32]. Shapiro et al. [33] found that lactate levels could correctly stratify patients according to mortality. Lactate levels of 0–2.4, 2.5–3.9 and ≥4 mmol/L were associated with mortalities of 4.9% (95% CI: 3.5% – 6.3%), 9.0% (95% CI: 5.6% – 12.4%) and 28.4% (95% CI: 21% –36%) respectively. Serial lactate measurements may be useful in documenting treatment response to various therapeutic interventions [34,35].

Lee et al. [36] mentioned in their study that elevated cardiac troponin (cTn) has been associated with worse outcomes in critically ill patients, but few studies have focused on whether these markers are related to outcomes in patients with severe pneumonia. Lee et al. [36] investigated the levels of cTnI in critically ill patients hospitalized for severe pneumonia and whether elevated levels of cTnI correlated with the clinical outcome of this patient group. A cTnI level greater than 0.034 ng/mL was considered positive. $P$ <0.05 was considered significant. A total of 152 patients (community-acquired pneumonia 39.5%, health care–associated pneumonia 40.8%, and hospital-acquired pneumonia 19.7%) were included in the study. Eighty-eight 58.0% patients had detectable cTnI levels (median, 0.049 ng/mL).

The role of biomarkers such as troponin in risk stratification of sepsis is still debated. Bessière et al. [37] undertaken a meta-analysis is to assess the relation between troponin elevation in sepsis and mortality. All observational studies from Embase, Medline and those manually searched up to September 2010 were included. Studies identified were those which reported on patients with a diagnosis of sepsis and if a 2 × 2 table could be constructed based on troponins and death. Thirteen studies encompassing 1,227 patients were included. The prevalence of elevated troponin was 61 % ([95 %] CI 58-64 %). Elevated troponin was significantly associated with all-cause mortality (RR 1.91; CI 1.63-2.24), with homogeneity across studies.

It should be pointed out that many advances have been made in the identification of biomarkers for sepsis. Among them procalcitonin indicate bacterial sepsis [38,39] and serum lactate indicates sepsis induced hypoperfusion [40,41,42].

In this present study it was observed the area under the receiver-operator characteristic (ROC) curves troponin I >0.035 ng/dl had the best area under curve followed by troponin I >0.015 ng/dl and troponin I >0.05 ng/dl, which are significantly

associated with blood culture positive. In our study it is found that different level of cutoff value of troponin I in sepsis are rather difficult to depict because there is vast variability in the sensitivity and specificity. The reduced level of sensitivity and specificity for different level of cut off value may be due to small number of sample size, patient may received multiple antibiotics before admitted to ICU and patient may had viral infection that we could not identified, which may influence condensed level of sensitivity and specificity at different level of cut off value of troponin I.

**Conclusions:**

Most of the patients were in 6$^{th}$ decade & above and male predominant. Troponin I level was higher in patients with sepsis. Limited level of sensitivity and specificity observed for troponin I at different cutoff value.

**Study Limitations:** Study population was selected from one selected hospital in Dhaka city with a very short period of time. Relatively small group of patients with SIRS, sepsis, and septic shock was also a limitation of the present study. Only ECG was done as the Echo cardiogram facility was not there in our ICU.

Recommendation:

The current study results observed cut-off value >0.05 ng/dl of troponin I showed poor sensitivity and specificity for prediction of sepsis, however sensitivity and specificity increased with decreased level of different cut-off >0.035 ng/dl and >0.015 ng/dl of Troponin I for better prediction of sepsis. Therefore this study recommended that further studies can be undertaken cut-off value >0.035 ng/dl of troponin I.

**References:**


1. Riedemann NC, Guo RF, Ward PA. The enigma of sepsis. The Journal of clinical investigation. 2003 Aug 15;112(4):460-7.
2. Thomas, L. Germs. *The New England journal of medicine,* 1972; 287:553–5.
3. Abraham E, Matthay MA, Dinarello CA, Vincent JL, Cohen J, Opal SM, Glauser M, Parsons P, Fisher Jr CJ, Repine JE. Consensus conference definitions for sepsis, septic shock, acute lung injury, and acute respiratory distress syndrome: time for a reevaluation. Critical care medicine. 2000 Jan 1;28(1):232-5.
4. Vincent JL. Procalcitonin: THE marker of sepsis?. Critical care medicine. 2000 Apr 1;28(4):1226-8.
5. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest. 1992 Jun 30;101(6):1644-55.
6. Favory R, Neviere R. Bench-to-bedside review: significance and interpretation of elevated troponin in septic patients. Critical care. 2006 Aug 4;10(4):224.
7. Turner A, Tsamitros M, Bellomo R. Myocardial cell injury in septic shock. Critical care medicine. 1999 Sep 1;27(9):1775-80.
8. Ammann P, Fehr T, Minder E, Günter C, Bertel O. Elevation of troponin I in sepsis and septic shock. Intensive care medicine. 2001 Jun 1;27(6):965-9.
9. Altmann DR, Korte W, Maeder MT, Fehr T, Haager P, Rickli H, Kleger GR, Rodriguez R, Ammann P. Elevated cardiac troponin I in sepsis and septic shock: no evidence for thrombus associated myocardial necrosis. PLoS One. 2010 Feb 3;5(2):e9017.
10. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Critical care medicine. 2001 Jul 1;29(7):1303-10.
11. Maeder M, Fehr T, Rickli H, Ammann P. Sepsis-associated myocardial dysfunction: diagnostic and prognostic impact of cardiac troponins and natriuretic peptides. CHEST Journal. 2006 May 1;129(5):1349-66.
12. Communal C, Sumandea M, De Tombe P, Narula J, Solaro RJ, Hajjar RJ. Functional consequences of caspase activation in cardiac myocytes. Proceedings of the National Academy of Sciences. 2002 Apr 30;99(9):6252-6.
13. Parker MM, Suffredini AF, Natanson C, Ognibene FP, Shelhamer JH, Parrillo JE.

Responses of left ventricular function in survivors and nonsurvivors of septic shock. Journal of Critical Care. 1989 Mar 1;4(1):19-25.

14. Smith A, John M, Trout R, Davis E, Moningi S. Elevated cardiac troponins in sepsis: what do they signify?. West Virginia Medical Journal. 2009 Jul 1;105(4):29-33.
15. Abraham E, Anzueto A, Gutierrez G, Tessler S, San Pedro G, Wunderink R, Dal Nogare A, Nasraway S, Berman S, Cooney R, Levy H. Double-blind randomised controlled trial of monoclonal antibody to human tumour necrosis factor in treatment of septic shock. The Lancet. 1998 Mar 28;351(9107):929-33.
16. Levy RJ, Piel DA, Acton PD, Zhou R, Ferrari VA, Karp JS, Deutschman CS. Evidence of myocardial hibernation in the septic heart. Critical care medicine. 2005 Dec 1;33(12):2752-6.
17. Hussain N. Elevated cardiac troponins in setting of systemic inflammatory response syndrome, sepsis, and septic shock. ISRN cardiology. 2013 Apr 11;2013.
18. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest. 1992 Jun 30;101(6):1644-45.
19. Van Bockel EA, Tulleken JE, Ligtenberg JJ, Zijlstra JG. Troponin in septic and critically ill patients. CHEST Journal. 2005 Feb 1;127(2):687-8.
20. Marino PL. Marino's the ICU Book. Lippincott Williams & Wilkins; 2013 Nov 14.
21. Schamroth L. An Introduction to Electrocardiography, 7th edition, Wiley-Blackwell, USA. 2002:127.
22. Ammann P, Maggiorini M, Bertel O, Haenseler E, Joller-Jemelka HI, Oechslin E, Minder EI, Rickli H, Fehr T. Troponin as a risk factor for mortality in critically ill patients without acute coronary syndromes. Journal of the American College of Cardiology. 2003 Jun 4;41(11):2004-9.
23. Hou YS, Wang H, Chen H, Wu LF, Lu LF, He Y. Pathfast presepsin assay for early diagnosis of systemic inflammatory response syndrome in patients with nephrolithiasis. BioMed research international. 2015 Feb 4;2015.
24. Mariappan P, Smith G, Moussa SA, Tolley DA. One week of ciprofloxacin before percutaneous nephrolithotomy significantly reduces upper tract infection and urosepsis: a prospective controlled study. BJU international. 2006 Nov 1;98(5):1075-9.
25. Margel D, Ehrlich Y, Brown N, Lask D, Livne PM, Lifshitz DA. Clinical implication of routine stone culture in percutaneous nephrolithotomy—a prospective study. Urology. 2006 Jan 31;67(1):26-9.
26. Kristien M, Spapen HD, Nguyen DN, Garbar C, Huyghens LP, Gorus FK. Cardiac troponins I and T are biological markers of left ventricular dysfunction in septic shock. Clinical Chemistry. 2000 May 1;46(5):650-7.
27. Spies C, Haude V, Fitzner R, Schröder K, Overbeck M, Runkel N, Schaffartzik W. Serum cardiac troponin T as a prognostic marker in early sepsis. Chest. 1998 Apr 30;113(4):1055-63.
28. Arlati S, Brenna S, Prencipe L, Marocchi A, Casella GP, Lanzani M, Gandini C. Myocardial necrosis in ICU patients with acute non-cardiac disease: a prospective study. Intensive care medicine. 2000 Jan 1;26(1):31-7.
29. Mehta NJ, Khan IA, Gupta V, Jani K, Gowda RM, Smith PR. Cardiac troponin I predicts myocardial dysfunction and adverse outcome in septic shock. International journal of cardiology. 2004 May 31;95(1):13-7.
30. Liu D, Su L, Han G, Yan P, Xie L. Prognostic value of procalcitonin in adult patients with sepsis: a systematic review and meta-analysis. PloS one. 2015 Jun 15;10(6):e0129450.
31. Howell MD, Donnino M, Clardy P, Talmor D, Shapiro NI. Occult hypoperfusion and mortality in patients with suspected infection. Intensive care medicine. 2007 Nov 1;33(11):1892-9.
32. Jansen TC, van Bommel J, Mulder PG, Rommes JH, Schieveld SJ, Bakker J. The prognostic value of blood lactate levels relative

to that of vital signs in the pre-hospital setting: a pilot study. Critical care. 2008 Dec 17;12(6):R160.

33. Shapiro NI, Howell MD, Talmor D, Nathanson LA, Lisbon A, Wolfe RE, Weiss JW. Serum lactate as a predictor of mortality in emergency department patients with infection. Annals of emergency medicine. 2005 May 31;45(5):524-8.
34. Nguyen HB, Rivers EP, Knoblich BP, Jacobsen G, Muzzin A, Ressler JA, Tomlanovich MC. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. Critical care medicine. 2004 Aug 1;32(8):1637-42.
35. Arnold RC, Shapiro NI, Jones AE, Schorr C, Pope J, Casner E, Parrillo JE, Dellinger RP, Trzeciak S, Emergency Medicine Shock Research Network (EMShockNet) Investigators. Multicenter study of early lactate clearance as a determinant of survival in patients with presumed sepsis. Shock. 2009 Jul 1;32(1):35-9.
36. Lee YJ, Lee H, soo Park J, Kim SJ, Cho YJ, Yoon HI, Lee JH, Lee CT, Park JS. Cardiac troponin I as a prognostic factor in critically ill pneumonia patients in the absence of acute coronary syndrome. Journal of critical care. 2015 Apr 30;30(2):390-4.
37. Bessiere F, Khenifer S, Dubourg J, Durieu I, Lega JC. Prognostic value of troponins in sepsis: a meta-analysis. Intensive care medicine. 2013 Jul 1;39(7):1181-9.
38. Riedel S, Melendez JH, An AT, Rosenbaum JE, Zenilman JM. Procalcitonin as a marker for the detection of bacteremia and sepsis in the emergency department. American journal of clinical pathology. 2011 Feb 1;135(2):182-9.
39. Jin M, Khan AI. Procalcitonin: uses in the clinical laboratory for the diagnosis of sepsis. Laboratory Medicine. 2010 Mar 1;41(3):173-7.
40. Samraj RS, Zingarelli B, Wong HR. Role of biomarkers in sepsis care. Shock (Augusta, Ga.). 2013 Nov;40(5):358.
41. Cho SY, Choi JH. Biomarkers of sepsis. Infection & chemotherapy. 2014 Mar 1;46(1):1-2.
42. Angus DC, Van der Poll T. Severe sepsis and septic shock. New England Journal of Medicine. 2013 Aug 29;369(9):840-51.