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The prognostic significance of troponin elevation in patients with sepsis: A meta-analysis

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ABSTRACT

Objective: To confirm the association between troponin elevation in patients with sepsis and mortality.
Background: Cardiac troponins are sensitive and specific biomarkers of myocardial injury; however their prognostic significance in patients with sepsis is still debated.
Methods: PubMed and Ovid MEDLINE were searched for original articles using MeSH terms 'Troponin' and 'Sepsis.' Studies reporting on mortality in patients with sepsis, severe sepsis or septic shock who had troponin measured were eligible for inclusion. Meta-analysis was conducted with Review Manager.
Results: Seventeen studies, with total sample size of 1857 patients were included. Elevated troponin was found to be significantly associated with mortality (Risk ratio: 1.91; 95% CI: 1.65–2.22; $p < 0.05$).
Conclusions: Troponin elevation in patients with sepsis confers poorer prognosis and is a predictor of mortality. Further studies are needed to see if more aggressive treatment of this subset of patients, or utilizing new therapeutic approaches will improve mortality.

Background

Sepsis is the most common cause of morbidity and mortality in intensive care units in the United States, with hospital mortality rate of 18–30%, depending on the series.[1] The mortality rate is even higher in patients with severe sepsis and septic shock, in whom rates of 28.3–41.1% have been reported.[2] With increasing availability of evidence-based therapies, the mortality rate of severe sepsis decreased from 39% to 27%.[3] However, an increase in the number of sepsis cases has resulted in increasing number of sepsis-related deaths, estimated at 215,000 annually in the United States.[1,3]

Cardiovascular abnormalities are frequent in sepsis and septic shock and may result in non-coronary artery disease-related myocardial injury.[4] Troponin is a protein found in skeletal and heart muscle fibers which regulates muscular contraction. It is made up of three sub-units: troponin C (which binds to calcium to produce a conformational change in troponin I), troponin T (which binds to tropomyosin), and troponin I (which binds to actin). Cardiac-specific troponins I and T are found only in the heart and are normally present in very small to undetectable quantities in the blood. However, when there is damage to heart muscle cells, cardiac-specific troponins I and T are released into circulation and can be measured by immunoassay methods. Hence cardiac troponins have emerged as sensitive and specific markers of myocardial injury facilitating early risk stratification.[5]

Troponin (cardiac troponin) elevation among patients with sepsis is common, but its role in risk stratification of patients with sepsis is still debated. Many studies have reported increased mortality in septic patients with troponin elevation,[6–11] while others did not.[12–14] This may be as a result of differences in the type of infection, troponin assays, cut-off thresholds for troponin elevation, or differences in the time when troponins were measured. Furthermore, the studies which failed to find a significant association between troponin elevation and mortality may have been inadequately powered to reach statistical significance. A meta-analysis on the prognostic value of troponin in sepsis was published by Bessière and colleagues which showed that elevated troponin in patients with sepsis is associated with increased mortality.[15] However, the meta-analysis included mostly studies with small sample sizes and did not conduct sub-group analysis based on the presence of septic shock. In addition, two recently published relatively large studies (total of 500 subjects) were not included in the original meta-analysis (Rosjo et al, 2011 and Tiruvoipati et al,

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2012).[13,16] Hence, we set out to perform an updated meta-analysis to determine if a decisive conclusion can be made on the association between troponin elevation in patients with sepsis and mortality.

Methods

Study research

We conducted a systematic review and meta-analysis, using methods that are in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group's recommendations.[17]

A systematic literature search of Ovid MEDLINE and Pubmed was conducted to identify all studies involving humans published up to February 2014, comparing outcome in patients with sepsis with and without troponin elevation. Search criteria combined Medical Subject Headings (MeSH) terms 'Troponin' and 'Sepsis.' The search was not restricted to any language. We subsequently searched and evaluated all reference lists of eligible articles obtained from the electronic search to ensure identification of all published studies on the subject.

Study selection, data extraction, and outcome measures

Two investigators independently read the results from electronic search to identify and scrutinize those articles relevant to this systematic review based on title or title and abstract. Relevant articles from the list of references of the reviewed papers obtained from the electronic search were also retrieved to determine eligibility for inclusion in this meta-analysis. Full articles were then retrieved for further assessment, and disagreements were resolved by consensus and by discussion with a third investigator. A form was designed to describe the characteristics of studies to be included or excluded as set out in the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions 5.0.2.[18] The outcome measure for this analysis was all cause mortality.

We designed a form to extract data on the following: total number of patients in each study and the number with and without positive troponin; the number of patients who died in each group (positive troponin and negative troponin groups); the type of troponin measured; the follow-up period; mean age; gender ratio; proportion of patients in septic shock; exclusion of patients with confounding co-morbidities; conduction of multivariate analysis; and the setting and country of the study.

Selection criteria

We applied the following screening criteria to determine qualitative eligibility: original article; observational study or clinical trial conducted on patients at least 18 years of age; blood sampling for troponin was performed; follow-up for at least 7 days or to hospital mortality; and a sample size greater than or equal to 10 patients.

Studies were included if they reported on patients with a diagnosis of sepsis, severe sepsis or septic shock as defined by the American College of Chest Physicians/Society of Critical Care Medicine consensus conference[19,20]; and information can be obtained on mortality among patients with and without positive troponin. In studies in which data was missing, the authors were contacted to provide the missing information. Studies in which the authors failed to respond were not included in the meta-analysis.

Quality assessment

The selected studies were evaluated for their methodological quality utilizing elements from the MOOSE checklist[17] by systematically noting whether there was: (1) blinding of the physicians involved in direct care of the septic patients to the troponin result at study entry; (2) multivariate analysis on possible predictors of study results; and (3) inclusion of patients with comorbidities (e.g. renal failure, ischemic heart disease, pulmonary embolism, myocarditis or chronic heart failure) that may influence troponin levels and accuracy. The included studies were then divided into three categories based on quality: (1) high quality if at least two of the three criteria were clearly described and accounted for; (2) low quality if only one criteria was described and accounted for; and (3) uncertain risk of material bias if none of the criteria was described (Table 1).

Statistical analysis

The pooled prevalence and its 95% confidence interval (95% CI) were computed by weighted averages in which the weight of each study is its sample size. Mantel Haenszel calculations were used to calculate the pooled risk ratios (RR) according to the random effects model. We assessed heterogeneity between trial results using Cochran's Q statistic and I^2 statistic. Heterogeneity was considered present at $p < 0.10$ and $I^2 > 50\%$.[21] Sensitivity analyses were performed by repeating analysis: (1) excluding any large studies to see how they influence the results; (2) taking account of study quality and sample size; (3) according to the type of troponin measured (troponin I or troponin T); and (4) comparing patients with sepsis and septic shock. Finally, a funnel plot was calculated to assess for publication bias, looking for asymmetry on visual inspection. Analyses were conducted using Review Manager (RevMan; Cochrane Collaboration), version 5.2.11 software.

Results

Baseline characteristics

A total of 221 citations were obtained from our electronic search. After reading titles and abstracts, eighteen potentially relevant studies were identified for further review. Five studies were removed because of failure to obtain missing information from the authors.[22–26] Using backtracking, four additional studies were added (Fig. 1). Seventeen studies, published between 1998 and 2012, with sample size range of 10–598 patients, mean age range 30–70 years, male gender range 44–75 % were included, encompassing a total of 1857 patients (Table 1).

Fifteen studies were prospective,[6–11,14,16,27,29–31,33,34] while two were retrospective in nature.[13,28] The largest of the studies is a retrospective study of 598 patients with severe sepsis in whom troponin I was measured.[28] Multivariate statistical analysis adjusting for known cardiovascular risk factors were performed in seven studies,[6,13,14,16,27,28,31] encompassing 1497 patients. Fifteen studies were set in the Intensive Care Unit (ICU),[6–11,13,14,16,28–32] while two were set in a general medicine unit.[27,33] The proportion of the patients who were admitted in septic shock ranged from 24.8 to 100%, and the most frequent source of sepsis was pulmonary infection. Seven studies were conducted in Europe,[7,9–11,16,32] three in North America,[6,30,31] two in South America,[29,34] two in Asia[27,33] and two in Australia.[8,13] One study (PROWESS trial) utilized data from a registry of patients from 11 countries[28] (Table 1).