Heart & Lung 44 (2015) 327–334

Contents lists available at ScienceDirect

Heart & Lung

journal homepage: www.heartandlung.org

Prognostic value of troponins in acute nonmassive pulmonary embolism: A meta-analysis

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ARTICLE INFO

Article history:
Received 4 February 2015
Received in revised form
24 March 2015
Accepted 25 March 2015
Available online 11 May 2015

Keywords:
Pulmonary embolism
Troponin
Mortality
Prognosis
Right ventricular dysfunction

ABSTRACT

The objective of our meta-analysis is to update the evidence on the prognostic value of elevated troponin levels in patient with acute normotensive pulmonary embolism (PE). We did a systematic literature review of database, including Pubmed, EMBASE, and Cochrane. Studies were included if those were done on normotensive patients with acute PE and serum troponin assay was done. The primary end point was short term all cause mortality. The secondary end points were short term PE related mortality and serious adverse events. Elevated troponin levels were significantly associated with the increased risk for short term mortality (odds ratio [OR], 4.80; 95% CI, 3.25–7.08, $I^2 = 54\%$), PE related mortality (OR, 3.80; 95% CI, 2.74–5.27, $I^2 = 0\%$) and serious adverse events (OR, 3.65; 95% CI, 2.41–5.53, $I^2 = 47\%$). Our study suggests that elevated levels of troponin identify a subgroup of patients with increased risk for short term mortality and serious adverse events.

Introduction

Acute pulmonary embolism (PE) is the third leading cause of cardiovascular death.[1] Acute PE has a wide spectrum of clinical manifestations and prognosis. The clinical presentation of acute PE varies from sudden death to cardiogenic shock to asymptomatic. Mortality attributable to PE ranges from 9% in patients who are hemodynamically unstable at the time of presentation to about 3% in patients who are stable in current era.[2] So far, guidelines exist for treating hemodynamically unstable patients with thrombolytics because of high risk for short term mortality; however, we are still lacking in a prognostic strategy which can identify a subgroup of patients who are hemodynamically stable but at risk for poor outcomes.[3] Risk stratification at the time of admission is important for the appropriate management of patients with acute PE. On one side of the spectrum are the patients who are normotensive at the time of admission and very low risk for death, who could be managed as an outpatient with newer anticoagulants. On the other side of the spectrum are the patients who are at risk for poor outcomes and need close monitoring and may benefit from more aggressive treatment like thrombolytics. Optimal management of these patients can lead to decrease health care cost and increased patient satisfaction.[4] Patients who are hemodynamically stable at the time of admission, but manifest right ventricular dysfunction (RVD) have a poor prognosis when compared to patients without RVD.[5,6] Various clinical, imaging and serum biomarkers have been evaluated to identify a subgroup of patients who have RVD and are at high risk for poor outcomes. Echocardiogram is a useful tool in risk stratification in acute PE by diagnosing RVD; however, it is not available round the clock in all institutions. Also, the prognostic value of echocardiogram for RVD in predicting short term mortality is too low to be useful in clinical practice.[7] Several serum biomarkers such as troponin, Brain Natriuretic peptide (BNP) or N

Abbreviations: PE, pulmonary embolism; hs-cTnT, high-sensitive cardiac troponin T; PLR, positive likelihood ratio; NLR, negative likelihood ratio; MOOSE, Meta-Analysis of Observational Studies in Epidemiology.

Name of Institute where Study was performed: The Wright Center for Graduate Medical Education, 501 Madison Avenue, Scranton, PA 18505, USA.

Financial support: There was no financial support provided by any institution for this study.

Conflict of interest: No conflict of interest.

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0147-9563/$ – see front matter © 2015 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.hrtlng.2015.03.007

terminal pro-BNP (NT-pro BNP), Heart-type fatty acid binding protein (H-FABP) has also been evaluated to identify patients with poor outcomes but the best prognostic tool is still unknown to date.[8–11] Previous meta-analysis on the use of troponin in patients with acute PE included few studies with small patient population size and the results were unsatisfactory for clinical usefulness in risk stratification.[8] We aimed to update the meta-analysis by adding seventeen more studies with larger patient population to further clarify whether elevated cardiac troponin levels are useful in clinical decision making.

Methods

Study objectives

The primary objective of this meta-analysis was to update the evidence whether elevated troponin levels (T or I) are useful in predicting short term (in-hospital or 30 day) all cause mortality in normotensive patients with acute PE. The secondary objectives were to assess whether elevated troponin levels are useful in predicting short term mortality (in-hospital or 30 day) resulting from PE and serious adverse events.

Data source and searches

A systematic search of Medline, EMBASE and Cochrane Database were performed. Following key words were used, "Troponin", "biomarkers" and "Pulmonary embolism". Additionally, references from previous trials, reviews, abstracts from annual meetings and web base were also searched to identify any relevant studies. The retrieved studies were carefully examined to exclude potentially duplicate or overlapping data. No language restriction was enforced. The manuscripts of all retrieved studies cited before December 2014 were reviewed. Abstracts were excluded from the analysis because non peer reviewed data may introduce bias in to the study.

Study eligibility

Studies were considered eligible for the analysis if they fulfilled the following criteria: 1) Design: Prospective or retrospective study; 2) Population: Patients admitted to the hospital with objectively confirmed acute PE and were normotensive (blood pressure $>$ 90 mm Hg) at the time of admission; 3)Cardiac specific troponin (T or I) assay was done at the time of admission or within 24 h of hospitalization; 3) Outcomes reported: short term(in hospital or 30 day) all cause mortality, PE related mortality, short term serious adverse events; 4) 2$\times$2 table can be constructed from the data to compute true positive, false positive, true negative, false negative.

Data extraction and validity assessment

Two independent reviewers (AB and PR) independently performed the literature search and identify relevant studies. A third investigator was available for arbitration in the event of discordance of the extracted data. The retrieved studies were carefully examined to exclude potentially duplicate or overlapping data. Meeting abstracts were excluded from our analysis (Fig. 1). Authors were contacted to get relevant data. Relevant data on study design, year of publication, patient population, inclusion criteria, exclusion criteria, mean age, gender, follow up period, type of troponin assay, timing of sampling, cut-off of troponin used and outcomes were extracted (Tables 1 and 2). When we identified studies that had been reported in multiple papers, the analysis was limited to the full text studies and a large patient population.

Study end points

The primary outcome of interest was in-hospital or 30 day all cause mortality. Secondary outcomes were in-hospital or 30 day mortality resulting from PE and serious adverse events.

Definitions

Serious adverse events were defined as composite of death, need for thrombolytics, endotracheal intubation, catecholamine infusion for sustained hypotension, cardiopulmonary resuscitation, or recurrent PE.

Normotensive pulmonary embolism: Patients with acute PE without systemic hypotension (blood pressure more than 90 mm Hg).[3]

Data synthesis and statistical analysis

We constructed 2$\times$2 tables for 30 day mortality and serious adverse events. We computed sensitivity, specificity, positive likelihood ratio and negative likelihood ratio by means of true positive, false positive, true negative and false negative. Likelihood ratios do not depend on prevalence rates, and there is general consensus that a positive likelihood ratio of greater than 10 and a negative likelihood ratio of less than 0.1 provide reliable evidence of satisfactory diagnostic performance.[38] A study level analysis was done using Review manager 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2008) and Meta-disc 1.4. Odds ratio (OR) and 95% confidence intervals (95% CI) were used as summary statistics for all outcomes. Studies were evaluated for heterogeneity by visual inspection of the confidence intervals and by means of I^2 [$I^2 = (Q - df)/Q$], where Q is the χ^2 statistic and df is degree of freedom. As a guide, an $I^2 > 30\%$ was considered as an indicator of statistical heterogeneity among the studies. A Mantel–Haenszel fixed effect model was used to calculate the pooled OR for homogenous end points. Random effect (DerSimonian) analysis was reported in the presence of significant heterogeneity. Even if there

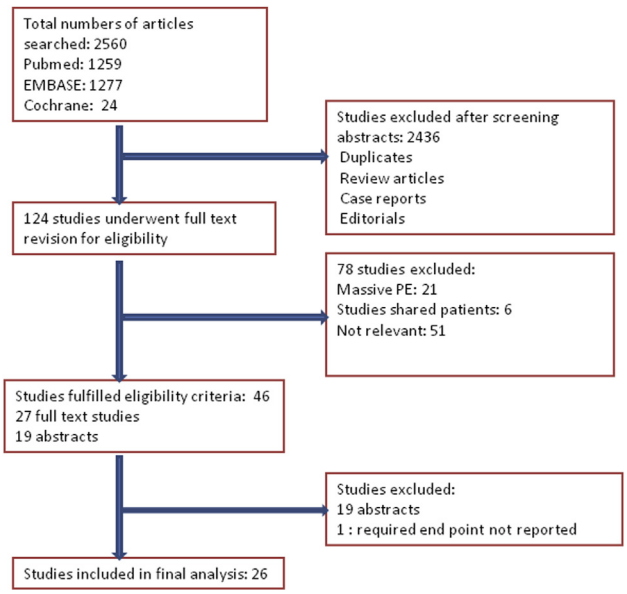

Fig. 1. Flow diagram for study selection. PE: Pulmonary embolism.