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Risk stratification in acute pulmonary embolism with heart-type fatty acid–binding protein: A meta-analysis☆,☆☆

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ABSTRACT

Objective: Heart-type fatty acid–binding protein (H-FABP) has emerged as a new biomarker in risk stratification of patients with acute pulmonary embolism (PE). We performed a meta-analysis of studies in patients with acute PE to assess the prognostic value of elevated H-FABP for short-term adverse outcomes.
Data source: Two independent reviewers systematically searched PubMed, EMBASE, and Cochrane Database until June 2014.
Data Selection: Studies were searched using MeSH word "fatty acid–binding protein" and "pulmonary embolism." Prospective studies were included if those were done on patients with acute PE and if serum H-FABP assay was done.
Data Extraction: Relevant data on study design, year of publication, patient population, inclusion criteria, exclusion criteria, mean age, sex, type of H-FABP assay, cutoff of H-FABP used, and outcomes were extracted. The primary end point was 30-day complicated clinical course and PE-related mortality. The secondary end point was right ventricular dysfunction (RVD). A random-effects model was used to pool study results.
Data Synthesis: Nine studies, including 1680 patients, reported data on the 30-day complicated clinical course. Elevated H-FABP was significantly associated with the increased risk of 30-day complicated clinical course (odds ratio [OR], 17.67; 95% confidence interval [CI], 6.02-51.89; $I^2 = 80\%$). Similarly, 6 studies, including 676 patients, reported 30-day mortality data. Elevated H-FABP was associated with increased risk of 30-day PE-related mortality (OR, 32.94; 95% CI, 8.80-123.21, $I^2 = 53\%$). The risk of RVD was significantly higher in patients with elevated H-FABP as compared with patients with normal H-FABP (OR, 2.57; 95% CI, 1.05-6.33, $I^2 = 57\%$). The prognostic sensitivity and specificity of H-FABP were 71% and 74% in predicting 30-day complicated clinical course and were 90% and 70% in predicting 30-day mortality.
Conclusion: This meta-analysis indicates that elevated H-FABP levels are associated with increased risk of 30-day complicated clinical course, mortality, and RVD.

1. Introduction

Acute pulmonary embolism (PE) is a major cause of mortality and morbidity despite significant advances in management. Goldhaber et al [1] reported 90-day mortality of about 52% in hemodynamically unstable patients and 14.7% in patients who are hemodynamically stable. Acute PE has a clinical spectrum ranging from asymptomatic to life threatening. The patients with acute PE has been divided into 3 groups: (1) massive PE, sustained hypotension (systolic blood pressure <90 mm Hg for at least 15 minutes or requiring inotropic support, not attributable to any other cause than PE); (2) submassive or intermediate risk, normotensive with right ventricular dysfunction (RVD) or myocardial injury; (3) low risk, who are hemodynamically stable with absence of the clinical markers of adverse prognosis that define massive or submassive PE [2]. Risk stratification of patients with acute PE is important for optimal management and enhanced outcomes. Patients who were hemodynamically stable at the time of admission but manifest RVD have a poor prognosis when compared with patients without RVD [3,4]. Echocardiogram is a useful tool in diagnosing RVD and helps in risk stratification of patients with acute PE. Several serum biomarkers such as troponin, brain natriuretic peptide (BNP) and N-terminal pro-BNP have also been reported to be important in risk stratification of patients with acute PE, especially when echocardiogram is

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not available [5,6]. These biomarkers are elevated in patients with RVD and identify patients at high risk for poor outcomes. Lately, several studies reported heart-type fatty acid–binding protein (H-FABP) to be a more sensitive and specific marker of early adverse outcomes as compared with troponin or natriuretic peptides in patients with acute PE [7–10]. This small protein (15 kd) diffuses more rapidly than troponins through interstitial spaces and appears in the circulation as early as 90 minutes, reaching its peak within 6 hours [8].

2. Methods

2.1. Study objectives

The primary objective of this meta-analysis was to assess the prognostic value of elevated H-FABP (above cutoff) in predicting short-term complicated clinical course and mortality in patients with acute PE. The secondary objective was to assess whether elevated H-FABP is associated with RVD.

2.2. Data source and searches

A systematic search of Medline, EMBASE, and Cochrane Database was performed. The following key words were used: "fatty acid–binding protein" and "pulmonary embolism." In addition, references from previous trials, 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 abstracts or articles of all retrieved studies cited before June 2014 were reviewed.

2.3. Study selection

The inclusion criteria were based on following attributes: (1) design, prospective or retrospective study; (2) population, patients admitted to the hospital for acute PE and H-FABP assay was done at the time of admission; (3) outcomes, 30-day complicated clinical course, 30-day PE-related mortality, and RVD; and (4) 2×2 table can be constructed from the data to compute true positive, false positive, true negative, and false negative.

2.4. Data extraction and validity assessment

Two independent reviewers (A.B. and P.R.) 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 included in 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, sex, type of H-FABP assay, cutoff of H-FABP used, and outcomes were extracted (Tables 1 and 2). When we identified studies that had been reported in multiple articles, the analysis was limited to the largest patient population, unless the necessary data had appeared only in another article.

2.5. Study end points

The primary outcome of interest was the 30-day complicated clinical course or PE-related mortality. The *complicated clinical course* was defined as death, need for thrombolytics, endotracheal intubation, catecholamine infusion for sustained hypotension, cardiopulmonary resuscitation, or recurrent pulmonary embolism.

Secondary outcome was the RVD. *Right ventricular dysfunction* was defined as follows: (1) right-sided cardiac thrombus, (2) right ventricular (RV) diastolic dimension (parasternal view) greater than 30 mm or an RV/left ventricular ratio greater than 1, (3) systolic flattening of the interventricular septum, (4) acceleration time less than 90 milliseconds or tricuspid insufficiency pressure gradient greater than 30 mm Hg in the absence of RV hypertrophy, and (5) RV dilation (4-chamber RV diameter divided by left ventricular diameter >0.9) on computed tomography [11].

2.6. Data synthesis and statistical analysis

We constructed a 2×2 table for 30-day complicated clinical course and mortality. We computed sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio by means of true positive, false positive, true negative, and false negative. 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 CIs 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 homogeneous end points. Random effect (DerSimonian) analysis was reported in the presence of significant heterogeneity. Even if there was little or no evidence of heterogeneity, a random-effects model was used for each outcome because of the arguments put forth by many authors for using random-effects models in medical decision-making contexts, especially in the case of rare events. A P value less than .05 was considered significant. Funnel plots were used to evaluate for publication bias by plotting standard error (log OR) of 30-day complicated clinical course. Funnel plot was not made for 30-day mortality and RVD because of few studies. Weighted symmetric summary receiver operating characteristic plots were computed using Moses-Shapiro-Littenberg method [12]. We also did a subgroup analysis of studies including only hemodynamically stable patients at the time of admission to predict the complicated clinical course and mortality. This meta-analysis was performed in accordance with the PRISMA statement [13]. As suggested previously [14], the studies were not scored based on their quality.

3. Result

Overall, 101 articles were found until June 2014. Review articles, case reports, and editorials were excluded as shown in Fig. 1. Twenty-seven studies were found in acute PE where H-FABP assay was obtained (7 abstracts from annual scientific meetings and 20 full-text studies). Five abstracts were excluded because 2 of them involved report on the same patients included in other analyzed full-text studies and 3 did not report required end points. Eleven full-text studies were excluded because 3 of them appeared to report on the same patients included in other analyzed studies and 8 studies did not report required end points. Two abstracts and 9 full-text studies were included in the final analysis [9,10,15–23]. Of a total of 11 studies, 2 studies have overlapping of patients, but they have different end points so they were included in the analysis of different end points [10,19].

3.1. Selected studies

Overall, 11 studies were included in the analysis. The main characteristics of the studies are shown in Tables 1 and 2. There were 2 studies, Lankeit et al [10] and Boscheri et al [23] which shared some patients with Dellas et al [17] and Wunderlich et al [20]. These studies shared patients, but reported different end points. Of the studies by Dellas et al and Lankeit et al, Dellas et al had more patients' volume so it was included in analysis of primary end points; however, Lankeit et al reported RVD as one of its outcomes and included in RVD analysis. Similarly, of the studies by Wunderlich et al and Boscheri et al, former study had more patients' volume and reported 30-day mortality as its outcomes but did not report 30-day complicated clinical course as

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