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ORIGINAL ARTICLE

Early Diagnostic Performance of Heart-Type Fatty Acid Binding Protein in Suspected Acute Myocardial Infarction: Evidence From a Meta-Analysis of Contemporary Studies

Q1 Li-Qian Xu, MD [a], Yun-Mei Yang, MD [a], Hong Tong, MD [b], Chang-Fu Xu, MD [b*]

Q2 [a]Department of Geriatrics, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, 310003, China
Q3 [b]Department of Cardiology, Tongde Hospital of Zhejiang Province, Hangzhou, 310012, China

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Q5 **Background** Although cardiac troponin is the cornerstone in diagnosis of acute myocardial infarction (AMI), the accuracy is still suboptimal in the early hours after chest pain onset. Due to its small size, heart-type fatty acid-binding protein (H-FABP) has been reported accurate in diagnosis of AMI, however, this remains undetermined. The aim is to investigate the diagnostic performance of H-FABP alone and in conjunction with high-sensitivity troponin (hs-Tn) within six hours of symptom onset. Furthermore, accuracy in 0 h/3 h algorithm was also assessed.

Methods Medline and EMBASE databases were searched; sensitivity, specificity and area under ROC curve (AUC) were used as measures of the diagnostic accuracy. We pooled data on bivariate modelling, threshold effect and publication bias was applied for heterogeneity analysis.

Results Twenty-two studies with 6602 populations were included, pooled sensitivity, specificity and AUC of H-FABP were 0.75 (0.68–0.81), 0.81 (0.75–0.86) and 0.85 (0.82–0.88) within six hours. Similar sensitivity (0.76, 0.69–0.82), specificity (0.80, 0.71–0.87) and AUC (0.85, 0.82–0.88) of H-FABP were observed in 4185 (63%) patients in 0 h/3 h algorithm. The additional use of H-FABP improved the sensitivity of hs-Tn alone but worsened its specificity (all $p < 0.001$), and resulted in no improvement of AUC ($p > 0.99$). There was no threshold effect ($p = 0.18$) and publication bias ($p = 0.31$) in this study.

Conclusions H-FABP has modest accuracy for early diagnosis of AMI within three and six hours of symptom onset. The incremental value of H-FABP seemed much smaller and was of uncertain clinical significance in addition to hs-Tn in patients with suspected AMI. Routine use of H-FABP in early presentation does not seem warranted.

Keywords Meta-analysis • Heart-type fatty acid binding protein • Acute myocardial infarction • Early diagnosis

Q4 *Corresponding author at: Department of Cardiology, Tongde Hospital of Zhejiang Province, 234 Gucui Road, Hangzhou, 310012, China. Tel: +86-571-89972433; Fax: +86-571-89972433., Email: changfu_xu@126.com

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Introduction

Approximately 15 million patients present to the emergency department (ED) with acute chest pain or other symptoms suggestive of acute myocardial infarction (AMI) in the United States and Europe each year, however, only a small proportion of these patients are found to have an AMI [1,2]. Electrocardiography (ECG) and cardiac troponin (cTn) assay are currently the cornerstones in diagnosis of AMI, quantifying cardiomyocyte damage and complementing clinical assessment [3,4]. A limitation of cTn assays is a delayed increase of circulating levels for three to four hours, serial measurements are required for 6 to 12 hours to overcome the accuracy deficit of this biomarker [2,4,5]. Delays in diagnosing disease interferes with prompt use of treatments, while delays in excluding disease holds back evaluation of alternative diagnosis and contributes to expensive overcrowding in the emergency department [6,7]. Recently, high-sensitivity cardiac troponin (hs-Tn) assays have been introduced to provide higher sensitivity for AMI than conventional cTn [8]. However, improvements in sensitivity, to some extent, have increased the number of positive hs-Tn assay results in various conditions with cardiac involvement other than AMI. Moreover, decision thresholds of hs-Tn as a rule-out strategy of suspected AMI are still uncertain, which requires further investigation [9].

Heart-type Fatty Acid-Binding Protein (H-FABP) is a small soluble cytoplasmic protein (15 kiloDalton) released from cardiomyocytes following an ischaemic episode. Due to its small size and solubility, H-FABP can be released more rapidly than structurally bound molecules like cardiac troponin. Its time course is reciprocal to that of troponin, which allows H-FABP to at least partly overcome the ''troponin-blind'' period within the early hours of symptoms onset [10–13]. Primary studies reported that H-FABP may be regarded as an early biomarker in diagnosis of AMI [14,15], however, some studies attempting to evaluate H-FABP for early diagnosis of AMI have produced disappointing results [16], and it is also noteworthy that the analysis of studies investigating additional use of H-FABP in suspected AMI produced inconsistent results [17–19]. In view of this, further investigation was warranted to assess the role of H-FABP alone and within a multimarker approach.

The sensitivity of a baseline measurement of assays depends on the time between symptom onset and blood draw. A limitation of cTn assay is the inability to detect low levels of cTn, and serial measurements are required for 6 to 12 hours to overcome the accuracy deficit of this biomarker [2,20]. Thus, patients with symptoms suggestive of AMI with an onset of discomfort within the previous six hours were identified by this study. According to the latest ESC guidelines, it was recommended to use the 0 h/3 h algorithm in estimating very early diagnostic accuracy of assays in suspected AMI patients [2]. As for hs-Tn, results reported in the primary studies indicate that, in patients who present within three hours of chest pain onset, the probability of false negatives is higher and a second measurement may be needed to avoid the inadvertent discharge of patients with an evolving AMI [9,21–23].

Herein, we present this study to investigate the diagnostic performance of H-FABP alone and in conjunction with hs-Tn in a pre-specified analysis of patients presenting with suspected AMI within six hours of chest pain onset. Furthermore, very early diagnostic accuracy of H-FABP within 0 h/3 h algorithm was also assessed.

Method

We undertook a meta-analysis in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [24] and the methods described in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy.

Search Strategy and Selection Criteria

We searched for the relevant studies (Supplementary Table S1 in the online version at DOI: 10.1016/j.hlc.2017.03.165) in the online database of EMBASE, PubMed from the date of their inception up to March 2016 with the assistance of a librarian. No language restriction was placed. The references in all the retrieved articles were also searched for any additional relevant studies. Two reviewers were asked to look through this literature and assess their eligibility for analysis.

Eligible studies had to meet the following criteria: (I) Studies that assessed the accuracy of H-FABP for AMI, reported participant demographics, and sensitivity and specificity of screening; (II) true positives (TP), false positives (FP), true negatives (TN), and false negatives (FN) were able to be calculated on the basis of sensitivity and specificity in respective publications; (III) AMI suspected patients presenting within six hours of acute chest pain onset. Systematic reviews were used only as a source of reference, conference abstracts were also included when they contained relevant published data. Finally, a total of 22 studies were included, any disagreement between them was resolved by discussion with a third party. The inclusion of all the studies based on the above criteria was achieved in two stages: in the first stage, the inclusion was based on title and abstract; and in the second stage, the full texts were considered. Very early presenters were defined as pre-specified subgroup analysis of patients within three hours of chest pain onset.

Adjudicated Final Diagnosis

Acute myocardial infarction was interpreted as recommended in relevant guidelines [25]. In brief, AMI was diagnosed when there occurred myocardial necrosis and was consistent with a clinical setting of myocardial ischaemia. Adjudication of final diagnoses of AMI was performed for all patients twice in studies assessing the accuracy of hs-Tn: once according to conventional cTn levels used onsite (this method was used in the initial analyses to examine the performance of hs-Tn assays) and once including levels of Roche hs-cTnT or hs-cTnI in order to take the advantage of

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