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Original Article

Point-of-care test of heart-type fatty acid-binding protein for the diagnosis of early acute myocardial infarction

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Aim: To investigate the efficacies of point-of-care test of heart-type fatty-acid binding protein (H-FABP) and its combinations with the conventional biomarkers in the diagnosis of early acute myocardial infarction (AMI).
Methods: 227 patients suspected of AMI were consecutively recruited in two centers. Biomarkers including H-FABP, myoglobin (MYO), creatine kinase-myocardial band (CK-MB) and cardiac troponin T (cTnT) were determined simultaneously at admission. AMI was defined according to the universal definition of myocardial infarction. Chi-Square test was adopted for the analysis.
Results: In patients presenting within 12 h of symptom onset, the sensitivity of H-FABP[93.0% (95% CI: 86.6%−96.9%)] was significantly higher than that of initial CK-MB [67.5% (95% CI: 58.1%−76.0%), $P<0.0001$], cTnT [69.3% (95%CI: 60.0%−77.6%), $P<0.0001$] and MYO [68.6% (95% CI: 54.1%−80.9%), $P<0.05$]. The negative predictive value of H-FABP [92.8% (95%CI: 86.3%−96.8%)] was significantly higher than that of initial CK-MB [74.7% (95% CI: 66.8%−81.5%), $P<0.001$] and cTnT [75.9% (95% CI: 68.1%−82.6%), $P<0.001$]. The sensitivity of H-FABP+cTnT combination [94.7% (95% CI: 88.9%−98.0%)] was significantly higher than that of admission cTnT [69.3% (95% CI: 60.0%−77.6%), $P<0.0001$], CK-MB+cTnT [75.4% (95% CI: 66.5%−83.0%), $P<0.0001$] and MYO+CK-MB+cTnT [74.5% (95% CI: 60.4%−85.7%), $P<0.05$]. The negative predictive value of H-FABP+cTnT [94.5% (95% CI: 88.4%−98.0%] was significantly higher than that of initial cTnT [75.9% (95% CI: 68.1%−82.6%), $P<0.001$] and CK-MB+cTnT [79.1% (95% CI: 71.2%−85.6%), $P<0.001$]. Subgroup analysis showed that the superiorities of both the sensitivities and the negative predictive values of H-FABP and H-FABP+cTnT combination occurred only in patients who presented within 6 h of the symptom onset.
Conclusion: Point-of-care test of H-FABP can be used as a valuable biomarker to detect or exclude an early-stage AMI. Combining H-FABP and cTnT provides the best performance for early AMI diagnosis.

Keywords: point-of-care test; heart-type fatty-acid binding protein; acute myocardial infarction; diagnosis

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Introduction

Acute myocardial infarction (AMI) is a primary life-threatening cardiac disease, early and correct diagnosis is of great importance to enable immediate and intensified treatment which consequently reduces mortality[1–3]. Unfortunately, at least one-fifth of AMIs are clinically unrecognized because of absence of chest discomfort or atypical ECG changes[4]. Thus, early AMI diagnosis relies crucially on the biochemical markers in these cases.

Heart-type fatty acid-binding protein (H-FABP) is a small cytoplasmic protein which is abundantly expressed in human heart[5]. It was first shown to be released from injured myocardium in 1988, after which its application as a biochemical marker has been investigated[6, 7]. Recently, the point-of-care immunochromatographic assay of H-FABP has been created to achieve a rapid determination of the whole blood H-FABP level. However, researches have shown inconsistent performances of H-FABP rapid penal test in the diagnosis of AMI. So the priority of H-FABP is worthy of further investigation.

We conducted this study in two centers to determine the value of the point-of-care test of H-FABP alone and in combination with cTnT in early AMI diagnosis, and hypothesized that, 1) H-FABP is superior to the conventional biomarkers in the diagnosis of early AMI; 2) Combining H-FABP and cTnT

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can improve the performance of single cTnT and is superior to other regular combinations.

Materials and methods

Study subjects

This study was conducted in two centers simultaneously in accordance with the Declaration of Helsinki and was approved by the local ethics board. Patients presenting chest pain more than 30 min and less than 12 h suspected of AMI were enrolled consecutively in the study. Patients' symptoms and past medical history were documented at admission using a pre-defined protocol.

Diagnostic criteria

The standard diagnosis was made after critical review of all the clinical pictures and relevant information by a senior cardiologist. AMI was defined as detection of initial or 12 h cTnT ≥0.1 ng/mL together with evidence of myocardial ischemia with at least one of the following: i) Symptoms of ischemia; ii) ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]); iii) Development of pathological Q waves in the ECG; iv) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality[1]. Diagnostic outcomes were first categorized into the following groups: i) ST-elevation myocardial infarction (STEMI); ii) non-ST-elevation myocardial infarction (NSTEMI); iii) unstable angina (UA); iv) chronic angina (CA); and v) non-cardiac chest pain (NCCP)[1, 2, 8]. The first two groups were later integrated into AMI group, and the last three into non-myocardial infarction (NMI) group.

Determinations of H-FABP and other biomarkers

Initial blood samples were collected from every subject upon hospital admission for the determinations of H-FABP and other biomarkers. A point-of-care H-FABP kit, using a rapid immunochromatographic method, was applied to qualitatively determine the H-FABP levels in whole blood samples with a cut-off level at 7 ng/mL. The test was interpreted within 10 min after the blood was applied into the sample slot of the test strip, and the results were judged as positive or negative by different types of the color changes. Trained medical staff, blinded to the standard diagnosis, was qualified to perform the H-FABP test. The package of H-FABP kit (20Test/kit, Pattern number: HFABPM20, Batch No 20070620) was supplied by Wuhan EasyDiagnosis Biomedicine Co, Ltd (Wuhang, China) (Figure 1). MYO, CK-MB and cTnT were determined from the initial blood samples using the immunofluorescence method, dry chemistry analysis and the enzyme-linked immunosorbent assay (ELISA) with cut-off levels of 46 ng/mL, 25 U/L and 0.1 ng/mL, respectively. Any results that were no less than the cut-off levels were defined as positive results. Conversely, those being less than the cut-off levels were defined as negative results. Regarding the combinations, positive results were defined as positive of any component markers, while negative results were defined as negative of all the component markers. cTnT was re-determined at least 12 h from the onset of the chest pain to fulfill a final diagnosis.

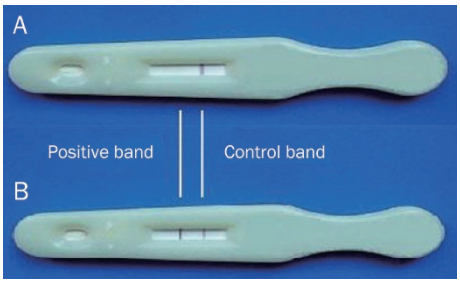

Figure 1. Point-of-care test of H-FABP. (A) Negative result: positive band remained pale while the control band turned red; (B) Positive result: both the positive and the control bands turned red.

Statistics

All the data were analyzed in MacMaster University, Canada. SAS 9.1 analysis software was used for the statistics, data were expressed as mean±SD. Student's *t* test and Chi-Square were used to compare the differences of the basic characteristics between AMI and NMI groups. Chi-Square test was also adopted to analyze the differences of the sensitivity, specificity, positive and negative predictive values. Fisher's exact test was used when any cell in the square was less than five. The level of significance was set at 0.05.

Results

Patient characteristics

227 patients, 163 male and 64 female, average age 64.5±11.6 years, were recruited in the period from Jan 2008 to Aug 2008. According to the diagnostic criteria, 114 patients were defined as AMI; 27 patients as UA; 20 patients as CA; and 66 patients as NCCP. Compared with the NMI patients, AMI patients were older, more likely to be male, more likely to have previous coronary artery disease, and more likely to have a heart function of New York class III and IV (Table 1). The average symptom-to-sample time (from symptom onset to initial blood sampling) of total AMI patients was 4.96±3.08 h (median 4 h), in which 38 (33.3%) patients were admitted within 3 h (2.03±0.80 h; median 2 h), 44 (38.6%) patients between 3 to 6 h (4.44±0.68 h; median 4.25 h), and 32 (28.1%) patients between 6 to 12 h (9.16±2.01 h; median 9 h) of symptom onset.

Superiorities of H-FABP and its combinations

H-FABP, CK-MB, and cTnT were measured in all the 227 subjects. The sensitivity of H-FABP [93.0% (95% CI: 86.6%−96.9%)] was significantly higher than that of initial CK-MB [67.5% (95% CI: 58.1%−76.0%), $P<0.0001$] and cTnT [69.3%(95% CI: 60.0%−77.6%), $P<0.0001$]. Similarly, the negative predictive value of H-FABP [92.8% (95% CI: 86.3%−96.8%)] was significantly higher than that of initial CK-MB [74.7% (95% CI: 66.8%–81.5%), $P<0.001$] and cTnT [75.9% (95% CI: 68.1%−82.6%), $P<0.001$]. The sensitivity of H-FABP+cTnT combination [94.7% (95% CI: 88.9%−98.0%)] was significantly higher than that of admission cTnT [69.3%

Table 1. Patients' characteristics.

Demographics	AMI (*n*=114)	NMI (*n*=113)	*P* value
Males *n*, (%)	93 (81.6)	70 (61.9)	0.001
Age (years)	67.1±11.1	61.8±11.5	<0.001
Previous coronary artery disease *n*, (%)	103 (90.4)	34 (30.1)	<0.001
Hypertension *n*, (%)	45 (39.5)	33 (29.2)	0.103
Diabetes *n*, (%)	18 (15.8)	10 (8.8)	0.112
Chronic renal dysfunction *n*, (%)	0 (0)	0 (0)	1.000
Heart function New York class III and IV *n*, (%)	9 (7.8)	2 (1.8)	0.032

(95% CI: 60.0%−77.6%), *P*<0.0001] and CK-MB+cTnT [75.4% (95% CI: 66.5%−83.0%), *P*<0.0001]. The negative predictive value of H-FABP+cTnT [94.5% (95% CI: 88.4%−98.0%] was also significantly higher than that of initial cTnT [75.9% (95% CI: 68.1%−82.6%), *P*<0.001] and CK-MB+cTnT [79.1% (95% CI: 71.2%−85.6%), *P*<0.001]. The sensitivity and negative predictive values of H-FABP, H-FABP+cTnT, H-FABP+CK-MB+cTnT had no significant difference. Also, the specificities and the positive predictive values of H-FABP, CK-MB, cTnT, H-FABP+cTnT, H-FABP+CK-MB+cTnT, and CK-MB+cTnT had no statistical difference (Figure 2, 3).

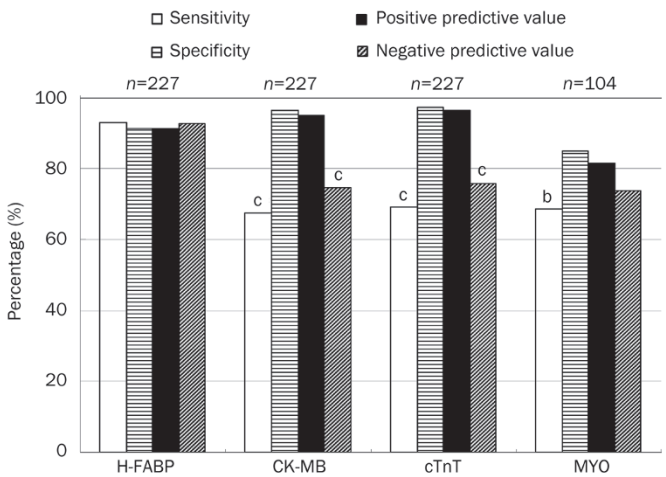

Figure 2. Sensitivity, specificity, positive and negative predictive values of different biomarkers. Compared with H-FABP, ^{b}P<0.05, ^{c}P<0.01 (result from subgroup analysis).

Performances of the biomarkers in different time windows

We separated the patients into 3 subgroups by symptom-to-sample time as: i) ≤3 h; ii) >3 h, ≤6 h (3−6 h); and iii) >6 h, ≤12 h (6−12 h). The sensitivities of H-FABP of the three time windows were 84.2% (95% CI: 68.7%−94.0%), 95.5% (95% CI: 84.5%−99.4%) and 100% (95% CI: 89.1%−100.0%), respectively, and the negative predictive values were 86.0% (95% CI: 72.1%−94.7%), 94.3% (95% CI: 80.8%−99.3%), and 100% (95% CI: 89.4%−100.0%) respectively. The sensitivity and negative predictive value of H-FABP were both significantly higher

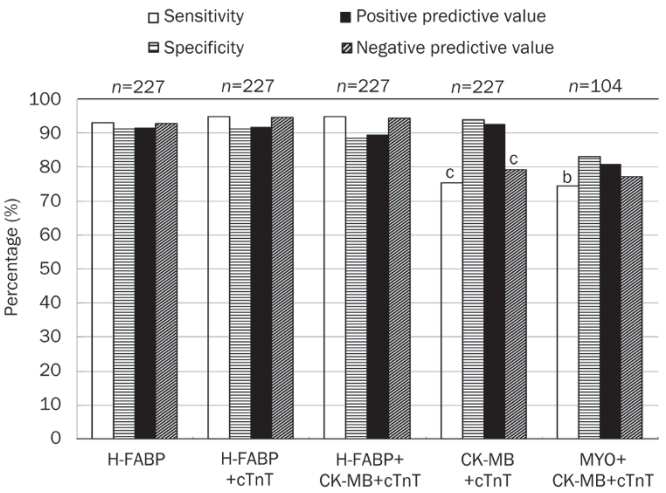

Figure 3. Sensitivity, specificity, positive and negative predictive values of H-FABP and different combinations of the biomarkers. Compared with H-FABP+cTnT, ^{b}P<0.05, ^{c}P<0.01 (result from subgroup analysis).

than that of initial CK-MB and cTnT within 3−6 h of symptom onset, which were more significantly higher when patients presented within 3 h of the chest pain. Conversely, neither of them reached significant difference when patients presented 6–12 h of the symptom onset. H-FABP+cTnT exhibited the same superiorities over initial cTnT and CK-MB+cTnT within 3 h or 3–6 h of the symptom onset. The sensitivities and negative predictive values of all the single and combined biomarkers increased by time and reached 100% within 6–12 h of symptom onset. No differences of the specificities or positive predictive values among single biomarkers or the combinations were found within the same subgroup (Figure 4).

Performances of H-FABP, MYO and the associated combinations

Additional detection of MYO were performed in one center, where 51 AMI patients and 53 non-AMI patients were included. The sensitivity of H-FABP was significantly higher than that of MYO [86.3% (95% CI: 73.7%−94.3%) *vs* 68.6% (95% CI: 54.1%−80.9%); *P*=0.0330]. The sensitivity of H-FABP+cTnT was significantly higher than that of MYO+CK-MB+cTnT [90.2% (95% CI: 78.6%−96.7%) *vs* 74.5% (95% CI: 60.4%−85.7%); *P*=0.0377] (Figure 2, 3). On the other hand, the negative

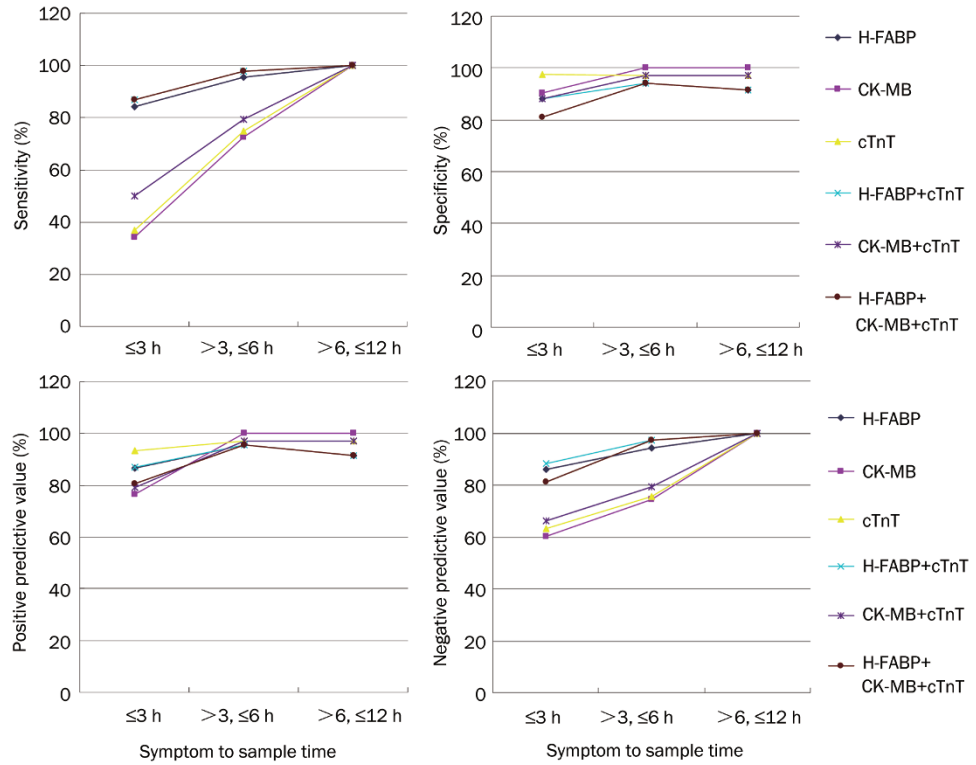

Figure 4. Sensitivity, specificity, positive and negative predictive values of the biomarkers in different symptom to sample time-frames.

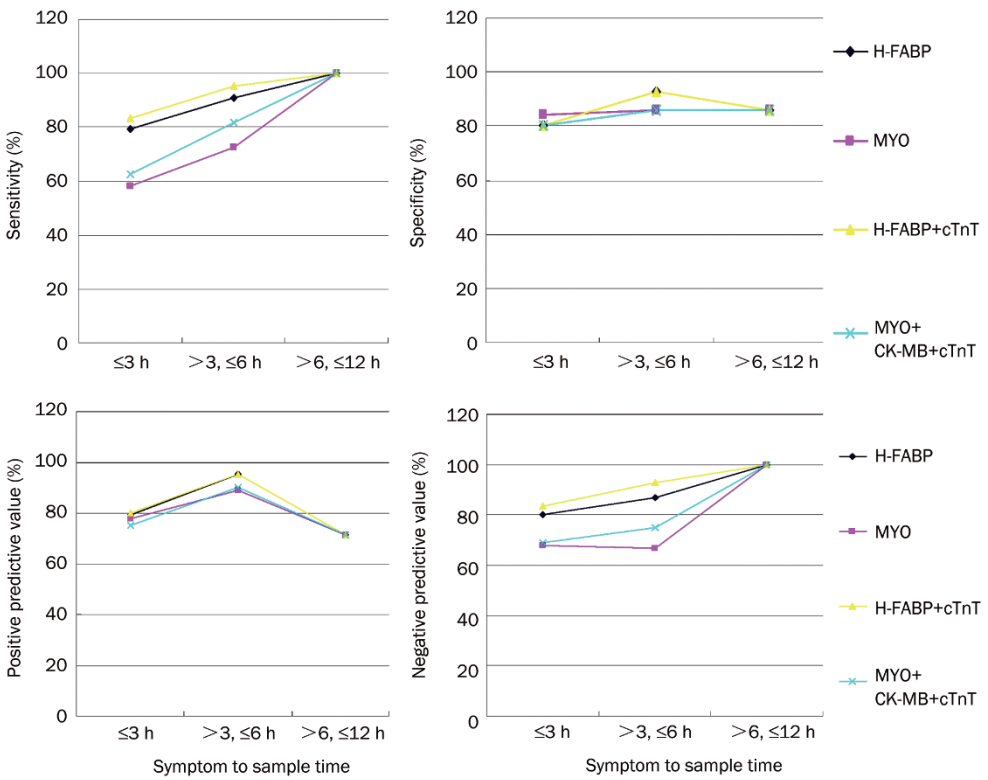

Figure 5. Sensitivity, specificity, positive and negative predictive values of the biomarkers including myoglobin in different symptom to sample time-frames.

predictive value of H-FABP was better than MYO [86.5% (95% CI: 74.2%−94.4%) *vs* 73.8% (95% CI: 60.9%−84.2%); P=0.093]. The negative predictive value of H-FABP+cTnT was better than MYO+CK-MB+cTnT [90.0% (95% CI: 78.2%−96.7%) *vs* 77.2% (95% CI: 64.2%−87.3%); P=0.077] (Figure 2, 3).

In the subgroups separated by different symptom to sample time, H-FABP presented better sensitivity and negative predictive value than MYO in patients admitted within 3 h or 3–6 h.

H-FABP+cTnT showed the same superiority over MYO+CK-MB+cTnT within 3 h or 3–6 h of the symptom onset, although the differences were not statistically significant. The sensitivities and the negative predictive values of H-FABP, MYO and the two combinations all reached 100% at 6–12 h of the incidence (Figure 5).

The specificities and the positive predictive values among H-FABP, MYO, H-FABP+cTnT and MYO+CK-MB+cTnT did not show significant difference in the total subjects or within each subgroup.

Discussion

This study was conducted in two cardiac centers simultaneously, which disclosed that the performance of point-of-care test of H-FABP was superior to that of CK-MB, cTnT and MYO by providing higher sensitivity and negative predictive values specifically in early stage of AMI (≤6 h of the symptom onset). In the mean time, H-FABP+cTnT combination showed significantly higher sensitivity and negative predictive values than that of single cTnT and the regular combinations including CK-MB+cTnT and MYO+CK-MB+cTnT.

Currently used biomarkers such as CK-MB and cTnT are both myocardial construction proteins and have higher cardiac specificity, which have being referred as key cardiac biomarkers for AMI diagnosis[1]. However, neither of them can identify AMI until more than 4 h after onset of the chest pain in most cases[9, 10]. MYO is more sensitive in the early phase of AMI, but its specificity is not satisfying[9]. Thus H-FABP would act as a fewer available cardiac biomarker with superior performance in the diagnosis of early-stage AMI.

The superior performance of H-FABP may be attributed to the following two factors: i) smaller molecular weight: H-FABP is a small cytoplasmic protein, which has a very low molecular weight of 15 kDa, while the molecular weight of MYO, CK-MB and cTnT are 18, 80 and 37 kDa respectively[11–13]. ii) steeper tissue-to-plasma gradient: The myocardial content of H-FABP (0.52 mg/g wet wt) is 4.5 fold lower than that of myoglobin (2.35 mg/g wet wt), yet the basic plasma level of H-FABP (2.8 μg/L) is 10-fold lower than the later (30 μg/L)[14, 15]. So H-FABP tissue-to-plasma gradient is at least two-fold steeper than that of myoglobin. This characteristic, along with the higher permeability of the endothelial barrier for small proteins, enable H-FABP to exhibit an early and significant release after myocardial necrosis and make it more easily being detected, thus endue H-FABP with a superior capability for early AMI diagnosis.

However, it has been noted that H-FABP isoform is produced not only in cardiomyocytes but also, to a lesser extent, in skeletal muscle, distal tubular cells of the kidney, specific parts of the brain, lactating mammary glands and the placenta[16]. In the clinical studies, serum H-FABP level is also elevated under heart failure, hypertension, aortic valve regurgitation, renal dysfunction and muscular exercise[17–20]. Our study demonstrated that H-FABP had a specificity that was slightly lower than CK-MB and cTnT, and was not superior to MYO in any time period within 12 h after onset of the symptoms. Besides, the positive predictive value of H-FABP did not show superiority to MYO, CK-MB or cTnT. Therefore, multiple physiological and pathological factors should be considered while the point-of-care test of H-FABP is applied in AMI diagnosis.

The multi-marker concept was put forward recently in diagnosing AMI, predicting disease risk and evaluating patient outcomes[21, 22]. Mion *et al* used an automated protein biochip microarray system, which allowed a simultaneous determination of six biomarkers, and found that H-FABP+cTnI combination presented the highest sensitivity (83.3%) and specificity (92.2%), and favored it as the most effective "two marker strategy" of the five combinations determined in the study[23]. We investigated the performances of different combinations including H-FABP+cTnT , CK-MB+cTnT, MYO+CK-MB+cTnT and H-FABP+CK-MB+cTnT in this study. As a result, the H-FABP+cTnT significantly improved the sensitivity and negative predictive value of single cTnT, and exhibited the highest sensitivity and negative predictive value as compared with CK-MB+cTnT and MYO+CK-MB+cTnT in early phase of AMI (≤6 h). Tri-marker test of H-FABP+CK-MB+cTnT did not improve the sensitivity and negative predictive value of H-FABP+cTnT. Although the specificity and the positive predictive value of H-FABP+cTnT were not superior to that of other combinations, it was not inferior to that of any single cardiac marker or combination. These findings suggested that H-FABP+cTnT was currently the most effective combination for the diagnosis of early AMI.

One limitation of this study was that we only assessed the performance of H-FABP from single measurement on the participants, sequential measurements were not performed, so the performances of H-FABP in different time windows were evaluated from different subjects, while not a dynamic investigation of the same population.

In conclusion, our study demonstrated that the point-of-care test of H-FABP was a more sensitive test for the AMI diagnosis compared with conventional cardiac markers, which can be used as a valuable biomarker to exclude an early-stage AMI (within 6 h after onset of the symptoms). Combining H-FABP and cTnT provides the best performance for early AMI diagnosis.

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Author contribution

Chun-jian LI, Zhi-jian YANG, ,Ke-jiang CAO, Jun HUANG designed research; Chun-jian LI, Jie-qi LI, Xiao-fang LIANG, Xiao-xiang LI, Jian-guo CUI performed research; Chun-jian LI, Qing GUO analyzed data; Chun-jian LI wrote the paper.

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