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Original Article

Clinical study of H-FABP for risk stratification and prognosis in patients with early cTnT-negative ACS

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Abstract: Objective: To explore the application value of early H-FABP detection for risk stratification and prognosis in early cTnT negative Acute Coronary Syndrome (ACS) patients. Methods: In 55 patients diagnosed with early cTnT negative ACS, levels of cTnT and H-FABP at 6, 12, 24, 48 hours from onset of symptoms were continuously detected. ROC curve of H-FABP for early prediction of evolution to myocardial infarction in cTnT negative patients was drawn. Patients were followed-up for 12 months and divided into 2 groups according to the presence of cardiovascular events. Level of H-FABP at early onset between patients in 2 groups was compared. ROC curve was adopted to determine H-FABP levels for prediction of cardiovascular events in patients with ACS. Patients were divided into high and low H-FABP value groups according to the cut-off value of ROC curve. Patients with cardiovascular events and no cardiovascular events survival in the 2 groups were observed. Results: Levels of cTnT gradually increased and reached the peak at 12 h after onset of symptoms and then decreased. Levels of H-FABP reached the peak within 6 h from onset and decreased slightly (12.82%) at 12 h and then decreased rapidly. Detection of H-FABP level within 6 h from onset had a good predictive value for early cTnT-negative ACS patients evolving to myocardial infarction. The predicted sensitivity and specificity was 87.5%, and 90.33%. H-FABP level in patients with cardiovascular events was significantly higher than those without cardiovascular events. In the high level H-FABP group, incidence of cardiovascular events was 54.5%, while in the low level group it was only 11.4%. Survival without cardiovascular events of the patients in the high-risk group was significantly lower than that in the low risk group (8.55 ± 1.08 VS. 11.23 ± 1.39). Conclusions: For the ACS patients with early negative cTnT results, H-FABP is a good index for early risk stratification and prognosis.

Keywords: Acute coronary syndrome, cardiac troponin T, heart type fatty acid binding protein, myocardial infarction, prognosis

Introduction

Early risk stratification in patients with acute coronary syndrome (ACS) is important for identifying high-risk patients quickly, providing reasonable treatment measures, and improving prognosis and survival rates [1, 2]. The clinical diagnosis and severity of patients with ACS are currently determined based on clinical manifestations, electrocardiographic (ECG) changes, and myocardial markers. But elderly patients or those with a history of myocardial infarction (MI) often present with atypical symptoms, and the sensitivity and specificity of ECG data are limited [3-6]. Myocardial necrosis-associated markers, including myoglobin (MYO), creatine kinase MB (CK-MB) subtype, cardiac troponin I (cTnI), and cTnT, are commonly used. Detection of Tn and the CK isoenzyme 4-6 h after onset of ACS is diagnostically significant. But the detection rate is low during early onset (≤ 6 h). MYO can be detected earlier, but due to its poor cardiac specificity the result is easily influenced by skeletal muscle injury. Thus, these indicators are not ideal for early diagnosis and evaluation of ACS [7, 8]. Traditional methods such as ECG, CK-MB, cTnI, and cTnT, are used to evaluate Tn-negative ACS patients and unstable angina (UA). However, some patients with ACS progress to MI. cTnT-negative patients with ACS tend to have increased risks for heart attack, angina

pectoris, heart failure, severe arrhythmia, and other life-threatening cardiovascular events [9].

Heart-type fatty acid binding protein (H-FABP) is a new biochemical marker of myocardial injury with a molecular weight of approximately 15,000. H-FABP is a soluble myocardial protein composed of 132 acidic amino acids that transport long chain fatty acids [10]. Severe myocardial ischemia causes myocardial cell damage. Because of its small molecular weight, H-FABP can be released quickly into the blood when myocardial cells are damaged, and plasma concentrations increase 1-3 h after myocardial injury, peaking at post 6-8 hours. H-FABP is eliminated completely by the kidney after 24 h [11]. H-FABP shows a higher sensitivity for diagnosing and evaluating the prognosis of patients with ACS during the early stage compared with other myocardial injury markers, such as cTnI, CK-MB, and cTnT, which has caught the attention of researchers worldwide [12].

This study identified early cTnT-negative ACS patients within 6 h from the onset of chest pain (unstable angina), and blood H-FABP and cTnT levels were determined at 6, 12, 24, and 48 h after onset. Progression of ACS or any other cardiovascular events observed in patients during the 12-month follow-up were examined to explore the value of H-FABP level in risk stratification and prognosis prediction for early cTnT-negative ACS patients.

Materials and methods

Patients

A total of 232 patients (191 men and 41 women; mean age, 61.99 ± 13.67 [range, 38-91] years) with unstable angina, non-ST segment elevation myocardial infarction (non-STEMI), and ST-elevation myocardial infarction (STEMI) diagnosed with ACS in the People's Liberation Army General Hospital from March 2010 to March 2012 were included. Patients with original renal dysfunction, cardiac insufficiency, chronic obstructive pulmonary disease, any connective tissue disease, infection, trauma, or malignant tumors were excluded. Fifty-five patients (44 men and 11 women; mean age, 63.13 ± 13.92 [range, 38-90 years] years) were cTnT negative in the first 6 h after admission for chest pain onset, and H-FABP levels were determined. ACS was diagnosed according to the general definition of acute MI of the US and European Heart Associations in 2012, the Treatment Guidelines of Cardiology for non-ST-elevation Acute Coronary Syndrome by the European Society in 2011, and the Treatment Guidelines for ST-elevation Myocardial Infarction and Percutaneous Coronary Intervention by the American Heart Association/American College of Cardiology in 2009.

Materials and methods

Blood cTnT levels were determined using an automatic electrochemical luminescence immunity analyzer and kit (Roche Science, Manheim, Germany). Blood H-FABP levels were determined by an enzyme-linked immunosorbent assay kit (Lanzhou Institute of Biological Products, Lanzhou, Gansu, China), with a detection limit of 0.5 ng/ml.

Venous blood sample was collected in anticoagulant tubes immediately after the patients were admitted to the hospital (mean time from symptom onset to blood sampling: 5.21 h; range, 50 min to 12 h). The blood was centrifuged at 3,000 rpm/min for 5 min, the plasma cTnT level was determined immediately, and the remaining plasma was divided and stored at -20°C for later H-FABP analysis.

Progression and prognostic evaluation

Early assessment of progression in early cTnT-negative ACS patients using H-FABP levels: All 55 patients with ACS were cTnT negative early after onset. A receiver operating characteristics curve (ROC) analysis was performed to determine the usefulness of the H-FABP level in predicting ACS progression to MI. The area under the curve (AUC) was calculated to evaluate the specificity and sensitivity of H-FABP to predict the development of MI in cTnT-negative patients early after symptom onset.

H-FABP level for prognosis prediction of early cTnT-negative ACS patients: The included patients were followed up for 12 months and were divided into two groups according to the occurrence of cardiovascular events. The H-FABP levels determined during the early stage were compared between the two groups. The ROC curve was used to determine the predictive value of H-FABP level (within 6 h after onset) for occurrence of cardiovascular events. The

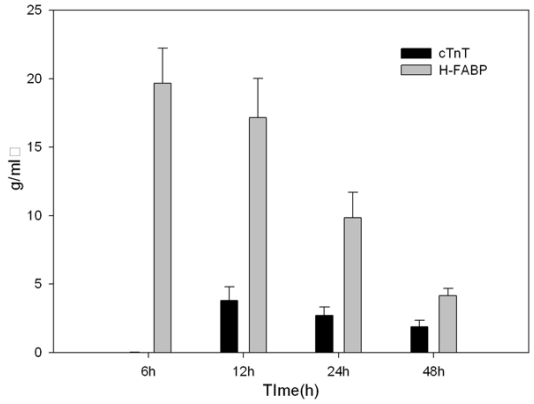

Figure 1. Blood levels of cardiac troponin T (cTnT) and heart-type fatty acid binding protein (H-FABP).

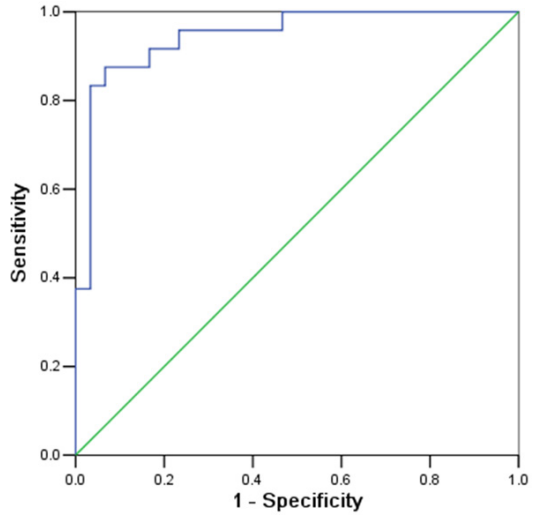

Figure 2. Receiver operating characteristic curve analysis demonstrates the value of the heart-type fatty acid binding protein (H-FABP) level for predicting the development of myocardial infarction in cardiac troponin T (cTnT)-negative patients with early onset acute coronary syndrome (ACS).

appropriate cut-off was determined according to the ROC curve, and the patients were divided into H-FABP high and low level groups. Cardiovascular events and survival of patients in the two groups were recorded.

Statistics

SPSS13.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Data are expressed as means ± SD. Mean differences between the two groups were compared using the *t*-test. Count data are expressed as rates (%), and a contingency table and the chi-square test were used to compare rates. An AUC value of 1.0 was set as an ideal prognosis prediction index, whereas an AUC <0.5 has no predictive value. A Kaplan-Meier survival analysis was performed to evaluate factors affecting the prognosis of patients with ACS. Two-sided *P*-values <0.05 were considered significant.

Table 1. Sensitivity and specificity of heart-type fatty acid binding protein (H-FABP) for predicting the development to myocardial infarction in cardiac troponin T (cTnT)-negative patients with early onset acute coronary syndrome (ACS)

		Diagnosis		Total
		MI, n (%)	UA, n (%)	
H-FABP (ng/ml)	≥15.47	21 (87.5)	3 (9.67)	24
	<15.47	3 (12.5)	28 (90.33)	31
Total		24	31	55

χ^2 = 33.31, P<0.01.

Results

Blood H-FABP levels in early cTnT-negative ACS patients

The mean H-FABP level in the early cTnT-negative ACS patients at 6 h after onset of chest pain was (19.67 ± 2.56) ng/ml (range, 0.11-66.72 ng/ml). H-FABP and cTnT levels detected at 6, 12, 24, and 48 h after symptom onset are shown in **Figure 1**. Blood cTnT levels peaked at 12 h but decreased to approximately 50% at post 48 h. The H-FABP level peaked at 6 h, decreased slightly (12.82%) at post 12 h, and then decreased approximately 79% at post 48 h.

Predictive value of H-FABP for the disease progression of early cTnT-negative ACS patients

All the fifty-five patients underwent routine drug therapy (Aspirin 300 mg, clopidogrel 300 mg, Lipitor 10 mg, Betaloc 25 mg, enalapril 10 mg), and 16 of them underwent percutaneous coronary intervention. Twenty-four patients (15 non-STEMI and 9 STEMI) were diagnosed with acute MI during their hospital stay. A ROC curve analysis was used to demonstrate the value of the H-FABP level for predicting the development to MI in early cTnT-negative ACS patients. The AUC

Table 2. Relationship between development of acute myocardial infarction (MI) and major adverse cardiac events (MACE) in patients with acute coronary syndrome (ACS)

		MACE		Total
		Yes	No	
Diagnosis	MI, n (%)	8 (33.3)	16 (66.7)	24
	UA, n (%)	3 (9.7)	28 (90.3)	31
Total		11	44	55

χ^2 = 3.37, P>0.05.

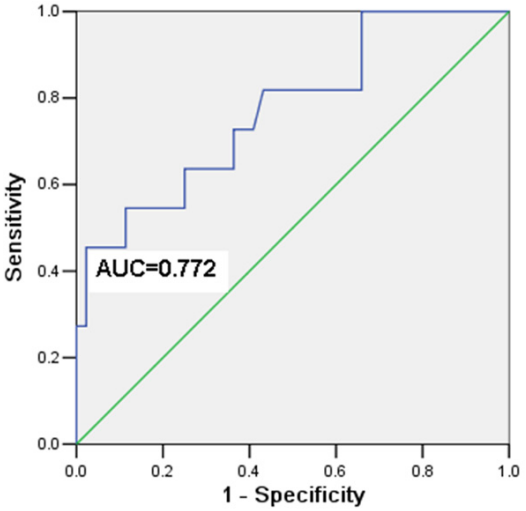

Figure 3. Receiver operating characteristic curve analysis of heart-type fatty acid binding protein (H-FABP) for predicting major adverse cardiac events (MACE) in cardiac troponin T (cTnT)-negative patients with early onset acute coronary syndrome (ACS).

was 0.946, the cutoff value was 15.47 ng/ml (**Figure 2**), sensitivity was 87.5%, and specificity was 90.33% (**Table 1**) (χ^2 = 33.31, *P*<0.01). A risk analysis showed a strong correlation between the H-FABP level and development to MI (relative risk [RR], 9.042).

Role of the H-FABP level in predicting the prognosis of early cTnT-negative ACS patients

Cardiovascular events in cTnT-negative ACS patients: All 55 patients were followed-up for 12 months, and the occurrence of major adverse cardiac events (MACE) was recorded after 12 months. MACE occurred in 11 patients, including two cardiac deaths, six nonfatal MI, and three nonfatal heart failures. The mean H-FABP level of the 11 patients at 6 h after hospital admission was 38.08 ± 8.43 ng/ml, whereas that in patients without MACE was 18.96 ± 2.85 ng/ml (*t* = 2.438, *P*<0.05).

Development of MACE in early cTnT-negative ACS patients: Among the included patients, 24 were diagnosed with acute MI during their hospital stay, and eight developed MACE (33.3%), whereas only three patients who did not suffer acute MI developed MACE (9.7%) (**Table 2**) (χ^2 = 3.37, *P* > 0.05).

Early detection of H-FABP for predicting MACE in early cTnT-negative ACS patients: An ROC curve was used to demonstrate the predictive role of H-FABP for MACE, with an AUC of 0.772 and a cutoff value of 44.71 ng/ml (**Figure 3**).

Baseline characteristics of the patients in the H-FABP high and low level groups: The baseline characteristics of the H-FABP high and low level groups are shown in **Table 3**. Significant differences in the frequency of diabetes and vascular lesions were detected between the groups, but no differences in age, sex, smoking, or high blood pressure were detected.

Analysis of the incidence of MACE in the high and low level H-FABP groups: The incidence of MACE was significantly higher in the high H-FABP level group than that in the low H-FABP level group (χ^2 = 7.73, *P*<0.01; **Table 4**) at the 12-month follow-up.

Survival analysis of patients without MACE in the high and low level H-FABP groups: As shown in **Figure 4**, the survival rate of patients without MACE was significantly higher in those who had lower h-FABP levels than those who had high levels (8.55 ± 1.08 VS. 11.23 ± 1.39, log rank = 11.441, *P* = 0.001).

Discussion

Myocardial Tn remains the most widely used marker for early diagnosis of myocardial injury because of its high sensitivity and specificity [13]. It is the "gold standard" for diagnosing acute MI but does have some disadvantages [14-16]. First, Tn can be detected 4-6 h after onset of chest pain based on the kinetic characteristics of Tn release into the myocardium necrosis region. Second, Tn is a muscle necrosis biomarker released into the bloodstream in many pathological conditions that cause tissue necrosis [17]. A series of studies has reported

Table 3. Baseline characteristics of the patients in the high and low heart-type fatty acid binding protein (H-FABP) groups

Clinic characteristics	H-FABP (ng/ml)		*P* value
	<44.71	≥44.71	
Cases, n	44	11	
Age	63.97 ± 12.65	59.90 ± 18.54	0.391
Gender, n (%)			
Male	34 (77.3)	10 (90.9)	
Female	10 (22.7)	1 (9.1)	0.312
Smoking, n (%)			
Yes	17 (38.6)	6 (54.5)	
No	27 (50.79)	5 (45.5)	0.339
Hypertension, n (%)			
Yes	28 (63.6)	5 (45.5)	
No	16 (38.29)	6 (54.5)	0.271
Diabetes, n (%)			
Yes	20 (45.5)	8 (72.7)	
No	24 (54.5)	3 (27.3)	0.032
Lesion vessels, n (%)			
Single	15 (42.8)	2 (20.0)	
Double	10 (28.6)	1 (10.0)	
Three	10 (28.6)	7 (70.0)	0.013

Table 4. Comparison of the incidence of major adverse cardiac events (MACE) in patients in the high and low heart-type fatty acid binding protein (H-FABP) level groups

H-FABP	MACE		Total
	Yes	No	
Low, n (%)	5 (11.4)	39 (88.6)	44
High, n (%)	6 (54.5)	5 (45.5)	11
Total	11	44	55

$\chi^2 = 7.73$, P<0.01.

that H-FABP confers a certain degree of sensitivity and specificity for an early diagnosis and assessment of ACS [18]. Orak [19] reported that the sensitivity and specificity of H-FABP for an early diagnosis of acute MI in 83 cases of sudden chest pain after <6 h were 98% and 71%, respectively, which were significantly higher than those of CK-MB (86% and 52%) and cTnT (77% and 20%). The AUC values for comparing the diagnostic accuracy of H-FABP, CK-MB, and cTnT levels obtained within 6 h were 0.967, 0.713, and 0.556, respectively. Figiel et al. [20] reported that H-FABP and cTnT levels can predict acute MI in patients within <3 h of chest pain, but the sensitivity and accuracy were 79% and 80 and 32% and 61%, respectively, and a similar result was seen at 4-6 h. The results suggest a higher sensitivity, specificity, and accuracy for using H-FABP to diagnose AMI in patients with <3 h chest pain, compared with CK-MB or cTnI. Thus, H-FABP can be used for determining early diagnosis and prognosis in patients with ACS.

The traditional risk score classifies cTnT-negative patients with ACS and unstable angina pectoris with low or moderate risk, and the treatment plan tends to be more conservative. However, the clinical condition of some of these patients worsened with the development of MI, recurrent angina pectoris, heart failure, and certain other life threatening events. As cTnT levels change later after myocardial injury occurs, this marker should be combined with other related myocardial markers. It is possible to detect acute myocardial necrosis using H-FABP in early stage patients with unstable angina pectoris. Ishii determined plasma concentrations of H-FABP and cTnI in 328 ACS patients onset <6 h immediately after admission to the hospital [21]. The 6-month follow-up results showed that plasma H-FABP concentrations > 9.8 g/l were independently correlated with cardiac events (RR = 8.96, *P* = 0.0004). In that study, the increase in plasma cTnI levels in patients with ACS onset ≤ 6 h was not related to cardiac events during the follow-up. Those results showed that the plasma H-FABP concentration was superior to cTnI for predicting cardiac events in patients with ACS within 6 months and can be used as an independent predictor of ACS.

In this study, we used the level of H-FABP as an early marker of myocardial injury to predict the progression and prognosis of early cTnT-negative patients with early onset ACS. Our study included 55 patients with ACS, who were negative for cTnT within 6 h after onset, with H-FABP detected at the same time. cTnT and H-FABP levels were determined after 12, 24, and 48 h, which suggested that cTnT levels increase gradually after 6 h since symptom onset, peaked at 12 h, and then decreased to approximately

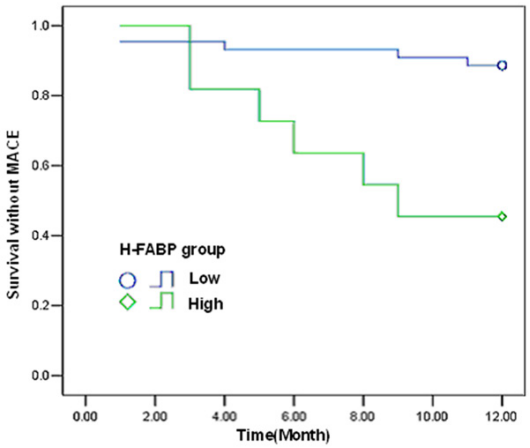

Figure 4. Survival analysis of patients without major adverse cardiac events (MACE) in the high and low level heart-type fatty acid binding protein (H-FABP) groups (log rank = 11.441, *P*<0.01).

50% after 48 h. H-FABP peaked within 6 h after symptom onset, decreased slightly at post 12 h (12.82%), and then decreased quickly by 79% of the peak level after 48 h. Twenty-four of the 55 patients developed acute MI during their hospital stay. H-FABP detected within 6 h was a good predictor for the incidence of acute MI in early cTnT-negative ACS patients. The AUC was 0.946, and the cutoff was 15.47 ng/ml, with a sensitivity of 87.5% and specificity of 90.33%.

Eleven patients developed MACE during the 12-month follow-up. Mean H-FABP levels were significantly higher in patients with MACE than in those without. As a result, the H-FABP level affected the prognosis of such patients. The AUC was 0.772, which confirmed the predictive value of H-FABP for early detection of MACE in cTnT-negative patients with ACS. The cutoff value for predicting MACE was 44.71 ng/ml and was used to determine the high and low H-FABP level groups. The low level group was at lower risk. The incidence of MACE in patients in the H-FABP high level group was 54.5%, compared with 11.4% in low level group (*P*<0.05). The survival rate of patients without MACE was significantly higher in those with lower h-FABP levels than in those with high levels. Our results are similar to those of a recent study. Viswanathan [22] evaluated 1,080 patients with a suspected diagnosis of ACS, and H-FABP and cTnT concentrations were detected 12-24 h after symptom onset. The incidence of major events (death, readmission with MI) at the 12-month follow-up was 10.1% (n = 96). Patients were divided into four groups according to their H-FABP level (<3.26, 3.27-6.48, 6.49-12.77, and > 12.7 μg/L). Risk of adverse events was significantly higher in patients with an H-FABP concentration of 6.49-12.7 μg/L, which was not associated with the cTnI level. The AUC indicating the accuracy of H-FABP to predict long-term adverse events was 0.79, whereas that for cTnI was 0.77. The predictive value of H-FABP for long-term adverse events was independent of age and creatinine levels in cTnI-negative patients, which may have affected the H-FABP concentration. CTnI-negative patients with a H-FABP concentration > 6.48 μg/L were considered high risk for long-term adverse events, such as death, re-infarction, and congestive heart failure. The risk of mortality was 2-5-fold higher during the 10 months after onset of ACS and two-fold higher during the development of congestive heart failure.

Many studies have evaluated myocardial markers for diagnosis and risk assessment of ACS, but few studies have focused on early cTnT-negative ACS patients. In this study, we confirmed H-FABP as an early predictive marker of myocardial injury and a good indicator of risk assessment and stratification. In addition, we adopted an H-FABP assay kit that could be applied easily and inexpensively in basic hospitals. However, due to our short follow-up period, further studies with more cases are needed to eliminate the effects of some confounding factors to further confirm the early risk assessment value of H-FABP in early cTnT-negative ACS patients.

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Disclosure of conflict of interest

None.

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