

## Original Research Article

# Quantitative analysis of heart type fatty acid binding protein in early detection of acute coronary syndrome

Kushal Tarapur, Adarsha Gopadi Krishna Bhat\*, Nithin Bhat, Manjunatha Handattu Hande

Department of Medicine Kasturba Medical College, MAHE, Manipal, Karnataka, India

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### \*Correspondence:

Dr. Adarsha Gopadi Krishna Bhat,  
E-mail: docadarshagk@gmail.com

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## ABSTRACT

**Background:** Coronary heart disease is a major cause of mortality, morbidity and disability in developed countries. Even though coronary heart disease mortality rates worldwide have reduced over the past five decades, coronary heart disease is the major cause of death in one-third of people more than 35 years of age. Many risk factors and biomarkers have been studied in the past and research is on in detecting the acute coronary syndrome at the earliest so that reperfusion therapy can be undertaken as early as possible to save the life of patients. Heart-type fatty acid binding protein is a newer modality of investigation developed for the above purpose.

**Methods:** Single centre cross-sectional observational study was conducted from 1 September 2017 to May 2019 with an aim to study novel cardiac biomarker h-FABP in patients with acute coronary syndrome and compare sensitivity and specificity of the same with that of troponin -T in the early detection of acute coronary events after fulfilling inclusion and exclusion criteria. The data of 80 patients were collected after getting informed consent. The clinical, demographic and investigations were performed as per the hospital protocol and such patients were recorded in the proforma. The additional test heart-type fatty acid binding protein is performed in the triage by collecting patient's serum and by using point of care analysis machine. Statistical analysis was performed using SPSS version 20.0 and results were obtained

**Results:** Out of 80 patients selected males were 35 and female are 45. Chest pain was present in 58 people, dyspnoea was in 28, sweating in 40 people, 35 had anterior wall MI, 30 had Inferior wall MI and 15 had global hypokinesia. Median values of h-FABP values were 82 ng/dl, 53.2 ng/dl, 35.3 ng/dl at 0-6 hours, 6-12 hours, and 12-24 hours respectively after the onset of symptoms with a significant  $p < 0.001$ . There were major differences between median values between different time groups of symptoms onset. Median troponin T values were 0.061 ng/ml, 0.350 ng/ml, 1.56 ng/ml after 0-6 hours, 6-12 hours and 12-24 hours of onset of symptoms respectively. There was no correlation between h-FABP and troponin-T values.

**Conclusions:** h-FABP rises early in coronary events in first 6 hrs of onset of symptoms of ACS serum levels of h-FABP decreases as time progresses in 24 hours. In comparison troponin-t levels continue to rise as time progresses. h-FABP serum levels can be used as novel marker for early detection of ACS.

**Keywords:** h-FABP, MI, Acute coronary syndrome, NSTEMI

## INTRODUCTION

Coronary heart disease is a major cause of mortality, morbidity and disability in developed countries. Even

though coronary heart disease mortality rates worldwide have reduced over the past five decades, coronary heart disease is the major cause of death in one-third of persons more than 35 years of age. According to 2018 heart

disease and stroke statistics update of the American heart association 16.5 million persons who are aged more than 20 years of age in the United States have coronary heart disease.<sup>1</sup> The lifetime risk is 35% in male and 24% in female. After achieving menopause, the incidence and severity of coronary disease increases sharply, with more than three times of those women with same age.<sup>2</sup> The diagnosis of myocardial infarction is based on the levels of cardiac biomarkers namely a rise and/or fall of troponin, and supportive evidence in the form of cardinal symptoms, electrocardiographic (ECG) changes, or imaging evidence, in the form of loss of viable myocardium or new-onset regional wall motion abnormality.<sup>3</sup> Cardiac biomarkers are the mainstay in the diagnosis of acute coronary events as definition includes disruption of normal cardiac myocyte membrane integrity resulting in the loss into the extracellular space.<sup>10</sup>

Cardiac biomarkers which are detectable in blood after myocardial injury are; troponin, creatinine kinase, myoglobin, heart-type fatty acid binding protein and lactate dehydrogenase.<sup>10</sup> Other etiologies like trauma, toxins, infection due to virus, bacteria and mismatch between oxygen demand and supply can also elevate cardiac biomarkers.<sup>11</sup> The early diagnosis and management of acute coronary events becomes a prime concern in view of this global trends of increasing mortality due to acute coronary events, especially in countries like India, where access to sophisticated coronary care facilities are limited. Various diagnostic modalities have been developed to diagnose acute coronary events early. Heart type fatty acid binding protein is a newer modality of investigation developed for the above purpose. Heart-type fatty acid-binding protein (h-FABP) is a novel marker of myocardial injury with putative advantages over cTn (cardiac troponin). Being present in abundance in the myocellular cytoplasm, it is released rapidly (<1 hour) after the onset of myocardial injury and could potentially play an important role in both earlier diagnosis of high risk patients presenting early after chest pain onset, as well as in risk-stratifying low-risk patients rapidly. Like cardiac troponin-T, h-FABP also has a potential role as a prognostic marker in other conditions where the myocardial injury occurs, such as acute congestive heart failure (CHF) and acute pulmonary embolism (PE).<sup>9</sup> There are not many studies conducted in this regard, hence this study of heart type fatty acid binding protein in early detection of acute coronary events was taken by us with following aim and objectives.

## METHODS

Cross-sectional single centred observational study was conducted from 1 September 2017 to May 2019 to estimate the level of h-FABP in patients with acute coronary syndrome at Kasturba medical college and hospital after obtaining ethical committee clearance. The study also aimed to compare the sensitivity and specificity of heart type fatty acid binding protein with

that of troponin-T in early detection of acute coronary event. In the trauma triage patients meeting the inclusion criteria selected for the study. Informed consent was taken from the patient or representatives. The clinical, demographic and investigations were performed as per the hospital protocol and such patients were recorded in the proforma. The additional test heart-type fatty acid binding protein is performed in the triage by collecting patient's serum of around 2 ml as per inclusion criteria by using point of care analysis machine. The test for novel cardiac marker, h-FABP was conducted in trauma triage using h-FABP kit by using fine care fluorescence immunoassay meter by using immunoassay principle. The range of detection is 1-120 ng/dl. The data of 80 patients was collected for statistical analysis and interpretation.

## Inclusion criteria

All patients over 18 years of age with clinical features suggestive of ACS and ECG suggestive of ACS-NSTEMI attending the emergency triage were included in the study.

## Exclusion criteria

Patients under the age of 18 years and ECG showing evidence of STEMI and chronic kidney disease, patients with malignancy, patients with autoimmune disorders, recent surgery in past 2 weeks, patients with recent history of seizures (<2 weeks), road traffic accidents (<2 week) were excluded from the study.

## Statistical analysis

Statistical analysis was performed using SPSS (statistical package for social science) version 20.0. Descriptive variables were described in terms of numbers and percentages for all categorical variables and continuous variables which are normally distributed were described in terms of mean±SD. Continuous variables which are not normally distributed were represented by using median. To compare median of continuous variables, which are not normally distributed in more than 2 groups Kruskal Wallis test was performed and Mann Whitney test was performed to compare two continuous variables which are not normally distributed.

## RESULTS

Out of total 80 patients 35 were male and 45 were females. Most of subjects in this study were in between age group of 51-70 years (Figure 1). Out of 80 patients chest pain was present in 58 (72%) patients, dyspnoea was present in 20 (31%) of patients and excessive sweating was complained by 40 (65%) patients. Duration of symptoms was varied in different patients. 40 patients presented within 6 hours of onset of symptoms, 25 patients presented between 6-12 hours and 15 patients presented after 12 hours of onset of symptoms and before

24 hours. Echocardiography showed anterior wall regional motion abnormality in most of the people followed by inferior wall changes and globally hypokinetic changes. 35 (43%) patients had anterior wall MI, 30 (37%) had patients-inferior wall MI, 15 (18%) patients had global hypokinesia. Since the data contains non continuous variables, median values of h-FABP were taken into account and Kruskal Wallis test was conducted to compare median values at different time intervals.  $p < 0.001$ , was considered significant for h-FABP test (Table 1).

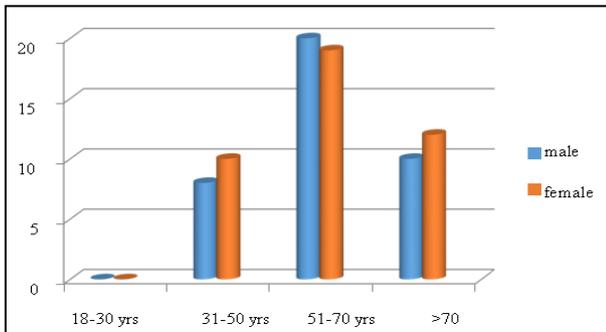


Figure 1: Age and sex distribution of patients.

Table 1: Comparison of median values (h-FABP) of subjects with different duration of symptoms onset.

Test	Onset of symptom (hours)	N	Median (range)	P value
h-FABP	0-6	40	82.0 (67.0-93.5)	<0.001
	6-12	25	53.2 (44.4-66.0)	
	12-24	15	35.3 (20.5-42.0)	

In Box Whisker plot (Figure 2), first group shows more chance of detecting ACS using h-FABP, when patient presents within 6 hours of onset of chest pain and other symptoms of ACS. The graph also depicts that as time progresses the detection of ACS using h-FABP test will decrease. Comparison between groups of different duration of symptoms of ACS using Mann-Whitney test is depicted in (Table 2). Significance difference was observed in comparison between groups;  $p < 0.001$ .

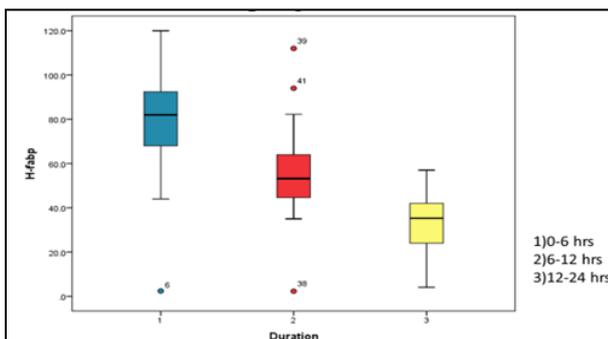


Figure 2: Box and Whisker plot for comparing h-FABP in different groups.

Log regression mean plot of h-FABP at different time duration of symptoms of ACS is shown in (Figure 3). The data analysed using mean values by log regression method, (X-axis value of h-FABP, y-axis was duration of onset of symptoms), which depicted that as duration of onset of symptoms increase, detection of ACS using h-FABP as a cardiac biomarker will be decreased. On the other hand, as duration of symptoms of ACS increase, there is more chance of detecting ACS using troponin-T as a marker (Table 3). The values were significant between different groups of onset of symptoms,  $p < 0.001$  (Table 4).

Table 2: Comparison between groups for onset of symptoms with h-FABP (Mann-Whitney test).

Test	Comparison of median between groups	P value
h-FABP	0-6 hours vs 6-12 hours	0.001
	6-12 hours vs 12-24 hours	0.002
	0-6 hours vs 12-24 hours	0.001
	82.0(67.0-93.5) vs 35.3(20.5-42.0)	

Table 3: Analysis of troponin-T at different time of onset of symptoms.

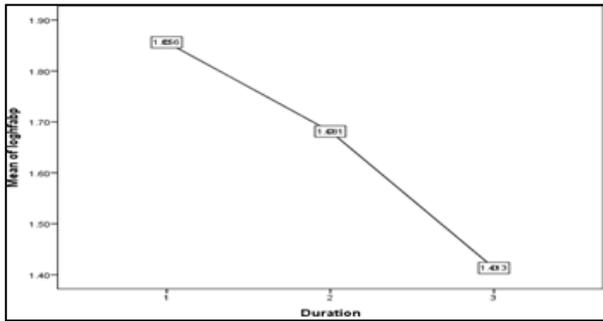
Test	Onset of symptom (hours)	N	Median (range)	P value
Troponin-T	0-6	40	0.061 (0.030-0.086)	0.001
	6-12	25	0.350 (0.272-0.731)	
	12-24	15	1.560 (0.35-2.84)	

Table 4: Comparison of troponin-T values at different time intervals of duration of symptoms using Mann Whitney test.

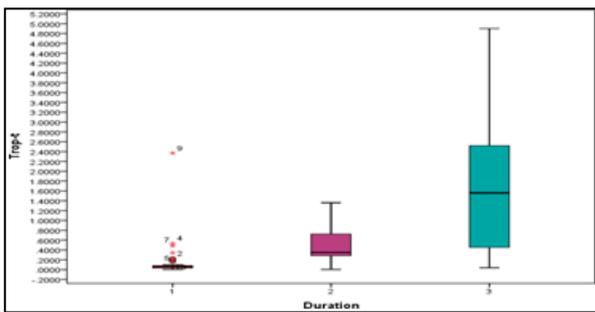
Test	Comparison of median between two sub groups	P value
Troponin-T value	0-6 hours vs 6-12 hours	0.001
	0.061 (0.030-0.086) vs 0.35 (0.27-0.73)	
	6-12 hours vs 12-24 hours	0.02
	0.35 (0.27-0.73) vs 1.56 (0.35-2.84)	
	12-24 hours vs 0-6 hours	0.001
	1.56 (0.35-2.84) vs 0.061 (0.030-0.086)	

Box and whisker plot depicting median values of troponin-T groups is depicted in (Figure 4) which shows that as duration of onset of symptoms increase, detection of ACS using troponin-T will increase. Median value of troponin-T in 40 patients in first 6 hours of symptom was

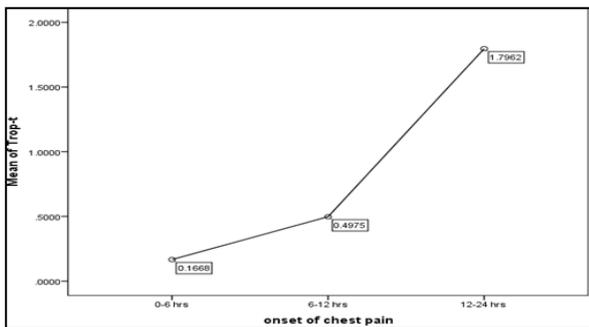
0.061 ng/ml, median value of troponin-T in 25 patients in 6-12 hours of symptom was 0.350 ng/ml and median values of troponin-T in 15 patients in 12-24 hours of symptom was 1.56 ng/ml.



**Figure 3: Log regression mean plot for h-FABP.**



**Figure 4: Box-Whisker plot showing values of troponin-T at different time intervals.**



**Figure 5: Log regression Mean plot of troponin-T.**

Troponin-T levels in different groups when compared with Mann Whitney test (Table 5), showed significant difference in troponin-T values,  $p < 0.001$ . Log regression mean plot of troponin-T (Figure 5) compared troponin-T and duration of onset of symptoms, and revealed that as duration of symptoms increase, detection of ACS using troponin-T will also increase. Spearman's correlation test showed there is no correlation between h-FABP and troponin-T.

**DISCUSSION**

In current study, a total of 80 patients were enrolled, out of which 45 were females and 35 were males. The

majority of participants belonged to the age group of 50-70 years. 35% of patients presented with dyspnoea, 58% presented with chest pain and 40% presented with sweating. 43% of patients were diagnosed with AWMI, 37% of patients had IWMI, and 18% of patients had global hypokinesia. All patients with acute myocardial infarction or acute onset global hypokinesia due to ischemia diagnosed by echocardiogram findings had elevated levels of h-FABP value. The echo findings and h-FABP were correlated. In our study, we observed that the patients who presented within the first 6 hours of onset of symptoms were having higher h-FABP values than who presented at a later time. After 6 hours, the detectability of h-FABP decreases. We found that in our study, the detectability of troponin-t in first 6 hours of onset of symptom was less, and it is greater in patients presenting after 6 hours of onset of symptom.

The study population was stratified into three different groups based on the time of presentation from the onset of symptoms. 40 patients belonged to the first group (onset of symptom; 0-6 hours), 25 patients belonged to the second group (6-12 hours) and 15 patients to the third group (12-24 hours). A comparison among the three groups, based on the duration of onset of symptoms showed a significant  $p < 0.001$  for both h-FABP and troponin-T. The h-FABP values were found to decrease as time elapsed, with a median of 82.0 ng/dl in the first group (0-6 hours), 53.2 ng/dl in the second group (6-12 hours) and 35.3 ng/dl in the third group (12-24 hours). The troponin-T values were found to increase as time progress, with a median of 0.06 ng/ml in the first group (0-6 hours), 0.35 ng/ml in the second group (6-12 hours) and 1.56 ng/ml in the third group (12-24 hours).

Vishwanathan et al conducted a case control study in Canada, which compared the troponin-T and h-FABP values.<sup>4</sup> The study included 955 subjects, out of which 452 subjects were positive for h-FABP in the first 6 hours of onset of chest pain. This study has demonstrated that the prognostic value of elevated h-FABP is supplementary to troponin-T, in low and intermediate risk patients with suspected ACS. Therefore, it can be considered as a reliable marker of myocardial ischemia, even in the absence of frank myocardial necrosis. Furthermore, this study showed that elevated h-FABP is an independent predictor of long-term outcomes among patients with suspected ACS, especially among patients with a negative troponin-T value.<sup>5</sup>

A Japanese based case control study conducted by Okomoto et al included 189 patients of chest pain and 75 normal healthy volunteers.<sup>6</sup> The overall sensitivity of h-FABP, within 12 hours after the appearance of symptoms, was 92.9%, while it was 88.6% with myoglobin and 18.6% with CKMB. The overall specificity of h-FABP was 67.3%, while it was 57.1% with myoglobin and 98.0% with CK-MB. The diagnostic efficacy rates with these markers were 86.2% (h-FABP), 80.4% (myoglobin) and 39.2% (CK-MB) respectively.

**Table 5: h-FABP in various studies of acute coronary syndrome.**

Reference number/study	N	Numbers of subjects positive for h-FABP in first 6 hours symptoms	h-FABP high in first 6 hours of symptoms	Study type
4	955	452	Positive	Case control
6	189	74	Positive	Case control
Jayadeva hospital Bengaluru 2013	53	50	Positive	Cross sectional
Manipal 2019	80	40	Positive	Cross sectional

They observed that h-FABP is more sensitive than both myoglobin and CK-MB, more specific than myoglobin for detecting AMI within 12 hours after the onset of symptoms, and shows the highest values for both diagnostic efficacy and ROC curve analysis. Thus they concluded that h-FABP has great potential as an excellent biochemical cardiac marker for the diagnosis of AMI in the early phase. 53 participants were included in a cross-sectional study conducted at Jayadeva hospital, Bangalore in 2014. The majority of patients (n=50) tested positive for h-FABP in first 4 hours of onset of chest pain.<sup>7</sup> Among the patients with a positive test result, 40 were males and 10 were females. 32 patients were diagnosed with STEMI, 14 were diagnosed with NSTEMI, 1 patient's ECG showed LBBB. In this study, the mean age of patient was 48.58±12 years, 22 patients were diagnosed to be hypertensive, and 20 patients were diagnosed with diabetes mellitus. This study concluded that h-FABP can be used as a novel cardiac biomarker in the early detection of acute coronary syndrome.

Gururajan et al in their study on 485 patients with chest pain showed h-FABP to be a good discriminator between patients with ischaemic heart disease and patients without ischaemic heart disease.<sup>12</sup> The levels of H-FABP were significantly raised in patients when compared to controls and non cardiac chest pain. Meta-analysis by Lippi et al showed combination of h-FABP with a conventional troponin immunoassay seems advantageous for increasing the sensitivity of the former biomarker, at the expense of a lower specificity.<sup>8</sup> The introduction of h-FABP testing would hence require careful assessment of laboratory data or clinical signs and symptoms for excluding sources of elevation different from acute myocardial infarction. They concluded that further studies are needed to assess the diagnostic effectiveness of combining h-FABP with a high-sensitivity troponin immunoassay. Summary of various studies involving the novel cardiac marker h-FABP is depicted in (Table 5).

#### Limitations

Limitations of current study included absence of normal control group for documenting normal range of h-FABP in study population. Actual magnitude of rise of h-FABP was not assessed. Further study has to be conducted on large sample size to arrive at definitive opinion. Patients

with ST segment elevated myocardial infarction were not included in current study.

#### CONCLUSION

In current study it was found that h-FABP rises early in coronary events in first 6 hours of onset of symptoms. Serum levels of h-FABP decreases as time progresses in 24 hours. In comparison, troponin-T levels continue to rise as time progresses. Thus h-FABP serum levels can be used as novel marker for early detection of ACS.

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