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HEART-TYPE FATTY ACID-BINDING PROTEIN (H-FABP) AS A NOVEL BIOMARKER FOR THE EARLY DIAGNOSIS OF ACUTE MYOCARDIAL INFARCTION IN COMPARISON WITH CARDIAC TROPONIN T

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ABSTRACT: BACKGROUND AND OBJECTIVE: At very early stages of acute myocardial infarction (AMI), highly sensitive biomarkers are still lacking. Human heart-type fatty acid-binding protein (H-FABP) has a high potential as an early marker for acute myocardial infarction (AMI) being more sensitive than current routine cardiac markers. The objective of this study is to determine the efficacy of a newly developed qualitative test to measure Heart-type fatty acid-binding protein (H-FABP) levels in the blood for the early diagnosis of acute myocardial infarction (AMI) in patients with chest pain and compared with cardiac Troponin T.
DESIGN: Prospective study. **METHODS:** Fifty patients with acute ischemic-type chest pain were prospectively enrolled and classified according to the American Heart Association/American College of Cardiology guidelines. An initial blood sample was obtained for H-FABP, cTnT, and CK-MB (first 4 hours of symptoms). After 4 hours (4 - 12 hours), repeat samples of H-FABP, cTnT, and CK-MB were obtained. **RESULTS:** Fifty patients presenting to hospital with a median symptom onset of 3.3 hrs (IQR 2-6 h) were enrolled in this study and 38 (76%) had AMI. At presentation, H-FABP gave the highest sensitivity of 77% (95% CI: 60.7-88.9) and specificity of 91% (95% CI: 58.7-99.8) and troponin T (cTnT) gave the highest specificity of 100% (95% CI: 69.2–100). This study demonstrated that H-FABP immunotest gave a better diagnostic classification at the early stage. Also, AMI was identified significantly earlier by H-FABP than cTnT (29 vs. 8 patients, p<0.05). **CONCLUSIONS:** Assessment of Heart-type fatty acid-binding protein (H-FABP) within the first 4 h of symptoms is superior to cTnT for detection of AMI, and is a useful additional biomarker for patients with acute ischemic chest pain.
KEY WORDS: Heart-Type Fatty Acid-Binding Protein; Troponin T; Acute Myocardial Infarction; Biomarkers.

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INTRODUCTION: In patients presenting with ischemic-type chest pain, the early establishment of a definite final diagnosis of acute myocardial infarction (AMI) is crucial for treatment in the emergency department ("timely diagnosis"). For a rapid and accurate diagnosis, the indicators of early coronary pathophysiologic events (i.e., the time of plaque rupture before complete coronary occlusion) are crucial ("early diagnosis"). The ideal biomarker for myocardial ischemia would therefore be indicative early in the cascade of events and allow a prompt diagnosis, aiding therapeutic decisions in the clinical setting[1]. According to the American Heart Association/ American College of Cardiology ST-elevation myocardial infarction (STEMI) and non-STEMI (non-STEMI) guidelines of myocardial infarction, a positive serum level of cardiac troponin is a constituent part of the final diagnosis[2]. However, because of its large molecular size, cardiac troponin T (cTnT) does not peak until approximately 6 to 12 hours after the onset of symptoms[3]. In addition, the electrocardiogram has only 50% sensitivity in the diagnosis of AMI[4-5].

Heart-type fatty acid-binding protein (H-FABP), a low molecular mass cytoplasmic protein (15 kD) abundant in heart muscle cells, has a high potential as a sensitive biomarker for early diagnosis of AMI[6-8]. H-FABP levels rise as early as 1-3 h after the onset of AMI, peak at 6-8 h, and return to normal within 24-30 h.

A one-step H-FABP immunochromatographic test so-called QuickSens® designed to detect H-FABP in whole blood samples is now commercially available[9-11]. The test result is available within 15 min after addition of blood samples. It requires no sample pretreatment and thus can be applied in emergency situation. Combined with the well-established markers, troponins, it may allow more accurate targeting of appropriate therapy and considerable cost savings than the current diagnostic tests. The aim of the present study was to evaluate the diagnostic performance of the H-FABP immunotest in patients suspected with myocardial infarction compared to cardiac troponin T (cTnT) and CK-MB.

METHODS: STUDY POPULATION AND SAMPLE COLLECTION:

The study took place between December 2010 to March 2011 at Sri Jayadeva Institute of Cardiovascular Sciences and Research Hospital, Bangalore, India. Patients presenting to the Emergency Department (ED) were screened for entry criteria: acute ischemic chest pain within the last 4 h, age >18 years. The exclusion criteria were, patients presented after four hours of symptom onset, the inability or unwillingness to give informed consent, age <18 years, and interhospital transfer, the renal insufficiency or any renal disease impairing renal clearance, Patients who underwent percutaneous transluminal coronary angioplasty or coronary artery bypass grafting within 30 days; had prior AMI within 30 days; had chronic muscle disease, pulmonary thromboembolism or pericarditis were also excluded. A total of 54 patients met these entry criteria, of whom 50 were included; the reasons for exclusion are listed in Fig. 1.

The clinical parameters assessed included history of cardiac events, physical examination, a recording of a 12-lead ECG, type and duration of symptoms, arteriosclerotic risk factors, and presence of renal impairment (with an estimated glomerular filtration rate of <30 ml/min). The time of onset of symptoms was carefully recorded for each patient at presentation. Two blood samples, one at 0 hour (at presentation) and after 4 hours (4-12 hours) of presentation were taken for H-FABP, cTnT & CK-MB measurement.

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LABORATORY ANALYSIS:

1. H-FABP Immunotest: A rapid chromatographic immunoassay designed for qualitative determination of H-FABP in blood samples was performed with a cut-off level of 10 ng/L (QuickSens®, 8sens.biognostic GmbH, Berlin, Germany). The test is based on a dual monoclonal antibody sandwich method, using two distinct monoclonal antibodies and the gold labeled method and requires 100–120 μL of blood sample and the result was interpreted within 15 min after sample application. Tests were judged to be positive or negative; invalid tests without control lines were repeated immediately.

2. Troponin T: The serum cTnT levels were measured quantitatively using the Elecsys-2010 troponin T immunoassay (Troponin T STAT (Short Term Around Time)) (Roche/Hitachi analyzer). The upper reference limit (ninety-ninth percentile) is 0.01 ng/L and the lowest concentration with a coefficient of variation of ≤10% was 0.03 ng/L.

3. CK-MB (Creatine Kinase-MB): CK-MB (Creatine Kinase-MB liquid) were measured quantitatively using the 912 Roche/Hitachi analyzer, lower limits of measurement 3 U/L, reference value 7-25 U/L, for MI >24 U/L.

ECG ANALYSIS: The initial 12-lead electrocardiograms of all patients. ST elevations ≥1 and ≥ 2 mm (at the J point) were noted. ST depression ≥0.5 mm at 80 ms after the J point and T inversion of ≥1.0 mm at the nadir were classified. Q waves were recorded if ≥0.03 s and ≥25% of the following R. The presence of left bundle branch block was noted separately.

FINAL DIAGNOSIS:

1. AMI: AMI was diagnosed when either the cTnT serum levels at admission or at 12 hours were >0.03 ng/ml, irrespective of the presence of ischemic features on the electrocardiogram in the absence of any other cause for the chest pain[12]. In the absence of cTnT levels at 12 hours, a typical increase and decrease in creatinine kinase levels of more than twice the upper level of normal at 24 hours also confirmed the final diagnosis of AMI (type 1 or 2)[2]. When this definition was met, we then further classified cases as STEMI and non-STEMI according to the electrocardiographic features. STEMI was diagnosed when ST elevation was found in 2 contiguous leads of >1 mV in leads I to III, aVL, aVF, V5 to V6, and ≥2 mV in V1 to V3. Classification of non-STEMI was by exclusion of STEMI.

2. UNSTABLE ANGINA: UA was diagnosed when the history and/or electrocardiographic changes were consistent with an acute coronary syndrome but cTnT negative at 12 hours and/or no typical increase and decrease in creatinine kinase levels at 24 hours. The history parameters included previous myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting. The electrocardiographic parameters included significant ischemic changes on the admission electrocardiogram (ST depression ≥0.5 mV, T inversion ≥1 mV) or evidence of coronary artery disease during the index hospital stay (positive coronary angiographic findings, positive stress test).Uninterpretable electrocardiographic tracings (pacemaker, left bundle branch block) did not contribute to the diagnosis of unstable angina but required a positive history of coronary artery disease and/or evidence of coronary artery disease with additional testing.

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3. NONISCHEMIC CHEST PAIN: Nonischemic chest pain was diagnosed by the exclusion of AMI and unstable angina.

STATISTICAL ANALYSIS: Data are presented as medians, interquartile ranges (IQR), means±standard deviation (SD) or 95% confidence intervals (95% CI). Diagnostic test criteria including sensitivity, specificity, negative and positive predictive values, and likelihood ratios were calculated by using MedCalc, version 7.0 (MedCalc Software, Mariakerke, Belgium). McNemar test was used to assess whether H-FABP or cTnI was positive earlier. The level of significance was set at $p < 0.05$

RESULTS AND DISCUSSION: Between December 2010 and March 2011, a total of 50 patients were enrolled out of 54 patients meeting the entry criteria (Fig. 1). Mean age was 48.58±12 years and 40 (80%) were male. Median time from symptom onset to first blood sample was 3.3 hrs (IQR 2-6 h). 22 patients (44%) had hypertension, 20 (40%) had diabetes, none had chronic renal failure (CRF), and there was no deaths during their hospital stay. Acute myocardial infarction was diagnosed in 38 (76%) individuals, of whom 34 (68%) had STEMI and 4 (8%) had NSTEMI. The non-AMI group consisted of 12 patients with a final diagnosis of hypertension, stable angina, pneumonia, paroxysmal ventricular tachycardia, reflux oesophagitis, and Gastric ulcer.

DIAGNOSTIC PERFORMANCE OF H-FABP IMMUNOTEST: The sensitivity and specificity of H-FABP at presentation (≤4 hrs) and after 4 hrs were 77% and 91%, 82% & 91% respectively. There were no differences in terms of age, gender, history, risk factors or ECG features in terms of h-FABP performance. However early presenter were very less likely to have sensitive initial cTnT test.

COMPARISON OF H-FABP AND CTNI: The sensitivity of cTnT at presentation was lowest (20%) when the symptom duration was <4 hours and increased to 95% when the symptom duration was >4 hours. The sensitivity of H-FABP for AMI was superior to cTnT for patients admitted within 4 hours of symptom onset. The sensitivity of H-FABP was greatest at 2 to 4 hours after symptom onset and decreased after >8 hours. In contrast, cTnT maintained a sensitivity of 95% at later points. The improvement in sensitivity of cTnT for AMI could be maintained at later points. The specificity of H-FABP, however was significantly lower than cTnT in all subgroups and for all periods. In 8 patients both H-FABP and cTnI were positive, H-FABP was positive earlier than cTnI in 29 patients. In this study, we demonstrated that H-FABP was positive significantly earlier than cTnI. All the patients presented to hospital within 4 hrs after symptom onset, when H-FABP might already be detectable, but not cTnI.

SENSITIVITIES, SPECIFICITIES AND PREDICTIVE VALUES FOR DIFFERENT CARDIAC MARKERS: The sensitivities and specificities of different cardiac markers are listed in Table 3. H-FABP gave the highest sensitivity (77%) for early exclusion of non-AMI patients, whereas cTnI gave the highest specificity (100%) for inclusion of AMI patients. The respective sensitivities of H-FABP, cTnT and CK-MB were 77%, 20%, and 10% ($p < 0.05$) for patients presenting within 4 hours and for >4 hours were 82%, 95%, 75% respectively. The respective specificities were 91%, 100%, 100%, ($p < 0.05$) for within 4hours and > 4 hours(4-12).

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CORONARY ANGIOGRAPHY & REVASCULARIZATION: Among 38 patients of AMI, 32 undergone coronary angiogram out of this, 23 patients had single vessel disease(SVD), 30 patients had DVD, 5 had TVD, 1 patients had normal coronaries & 20 patients had undergone PTCA(10 LAD, 8 RCA, 2 LCX) 4 had Coronary Artery Bypass Graft (CABG) surgery & 14 patients were medical managed.

RECEIVER OPERATOR CHARACTERISTIC CURVES FOR DIFFERENT CARDIAC MARKERS:
The areas under the receiver operator characteristic (ROC) curves to distinguish AMI from non-AMI within 4 hrs after the onset of symptoms were 0.83±0.05 (95% CI: 0.70– 0.92) for H-FABP, 0.55±0.02 (0.40–0.69) for CK-MB, and 0.60±0.03 (95% CI: 0.45–0.73) for cTnI. The area under the curve for H-FABP was significantly greater than those of the other cardiac markers within 4 hrs after the onset of symptoms. Thus, H-FABP has great potential as an excellent cardiac marker for diagnosis of AMI in the early phase.

DISCUSSION: The use of biomarkers aids in the process of diagnosing myocardial infarction in the emergency department and helps in risk stratification of patients, allowing appropriate treatment to be given, and has proved superior to electrocardiographic guidance alone[1]. Cardiac troponins have revolutionized in decision making and led to a redefinition of myocardial infarction in 2000[12] that included elevated troponins as an obligatory diagnostic criterion. With respect to revascularization, the period for optimal treatment is within the first 4 hours after the onset of plaque rupture. However, a number of studies have reported a low sensitivity of cardiac troponins in the first 6 to 12 hours[3, 12-14]. The data of the present study have confirmed the early sensitivity issue of cTnT.

In a number of studies, H-FABP has been reported to be particularly sensitive within the first few hours after the onset of coronary occlusion and symptoms[15-20]. The reason for this high sensitivity has been explained by its small molecular weight (15 kDa) and its cytoplasmic unbound abundance, resulting in rapid release from damaged myocardial cells[6]. A high sensitivity early in myocardial infarction has been noted in several, mainly selected, study population groups, demonstrating a promising potential role of H-FABP as a decision tool in the early diagnosis of myocardial infarction[21-24]. The release characteristics of H-FABP after occlusive AMI showed elevated serum concentrations 30 to 90 minutes after the onset of symptoms, with peak levels reached at 4 to 6 hours, and normalization of serum levels to baseline levels owing to rapid renal clearance within 20 hours. The data of the present study support the idea that H-FABP is a sensitive marker in the first 4 hours after symptom onset. Given the relatively high prevalence of AMI in the study population, high sensitivity translated into high negative predictive values for H-FABP, suggesting a possible use of this marker, especially for the early rule out of AMI.

The low H-FABP specificity of (90%) compare with cTnT(100%) may be attributed to numerous factors first, renal insufficiency however present study there were no renal failure patients. Second, H-FABP can be released from ischemic myocardium, as well as from infracted myocardium[6].

Third, H-FABP release of noncardiac origin might play a role in patients with acute chest pain and H-FABP is also present in the skeletal muscle and other tissues at low concentrations[6,24], although relative cardiospecificity is generally reported to be much greater than for myoglobin or creatinine kinase-MB. No study data on recent physical activity, injury, noncardiac surgery, or intramuscular injections were collected to address this issue.

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Patients with AMI presented with a symptom duration of <4 hours, H-FABP performed significantly better than cTnT as a marker to differentiate between acute STEMI and non-AMI conditions. When analyzing patients with non-STEMI, however, we found that H-FABP performed particularly poorly, irrespective of symptom duration. Because non-STEMI is a diagnostic model reflecting a thrombembolic, often repetitive, microvascular occlusion from an upstream thrombus-laden ruptured plaque, misclassification by H-FABP testing could be attributed to the small amounts of H-FABP being rapidly cleared from serum in contrast to the large molecular cTnT, which cumulates to finally maintain elevated serum levels. A gain in sensitivity of a rapid-release biomarker in the early phase of STEMI could be explained if the affected myocardial mass is large enough. Confining electrocardiographic interpretation to discriminating normal from abnormal initial electrocardiographic tracings, H-FABP proved a usable predictor of AMI in cTnT-negative patients with abnormal electrocardiographic findings and early presentation within the first 4 hours after symptom onset.

LIMITATIONS:

1) The sample size of the total study population was too small to allow for a generalization of the results. However, the study results are in accordance with the reported test characteristics of H-FABP[25-26], and the investigation was aimed at testing the potential role of H-FABP in early risk stratification of acute ischemic-type of chest pain in the clinical setting of a real world emergency department.
2) This study only studied the potential benefit from a twice measurement of H-FABP at admission and after 4 hrs, sequential measurements were not performed.
3) A multimarker approach (including biomarkers of concomitant cardiac conditions, such as proBNP, myoglobin) was not taken, which could have further elucidated the false-positive rate in H-FABP testing. However, the present study was designed with cTnT and CK-MB as the comparator, and priority was given to determine whether H-FABP added significant information to aid in the clinical assessment of patients with acute ischemic type of chest pain.

CONCLUSION: In this study, we aimed to evaluate the accuracy of HFABP in a point-of-care setting for early diagnosis of myocardial damage in patients presenting to the ED suspected of AMI. For patients presenting within 4 h of symptom onset the sensitivity of H-FABP is significantly higher than cTnT. H-FABP could not by itself diagnose AMI with adequately high accuracy, but when positive, it was usually faster than cTnT. In order to decrease the risk of falsely excluded patients with ongoing AMI, a combined measurement of two biochemical markers, an early one such as HFABP and a later marker such as troponins may provide the optimum diagnostic performance.

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Table-1. Baseline, Clinical, electrocardiographic, and biomarker characteristics at initial presentation

	All patients n=50	AMI n=38(76%)	No AMI n=12(24%)	P value
Age (mean yrs ± SD)	48.58 ± 12	49.52 ± 10	48.62 ± 14	NS
Male	40(80%)	33(86.8)	7(58.3)	NS
Female	10(20%)	5(13.2)	5(41.7)	NS
Pain to admission (hrs) median 95CI	3.3hrs(2-6)	2.3hrs(1.8-5)	4hrs(3-7)	NS
Previous history				
a) AMI	06(12%)	05(10%)	01(2%)	NS
b) PCI	02(4%)	01(2%)	01(2%)	NS
c) CABG	00	00	00	----
d) ANGINA	02(4%)	00	02(4%)	NS
Renal failure	00	00	00	---
Riskfactor				
a) DM	20(40%)	16(32%)	04(8%)	NS
b) HTN	22(44%)	18(36%)	04(8%)	NS
c) Smoker	28(56%)	22(44%)	06(12%)	NS
d) Ex-smoker	04(8%)	02(4%)	02(4%)	NS
e) High cholesterol	32(64%)	28(56%)	04(8%)	NS
f) FHx of IHD	04(8%)	02(4%)	02(4%)	NS
Admission				
a) HR	72.9 ± 17.1	75.56 ± 17.9	77.0±16.35	NS
b) Systolic BP	136.4 ± 25	133.2 ± 34.26	134.67±10.49	0.024
c) Diastolic BP	71 ± 16.8	71.44 ± 18.44	79.0±13.99	NS
d) Typical chest pain	40	36	08	NS
e) Atypical chest pain	10	02	04	NS
ECG-initial findings				
a) ST elevation	32(64%)	32(84.2%)	00	----
b) ST depression / T inversion	14(28%)	04(10.52%)	08(66.6%)	----
c) LBBB	01(2%)	01(2.63%)	00	----
d) Normal	02(4%)	00	04 (33.3%)	----
e) Arrhythmia	01(2%)	01(2.63%)	00	----
Initial biomarkers				
a) H-FABP +	30(60%)	29(76%)	01 (8.3%)	<0.001
b) cTnT +	08(16%)	08(21%)	00	<0.001
c) CK-MB +	04(8%)	04(10.5%)	00	<0.001

AMI: acute myocardial infarction; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention.

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Table - 2.Management and final treatment of patients with acute chest pain

	All patients (n=50; 100%)	AMI (n=38; 76%)	No AMI (n=12; 24%)	P value
Acute management				
a) In-patient	44(88%)	38(100%)	06(50%)	0.05
b) ICU-2	29(58%)	29(76.3%)	00	<0.05
c) ICU-3	15(30%)	09(23.6%)	06(50%)	<0.05
Coronary angiography	35(70%)	32(84%)	03(25%)	NS
a) Interval to Catheterization (hrs) (median,95 %CI)	36hrs (17.6-62.3)	24hrs (15.4-58.3)	52hrs (19.6-78.5)	NS
b) Normal coronaries	02(5.7%)	01(3%)	01(33%)	NS
c) SVD	24(68.5%)	23(72%)	01(33%)	NS
d) DVD	04(11.4%)	03(9.3%)	01(33%)	NS
e) TVD	05(14.2%)	05(15.6%)	00	NS
Revascularization/treatment				
a) PCI	22(44%)	20(5.2%)	02(16.6%)	<0.05
b) CABG	04(8%)	04(10.5%)	00	NS
c) Conservative	24(48%)	14	10(83.3%)	<0.05

ICU = Intensive care unit admission for thrombolysis, circulatory or respiratory stabilization.

Table-3. Sensitivities, specificities, likelihood values and predictive values of different cardiac markers for diagnosis of AMI.

	H-FABP		Troponin T		CK-MB	
	On admission ≤ 4 hrs	After 4 hrs (4-12h)	On admission ≤ 4 hrs	After 4 hrs (4-12h)	On admission ≤ 4 hrs	After 4 hrs (4-12h)
Sensitivity [%] (95% CI)	76.92 (60.7-88.9)	82.05 (66.5-92.5)	20 (9.1-35.6)	95 (83.1-99.4)	10 (2.8-23.7)	75 (58.8-87.3)
Specificity [%](95% CI)	90.91 (58.7-99.8)	90.91 (58.7-99.8)	100 (69.2-100)	100 (69.2-100)	100 (69.2-100)	100 (69.2-100)
Positive predictive value[%]	96.8	97	100	100	100	100
negative predictive value[%]	52.63	58.82	23.8	83.3	21.7	50
LR[+]	8.46	9.03	1.0	1.0	1.0	1.0
LR[-]	0.25	0.2	0.8	0.05	0.9	0.25

ORIGINAL ARTICLE

Table-4. Area under receiver operating characteristic curves (z-statistic)

Biomarker	Patients admitted ≤ 4 hrs from symptom onset				Patients admitted ≥ 4 hrs from symptom onset			
	AUC ± SE	Z statistic	95% CI	P value	AUC ± SE	Z statistic	95% CI	P value
H-FABP	0.83±0.05	5.96	0.70-0.92	<0.0001	0.86±0.05	6.62	0.73-0.94	<0.0001
cTnT	0.60±0.03	3.12	0.45-0.73	0.0018	0.97±0.01	27.22	0.88-0.99	<0.0001
CK-MB	0.55±0.02	2.08	0.40-0.69	0.0374	0.87±0.03	10.81	0.75-0.95	<0.0001
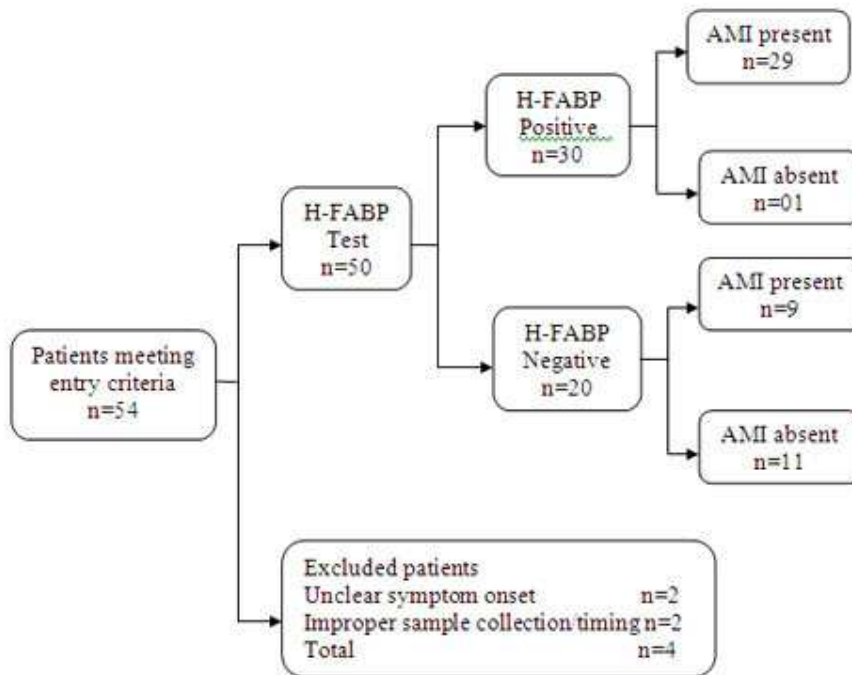
Fig-1. Flow chart of study population at initial presentation