Original Article

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Role of Clinical Evaluation of Ischaemia Modified Albumin in Diagnosis of Acute Coronary Syndrome: Unstable Angina to Myocardial Infarction

Biochemistry Section

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ABSTRACT

Introduction: Acute Coronary Syndrome (ACS) includes a spectrum of disorders ranging from unstable angina to myocardial infarction. Since, ACS is an important cause of mortality in the world, early diagnosis of the disease is very important. Ischaemia Modified Albumin (IMA) is an ischaemia biomarker that has been approved by the US Food and Drug administration and has clinical application. Although, many studies have been done on IMA as a biomarker in ACS patients, role of IMA for differentiating patients with unstable angina, Non ST-Segment Elevation Myocardial Infarction (NSTEMI) and ST-Segment Elevation Myocardial Infarction (STEMI) requires further study.

Aim: To assess the diagnostic role of IMA in ACS patients and evaluate correlation between IMA and necrotic biomarkers such as cardiac Troponin I (cTnI) and Creatine kinase-myoglobin binding (CKmb) in ACS patients.

Materials and Methods: The study included 75 subjects with ACS, who were divided into three groups of 25 patients each: Unstable angina, NSTEMI and Myocardial Infarction (MI) and 25 healthy people as control. They were enrolled into the study from the Fatemeh Zahra Heart Center, Sari, Iran, between November 2015 and October 2016. IMA was measured by the Cobalt-Albumin Binding (CAB) assay, cTnI was measured by rapid immunoassay and CKmb was estimated utilising colorometric enzyme method by commercial kits. The correlation between IMA and necrotic biomarkers was determined using a Pearson correlation analysis. Receiver Operator Characteristic (ROC) curve was used to assess role of IMA in diagnosis of ACS.

Results: IMA levels in unstable angina patients were significantly higher than NSTEMI and MI ($p<0.001$). While there was no significant difference in IMA levels between NSTEMI and MI ($p=0.675$). Bivariate correlation analyses were performed to assess for any relationship between IMA levels and two common cardiac biomarkers ($p>0.5$, $r=0.25$). The area under the ROC curve of IMA for ACS patients was 0.783. The sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of IMA was 74.7%, 72%, 88.9% and 48.6% respectively.

Conclusion: IMA is a useful biomarker in diagnosis of ACS especially unstable angina patients and there is no significant correlation between IMA and necrotic biomarkers (cTnI and CKmb) in ACS patients.

Keywords: Creatine kinase myoglobin binding, Cardiac troponin I, Cobalt-albumin binding assay

INTRODUCTION

According to the heart disease and stroke statistics-2016 Update, One of every seven deaths occurred in the United States in 2013 due to Coronary Heart Disease (CHD). The prevalence of new and regressive coronary attack is estimated 6,60,000 and 3,05,000 Americans yearly [1].

ACS which can be considered as a subset of CHD, is a term that refers to a set of clinical symptoms indicative of myocardial ischaemia and encompasses a spectrum of conditions which include unstable angina, NSTEMI and STEMI [2-4].

Most cases of ACS are due to rupture of an atherosclerotic plaque in a coronary artery and lead to formation of a thrombus [5]. In majority of patients with ACS including unstable angina and NSTEMI, thrombus causes partial and intermittent obstruction. On contrary complete occlusion of the coronary artery is the main cause of STEMI [6].

Unstable angina and NSTEMI have similar clinical presentations and pathophysiologic origins and also differ in severity and necrotic biomarker releasing changes [3]. This means that NSTEMI is severe enough to cause myocardial damage and release CKmb and cTnI [3,7].

Clinical presentation, electrocardiogram and biochemical markers are important components for the diagnosis of ACS. Most conventional biomarkers such as CKmb, and cTnI are indicative of cell necrosis [8]. Finding a biomarker that increases before necrosis can be highly effective in early diagnosis of ACS [9].

IMA which is a form of human serum albumin was introduced as a potential biomarker of myocardial ischaemia by US Food and Drug administration [10]. In the ischaemic condition, the N-terminal sequence of human albumin (NH_2-Asp-Ala-His-Lys) undergoes transient modifications by free radicals, these modifications lead to a reduced metal binding capacity for cobalt in comparison to non ischaemic normal controls, hence concentration of IMA increases [11-14].

The present study was aimed to determine the correlation between IMA with CKmb and cTnI in ACS patients and compare usefulness of this biomarker for the diagnosis of unstable angina, NSTEMI and MI subjects.

MATERIALS AND METHODS

The present non interventional case control study was conducted at the Department of Clinical Biochemistry in collaboration with Department of Cardiology in Mazandaran University of Medical Sciences, Sari, Iran. Ethical approval to carry out this study was given by the Research Ethics Committee of Mazandaran University of Medical Science, Iran.

Patient Selection

A total of 75 ACS patients with age group of 30 to 80 years including 41 male and 34 female, were taken up for the study. ACS patients were diagnosed by cardiologists on the basis of history, physical examination, chest pain duration, ECG changes and cardiac biomarkers (CKmb and cTnI).

The ACS patients were divided into three groups including unstable angina (25 subjects), NSTEMI (25 subjects) and STEMI (25 subjects), by physicians according to American College of Cardiology/American Heart Association (ACC/AHA) guideline for the management of patients with ACS [15]. Twenty five subjects as control group with age and sex matched individuals, normal ECGs and without any malignant or cardiac disease were also enrolled in the study. Patients and control groups gave the informed consent before the study.

Exclusion Criteria

Patients with renal, hepatic and infectious disease, diabetes mellitus, stroke and cirrhosis were excluded from the study.

Sampling

On admission, 5 mL blood was collected from the patients using standard aseptic techniques. The samples were centrifuged and serum was separated for measuring IMA, cTnI and CKmb. The cTnI was measured by rapid immunoassay (Immunochromatography) method using a kit from Nano-check TM AMI cardiac test. A cTnI>0.5 ng/mL was considered as positive value. CKmb was measured by a colorimetric enzyme assay (Pars Azmoon Kit) on a Hitachi autoanalyser. Remaining part of the sample was kept at -70°C for assay of IMA.

Laboratory Measurements

Ischaemia modified albumin was measured by the CAB assay [16]. Briefly, 3 µL $CoCl_2$ and 40 µL sample were added to 131.8 µL KH_2PO_4 as a buffer solution. After 10 minutes incubation at room temperature, 5.2 µL Dithiotritol (DTT) was added. Finally, 20 µL 9% NaCl was added. The absorbance was measured at 470 nm and reported by Absorbance Unit (ABSU) parameter.

STATISTICAL ANALYSIS

The statistical analysis was executed using SPSS version 19.0. Student's t-test was applied for comparison of means of ACS and control groups and one-way ANOVA test was performed between three groups of ACS. The correlations among IMA and cardiac biomarkers were evaluated in ACS patients using a Pearson correlation analysis. ROC curve analysis was performed and the optimal cut off for the IMA was selected. The sensitivity and specificity of IMA were assessed by ROC curve. All the data was expressed as mean±standard deviation and a two-tailed p-value <0.05 was considered to be statistically significant.

RESULTS

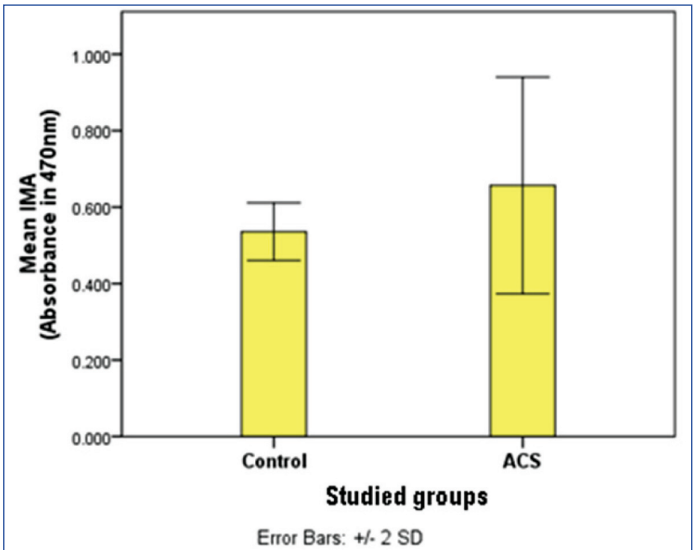
Baseline demographic and clinical characteristics of study population are shown in [Table/Fig-1].

As shown in [Table/Fig-1], cTnI levels (p<0.001) and CKmb levels (p<0.001) were elevated in ACS group compared to control group. IMA levels in ACS patients were significantly higher than controls (p<0.001) [Table/Fig-2]. Furthermore, IMA levels were significantly higher in patients with unstable angina compared with NSTEMI and MI (p<0.001) but there was no significant difference between NSTEMI and MI (p=0.675) [Table/Fig-3].

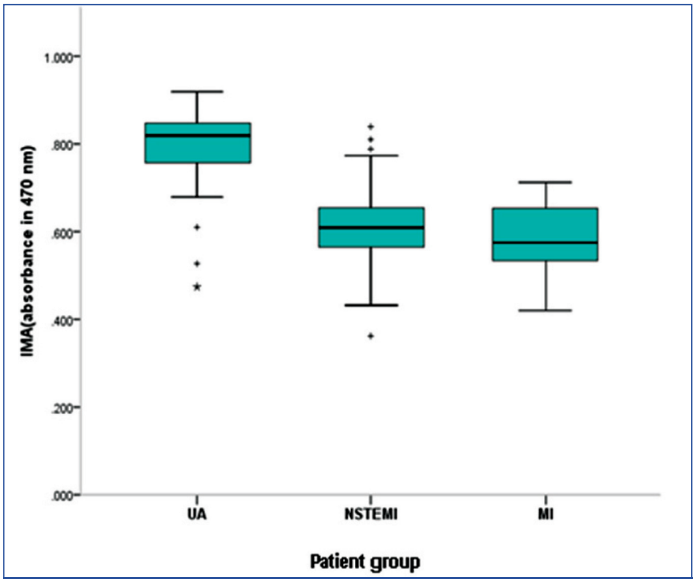
Bivariate correlation analyses were performed to assess for any relationship between IMA levels and two common cardiac biomarkers, cTnI and CKmb in ACS group. There was no positive or negative correlation between the levels of IMA and common cardiac biomarkers in unstable angina, NSTEMI and MI groups (p>0.05). The area under ROC curve for diagnostic ACS based on IMA levels was 0.783 (95% CI, 0.696-0.869, p<0.001). Separate entity wise ROC curve analysis for UA, NSTEMI and MI is also presented in [Table/Fig-4]. IMA levels >0.556 ABSU yielded a sensitivity of 74.7% and a specificity of 72%, a PPV of 88.9% and a NPV of 48.6% for the diagnosis of ACS.

Variable	ACS (n=75)			Control (n=25)	p-value
	UA (n=25)	NSTEMI (n=25)	MI (n=25)		
Age (years)	63.32±13.41	64.36±14.53	58.24±14.74	61.92±10.41	-
Gender (M/F)	F:11 M:14	F:15 M:10	F:8 M:17	F:12 M:13	-
cTnL (ng/mL)	0.652±0.404	21.87±15.9	40.85±24.80	0.257±0.093	p<0.001* p<0.001** p=0.01***
CKmb (U/L)	20.64±2.71	34.96±27.69	114.36±114.66	20.24±4.03	p<0.05* p<0.001** p<0.001***
IMA (ABSU)	0.874±0.111	0.609±0.119	0.575±0.086	0.535±0.037	p<0.001* p<0.001** p=0.675*** p<0.05****

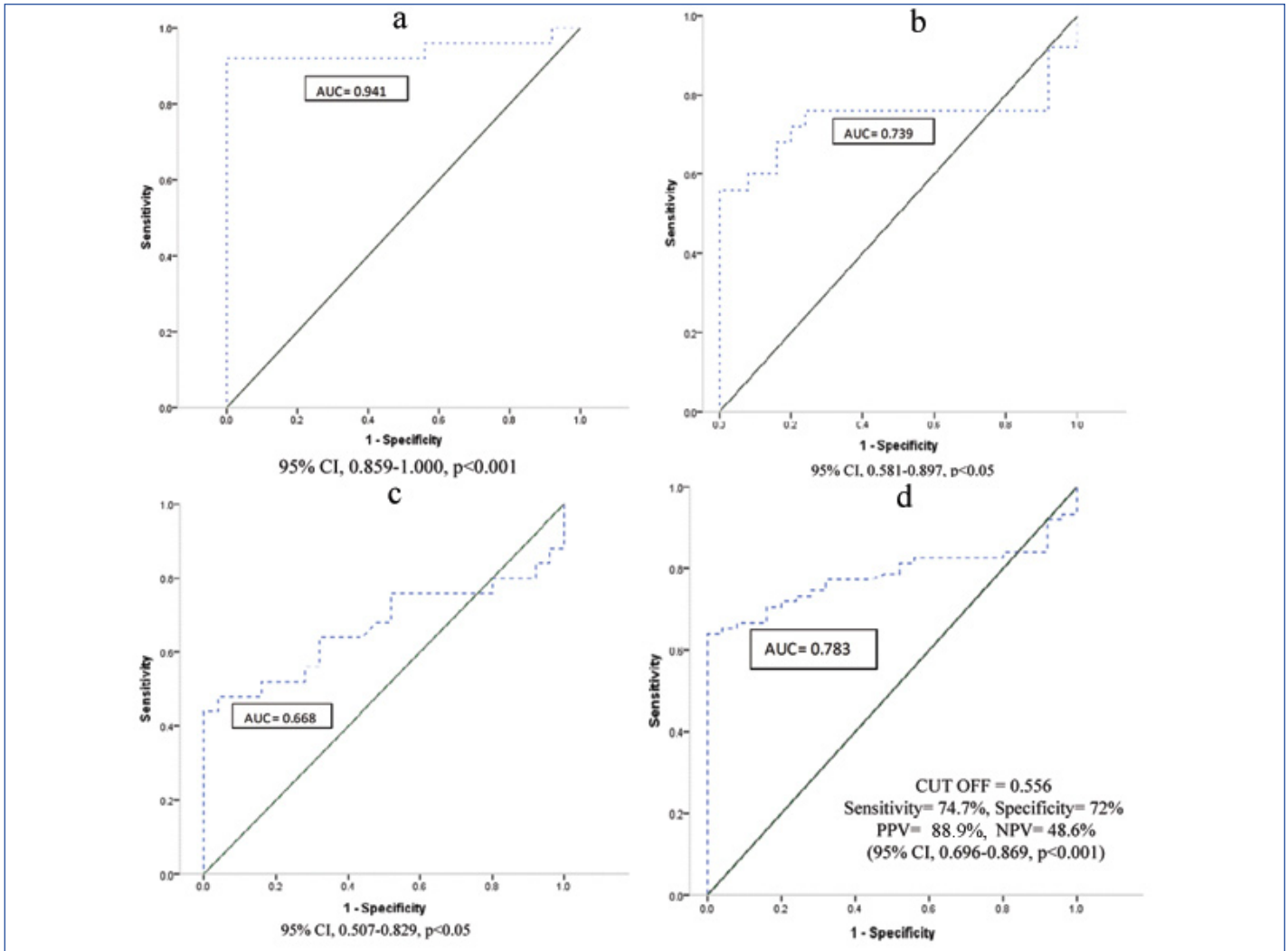
[Table/Fig-1]: Clinical characteristics of the study groups.
Data were presented as mean±standard deviation, p-value significant at 0.05 level
ACS: Acute coronary syndrome; UA: Unstable angina; NSTEMI: Non ST-segment elevation myocardial infarction; MI: ST-segment elevation myocardial infarction; IMA: Ischaemia modified albumin; cTnI: Cardiac troponin I; CKmb: Creatin kinase myoglobin binding.
*Unstable angina vs. NSTEMI; **Unstable angina vs. MI; ***NTEMI vs MI; **** ACS vs. Control



[Table/Fig-2]: IMA levels in ACS patients and control group (p-value <0.05).



[Table/Fig-3]: IMA levels in ACS group.
(p-value UA<0.001), (p-value NSTEMI and MI=0.675)



[Table/Fig-4]: Receiver operator characteristic curves: a) ROC of IMA in unstable angina group; b) ROC of IMA in NSTEMI; c) ROC of IMA in MI; d) ROC of IMA in ACS.

DISCUSSION

In the present study we assessed IMA using CAB assay© proposed by Lee E et al., to investigate role of IMA in diagnosis of unstable angina, NSTEMI and MI patients and hypothesised that measuring the level of IMA in combination with necrotic biomarkers (cTnI and CKmb) can improve the efficiency of ACS diagnosis, especially diagnosis of unstable angina [16]. Many studies have been done on the role of IMA in diagnosis of ACS [9,11,13,17-20] and in most of them, IMA were measured using Albumin Cobalt Binding test (ACB test©) described by Bar-Or D et al., [21].

Using of buffering system, low sample volume and resistance to pH changes are some advantages of CAB assay compared to ACB test [22].

In this study, we reported that IMA levels in the ACS patients were significantly higher than control group. This finding was similar to the results of other studies [11,17,18,20]. Moreover, our results showed that IMA levels were significantly higher in individuals with unstable angina compared to the other two groups of patients ($p<0.05$), whereas there was no significant difference in IMA levels between MI patients and NSTEMI. In support of our results, Kountana E et al., showed IMA levels as a useful tool for excluding unstable angina [23]. One study also represented IMA as a potential biomarker in diagnosis of unstable angina [24]. They hypothesised that lesser albumin will be exposed to free radicals in myocardial necrosis compared to non necrotic damage, so less IMA will be made. Furthermore, myocardial necrosis causes limiting IMA access to circulation. However, other studies showed IMA as a poor discriminator between MI and unstable angina [20,25].

In a recent study on the role of IMA in CAD, IMA came out to be as a strong predictor of CAD in patients with unstable angina pectoris [26].

According to the results of the present study and mentioned studies above, IMA can be a good biomarker in early diagnosis of ACS in emergency room. Our study showed that there was an elevated level of CKmb and cTnI besides IMA levels in NSTEMI and MI patients, while IMA was a significant biomarker in unstable angina patients. So, we suggested elevated level of IMA without increased level of cardiac biomarker such as CKmb and cTnI may be a useful biomarker in diagnosis of unstable angina. Since, bivariate correlation analysis of IMA with cTnI and CKmb showed no significant correlation in unstable angina, NSTEMI and MI patients so, more studies are needed. The correlation results are in agreement with those reported by Ertekin B et al., and Chek J et al., and Bonorino NF et al., [18,27,28].

Based on the results of ROC curve analysis for IMA, the sensitivity and specificity was found to be 74.7% and 72% respectively. A study demonstrated a sensitivity of 76% and a specificity of 74% for IMA assay in CAD patients, which were quite close to our results [26]. Although, many studies suggested high specificity for IMA in ACS [11,18,29]. There are many studies that expressed increased level of IMA in non cardiac ischaemia conditions like type 2 diabetes mellitus, Liver disease, thyroid disorders and pregnancy [30-33]. Thus, IMA may not be a specific marker for cardiac ischaemia and this observation may be due to non usage of IMA as much as cTnI and CKmb in emergency room.

In a study done by Reddy CB et al., on 89 subjects, IMA levels were higher in patients with unstable angina compared to NSTEMI [20]. However, firstly, they indicated that positive IMA levels alone cannot differentiate between unstable angina and MI and secondly it wasn't possible to distinguish between AMI and unstable angina (area under ROC curve 0.66).

Our results are in agreement with first part, IMA levels should be investigated besides another cardiac marker to differentiate between unstable angina and MI. However, contrary to second part, in the present study the AUC for IMA concentration in unstable angina and MI was 0.941 and 0.668, respectively. The results of the present study supported that IMA plays an important role in diagnosis of ACS and besides another cardiac markers (CKmb and cTnI), IMA can be a differential biomarker between unstable angina and MI.

LIMITATION

Limited number of participants were enrolled in the study, albumin-adjusted IMA levels were not calculated, increased level of IMA in such non ischaemic condition and using a colorimetric assay (CAB assay) as an indirect measurement method were considered as limitations of the present study.

CONCLUSION

The results of the present study confirms the valuable role of IMA in diagnosis of ACS especially unstable angina patients. On the other hand, our results suggest that increased level of IMA without elevated levels of necrotic biomarkers such as cTnI and CKmb can be a useful biomarker in diagnosis of unstable angina, although further studies are required to assess IMA in unstable angina patients.

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