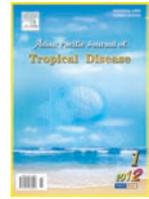




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## Diagnostic efficacy of ischemia modified albumin and its correlation with lipid profile, oxidative stress in acute myocardial infarct patients on admission

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### ABSTRACT

**Objective:** To evaluate the diagnostic efficacy of ischemia modified albumin (IMA) and its correlation with lipid profile, oxidative stress in acute myocardial infarct (AMI) patients attending Cardiology Emergency Department (ED). **Methods:** At presentation serum IMA in conjunction with electrocardiogram (ECG) and cardiac troponin T (CTnT) was evaluated in 35 AMI patients attending the ED within 6 hours of chest pain. These patients were subjected to standardized diagnostic procedures and treatment. Thirty five healthy volunteers were enrolled as control. **Results:** IMA showed a higher level in ischemic patients than in control with the highest sensitivity (77%) in comparison to CTnT and ECG. With CTnT or ECG, IMA documented a sensitivity of 83% and 88%, respectively. Whereas with both CTnT and ECG, IMA identified 94% of AMI patients with the highest negative predictive value (90%). **Conclusions:** IMA has evolved as a cost effective, highly sensitive, early diagnostic marker of cardiac ischemia and an earlier rule out test in AMI patients.

## 1. Introduction

Coronary artery disease (CAD) is predicted to be the leading cause of morbidity and mortality in developing countries by the year 2020[1,2]. Approximately 30% patients presenting at emergency department with chest pain actually develop acute myocardial infarction (AMI)[3]. Cardiac ischemia is the most common mechanism underlying acute coronary syndrome (ACS) that when prolonged, may lead to myocardial damage and cell death. Myocardial ischemia results from lack of adequate blood perfusion of myocytes, leading to a deficiency of oxygen and nutrients, thus compromising their vital functions[4]. Diagnosis of ischemia is difficult in patients presenting with acute chest pain with uninterpretable baseline electrocardiogram (ECG), normal ECG during pain, or without evidence of myocardial necrosis[5,6]. None of the traditional clinical variables,

12-lead ECG, biochemical markers of necrosis and imaging techniques can be considered a true gold standard in diagnosing or ruling out cardiac ischemia[7]. Lack of a sensitive marker hinders appropriate discharge of non-AMI patients resulting in numerous expenses and patient mismanagement[8,9].

Ideally, it is essential to identify myocardial ischemia before the onset of irreparable myocardial cell damage. Recently, a new parameter ischemia modified albumin (IMA) has been developed and observed to be very useful for the detection of acute myocardial ischemia that identifies the patients having potential coronary artery lesion, with high risk of adverse cardiac events.

With these views, the present piece of work was conducted with an objective to estimate serum IMA in AMI patients and to compare its clinical performance with cardiac troponin T (CTnT) and ECG-alone as well as in combination.

## 2. Materials and methods

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Thirty-five AMI patients between age group of 40–70 years admitted to the coronary care unit within 6 hours of chest pain were enrolled in the study during the period from May 2008 to September 2009. All of them were diagnosed on the basis of clinical examinations and ECG findings. Thirty five age/sex matched healthy individuals without any history of coronary artery disease from the hospital staffs were taken as control.

A volume of 2 mL of blood was collected from AMI cases immediately after admission for analysis of serum IMA, serum malondialdehyde (MDA) as well as cardiac marker CTnT before administration of any heparin/thrombolytic treatment. Other biochemical parameters like fasting plasma glucose (FPG), lipid profile were analyzed in the venous blood using FLEXOR–XL autoanalyzer. All the controls were also subjected to estimation of above biochemical parameters as well as estimation of serum IMA.

Serum IMA assay<sup>[10]</sup> was performed in the blood sample collected within 6 hours of chest pain *i.e.*, immediately after admission by adding a known amount of cobalt to serum and measuring the unbound cobalt that forms a color complex with dithiothreitol (DTT) using spectrophotometer at 470 nm wavelength.

The whole process involved addition of 200  $\mu$ L of patient's serum to 50  $\mu$ L of COCl<sub>2</sub> solution (1 g/L) followed by vigorous mixing and then 10 minutes of incubation. A volume of 50  $\mu$ L of DTT (3 g/L) was then added and mixed well. After 2 minutes of incubation, 1 mL of 9 g/L solution of NaCl was added. The absorbance of the assay mixture was read at 470 nm wavelength. The blank was prepared in the same way with the exclusion of DTT. One IMA unit was defined as  $\mu$ g of free cobalt in the reaction mixture per mL of serum sample.

Serum CTnT levels were measured by electrochemiluminescence immunoassay using Elecsys 2010 analyzer. Plasma MDA derived from lipid peroxidation was determined as TBA reactive substances<sup>[11]</sup>. The results obtained from cases and

controls were statistically analyzed using students-*t* test and pearsons' correlation coefficient.

Women with pregnancy, patients with very high/low serum albumin level as well as patients suffering from renal disease, hepatic disease, peripheral vascular disease and brain ischemia were excluded from the study. The study has been approved by Institutional Ethical Committee.

### 3. Results

In the present study, majority of patients (46%) were in the age group of 51–60 years with a male predominance (75%). Smoking was prevalent in 31% of cases followed by hypertension in 23% of cases. Diabetes was associated with 15% of cases only.

Biochemical analysis of the study group revealed significant rise in fasting plasma glucose and total cholesterol in AMI patients as compared to controls. HDL-cholesterol and LDL-cholesterol also registered marked change in the AMI patients. The ischemic marker serum IMA documented a prominent rise in these cases, with a mean value of 95.80 U/mL in relation to control. Serum MDA, an oxidative marker showed a marked rise in these cases revealing a state of oxidative stress (Table 1).

**Table 1**  
Biochemical parameters in AMI patients and healthy controls (mean $\pm$ SD).

Variables	Control (n=35)	Cases (n=35)
Fasting plasma glucose (mg/dL)	85.90 $\pm$ 10.45	101.06 $\pm$ 19.40*
Total cholesterol (mg/dL)	136.70 $\pm$ 26.70	185.20 $\pm$ 24.70*
Triglyceride (mg/dL)	111.20 $\pm$ 17.70	148.90 $\pm$ 27.20
HDL-cholesterol (mg/dL)	46.50 $\pm$ 3.03	40.80 $\pm$ 2.20*
LDL-cholesterol (mg/dL)	66.60 $\pm$ 23.90	113.70 $\pm$ 23.50*
VLDL-cholesterol (mg/dL)	22.20 $\pm$ 3.50	29.77 $\pm$ 5.54
Serum MDA (nmol/mL)	2.77 $\pm$ 0.29	4.38 $\pm$ 0.64**
IMA (U/mL)	77.45 $\pm$ 6.37	95.80 $\pm$ 15.20**

\**P*<0.01, \*\**P*<0.001 comparing with the control.

**Table 2**  
Diagnostic efficacy of IMA assay in both troponin positive and negative patients.

IMA level	Troponin positive AMI patients	Percentage (%)	Troponin negative AMI patients	Percentage (%)
↑ IMA (>85 U/mL)	7	70	20	80
↓ IMA (<85 U/mL)	3	30	5	20

The levels of IMA in AMI and control subjects were depicted in Figure 1. The upper limit of the cut off value of serum IMA was taken to be 85 U/mL which was calculated from 95<sup>th</sup> percentile of 102 apparently healthy volunteers. This is similar to the cut off value taken by Sbarouni *et al*<sup>[12]</sup> and Sinha *et al*<sup>[5]</sup> whereas it was taken to be 70 U/mL by Cui *et al*<sup>[13]</sup>.

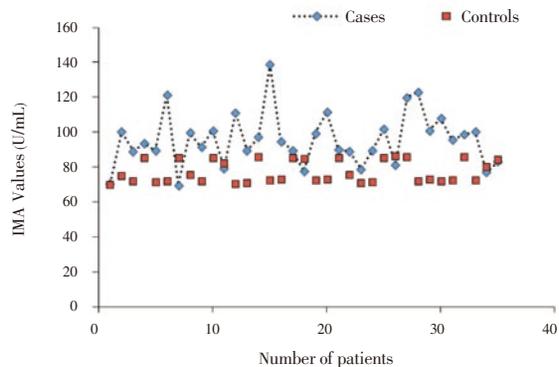
Amongst 35 AMI patients, troponin T was detected in 10 number of cases at presentation. Rest 25 remained troponin negative revealing a sensitivity of only 29%. Serum IMA assay on these cases revealed, 70% of troponin positive as well as 80% of troponin negative patients had serum IMA level more than 85 U/mL (Table 2).

Clinical performance of IMA when analyzed alone as well as in combination was shown in Table 3. Serum IMA assay registered high sensitivity in comparison to ECG and CTnT whereas IMA in combination with CTnT or ECG revealed better sensitivity as compared to combination of ECG and CTnT. When all these three were included together, the analysis registered the highest sensitivity with a large negative predictive value (NPV) in comparison to IMA alone or its combination with either ECG or CTnT. However, its specificity remained low in comparison to ECG and CTnT when analyzed alone or in combination. The NPV of IMA also revealed high value in comparison to both ECG and CTnT and also in conjunction with these together.

**Table 3**  
Clinical performance of IMA alone and in combination.

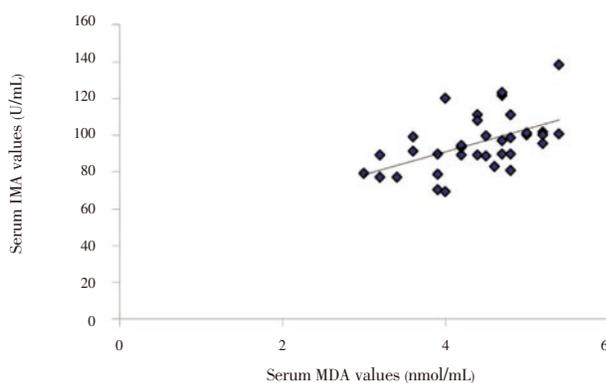
Tests	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
IMA	77	66	71	72
ECG	54	93	90	65
CTnT	28	97	91	55
ECG + CTnT	71	90	89	74
IMA + CTnT	83	62	71	77
IMA + CTnT + ECG	94	59	72	90

PPV: Positive predicative value.



**Figure 1.** Serum IMA values in study population.

The graphical representation of correlation between serum IMA with MDA documented a significant positive association with  $r$  value of 0.5 pointing the origin of IMA as a product of oxidative stress (Figure 2).



**Figure 2.** Correlation of serum IMA with MDA in AMI patients.  $r$  value=0.5;  $P < 0.001$  comparing with the control.

#### 4. Discussion

Atherosclerosis is one of the major causes of AMI<sup>[14]</sup>. Prolonged ischemia can lead to myocardial cell death and is a precondition to infarction<sup>[15]</sup>. Therefore, identification of myocardial ischemia at the earliest stage is very much essential to prevent the devastating consequences of the disease.

Currently there is no well defined biochemical marker for identification of myocardial ischemia. Biochemical markers like CKMB, CTnT and myoglobin used in assessing

cellular necrosis are not suitable for diagnosing myocardial ischemia<sup>[16,17]</sup>. From a diagnostic standpoint, the aim is to try to develop markers that can identify patients with AMI even when there is no evidence of myocyte necrosis.

Again in cases with cardiac ischemia, it may be more difficult to reach at a diagnosis when the patient has acute chest pain with a nondiagnostic ECG and alteration in normal markers for necrosis. In such cases patients are at increased risk for subsequent coronary events but they may often be discharged because there is insufficient evidence to justify hospital admission<sup>[18]</sup>.

Recently introduction of IMA assay that has received approval from the US Food and Drug Administration<sup>[19]</sup> can be considered to be used to identify these ischemic patients as well as to rule out patients who do not have ACS.

The present study registered a significant rise in serum IMA in AMI cases as compared to control, similar to the observations of the previous studies that distinguishes myocardial ischemic patients from non-ischemic patients<sup>[10,20,21]</sup>. CTnT, a marker of cardiac cell death revealed lower sensitivity than serum IMA similar to the results of Sinha *et al*<sup>[5]</sup> establishing the role of IMA as a better sensitive marker than CTnT.

The sensitivity of IMA for the diagnosis of acute ischemic chest pain is significantly greater than that of ECG and CTnT used alone as well as in combination with them. These observations are in agreement with the previous studies<sup>[5,21,22]</sup> where sensitivity of nearly 82% of IMA assay has been reported.

Conventional emergency department testing of AMI patients includes ECG and CTnT. In this study the presentation of ECG combined with CTnT identified 71% of patients. With addition of IMA to either ECG or CTnT or both, sensitivity for diagnosis was increased to a larger amount. Thus estimation of IMA in addition to current standard tests identifies more number of AMI patients who could be benefited from earlier treatment. This view is in concurrence with the opinion of other researchers<sup>[5,23,24]</sup>.

For ruling out ACS, the NPV for all three tests combined together was the highest (90%), which was significantly greater from any test used alone or in combination. All these results are in agreement with Sinha *et al*<sup>[5]</sup>. The present study is also in concurrence with studies of Keating *et al*<sup>[23]</sup> and Collinson *et al*<sup>[24]</sup>, in which rise in sensitivity and NPV was reported with the addition of IMA to standard conventional diagnostic tests. However, the specificity of IMA is low in AMI cases in comparison to ECG and CTnT whether taken alone or in combination.

The current study registered a significant rise in serum MDA level with a prominent positive correlation with serum IMA level. This observation is in agreement with the results of Senes *et al*<sup>[25]</sup> and Kumar *et al*<sup>[26]</sup> having similar positive correlation between IMA and TBARS strengthening the fact that oxidative stress resulting from reperfusion injury causes myocardial cell damage that may be the probable underlying

cause for increased serum IMA level.

Thus IMA appears to be a sensitive biomarker of myocardial ischemia in AMI patients presenting to the emergency department. Its ability to detect ischemia before myocyte destruction would allow for earlier and accurate management decisions as well as its role in a definitive biochemical ruling out strategy. While the specific molecular alterations and events that induce albumin modification have been only partially elucidated, better understanding of ischemic and reperfusion events at subcellular level needs further research in future.

### Conflict of interest statement

We declare that we have no conflict of interest.

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