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Assessment of Ischemia Modified Albumin and Cardiac Troponin (I) as an Early Diagnostic Markers of Myocardial Ischemia among Patients with Acute Chest Pain

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Abstract

Introduction: Cardiac biomarkers have been emphasized as central to the diagnosis and risk stratification strategy for AMI by numerous clinical practice guidelines. **Aim**: To assess the diagnostic value of Ischemia -modified albumin (IMA) with standard biomarkers (CK-MB, LDH, and AST) troponin I [cTnI] in the early diagnosis of cardiac ischemia. **Method**: This is cross-sectional study was done 150 with patient's acute chest pain as target population patients attending to the emergency department of Al Shab Hospital Khartoum. Every case was reviewed by a cardiologist. A clinical diagnosis of ischemia was assigned and correlated with biomarker test results. **Results**: 127 (84.7%) had myocardial ischemia. Receiver operating characteristic curves demonstrated IMA as highly sensitive but somewhat low specific for the presence of ischemia (area under curve, 0.878; P = .00). With a cut point of 88.16 U/mL, the IMA test had 84.6% sensitivity and 81% specificity for diagnosing ischemia and a negative predictive value of 77.9%. IMA was positive in 127 of 96 patients with electrocardiographic (ECG) evidence of ischemia and 31 of 127 patients with coronary ischemia but negative ECG. Among the same patients, the ECG and cTnI triad had a sensitivity of 64% and 24% respectively. The combination of IMA and ECG increased the sensitivity to (94.5%), and IMA, ECG, cTnI to 95.8%for detecting ischemia. IMA is highly sensitive and has a high negative predictive value, which might improve the usefulness of standard biomarkers of myocardial ischemia. **Conclusion**: Ischemia Modified Albumin has evaluated as highly sensitive, early diagnostic marker of among acute chest pain patients.

Key words: Ischemia Modified Albumin, Cardiac Troponin (I), Myocardial Ischemia, Biomarker, Chest Pain, Ischemic Heart Disease.

1. INTRODUCTION:

Myocardial ischemia occurs when blood flow to your heart is reduced, preventing it from receiving enough oxygen. The reduced blood flow is usually the result of a partial or complete blockage of your heart's arteries (coronary arteries) [1]. The coronary artery disease (CAD), also known as ischemic heart disease (IHD) [2] is a group of diseases that includes: unstable angina or non-ST-segment-elevation myocardial infraction (NSTEMI), stable angina or ST-segment-elevation myocardial infraction (STEMI) and sudden cardiac death [3]can develop slowly as arteries become blocked over time or it can occur quickly when an artery becomes blocked suddenly [4].Chest pain or discomfort which may travel into the shoulder, arm, back, neck, or jaw [5].The first sign is occasionally a heart attack[6] other complications include heart failure or an irregular heartbeat [6].The underlying mechanism involves atherosclerosis of the arteries of the heart [7] .Atherosclerosis is a sequence of pathophysiologic processes in coronary arteries, where inflammatory cytokines plays an important role causing plaque's destabilization and rupture, myocardial ischemia and infarction [8] . Chest pain is a common presentation to the emergency department and accounts for approximately 5–10% of all visits [9]. A number of tests may help with diagnosis including electrocardiogram (ECG), cardiac stress testing and coronary angiogram, among others [10].

Diagnosis of ischemia is difficult in patients presenting with acute chest pain, particularly those with uninterruptable baseline ECGs, normal ECGs during pain, or without evidence of myocardial necrosis. But most of these patients have relatively unremarkable electrocardiograms. Rates of missed ACS among patients who present to the emergency department remain inappropriately high, ranging from 2 to 5% [11].

A gold standard in diagnosis of the necrosis of myocardium is troponin due to its high sensitivity and specificity. However, Troponins are not very early markers, and up to 4 hours from the onset of symptoms their sensitivity does not exceed 50% [12].

Assessment of the cardiac biomarkers levels (Myoglobin, CK-MB and Troponin) are one of the most essential and effective ways for detecting myocardial damage. The current conventional cardiac markers, CK-MB, Troponin (I) and (T) are sensitive and specific tests for the detection of myocardial necrosis, but they show a greater rise approximately 3-6 hours after the onset of the myocardial cell injury and thus, the patients may wait before they are diagnosed and treated; moreover, the usual biomarkers may not rise during reversible myocardial ischemia and other diagnostic tools such as stress testing, and echo cardiology are not routinely available [13a].

Recent efforts have focused on improving the accuracy of identifying patients with ACS who are at high risk of having an adverse event within the short term after assessment. During acute ischemia of myocardium, the ability of binding ions such as copper, zinc and cobalt is decreased, therefore a form of albumin is produced, which is described as ischemia modified albumin (IMA). In recent years, a number of studies have been conducted on the use of IMA in the diagnosis of ACS with variable results [14] . Previous studies shown that IMA levels rises within minutes after cardiac ischemia. IMA is a serum albumin in which the N-terminus

has been chemically modified. The diagnostic albumin CO2+ binding (ACB) test for IMA is based on the observation that affinity of serum albumin for CO2+ is reduced after N-terminus modifications [15]. The amino terminal of plasma albumin normally has an affinity to cobalt, copper, and other heavy metal ions, and the N-terminal of albumin is modified during exposure to ischemic condition, due to the generation of oxidative free radicals and reactive oxygen species, resulting in the generation of IMA with a low binding affinity to heavy metals [16]. Reports that IMA is increased within a few minutes after the onset of myocardial ischemia and continues to increase for 6–12 h suggest that it could be applied effectively to the detection of myocardial ischemic condition prior to the progression to myocardial necrosis [17]. IMA approval from the US Food and Drug Administration as only one clinical test for ischemia [18].

Clinical studies indicate that Ischemic Modified Albumin (AMI) appears to offer on admission an early test to diagnose cardiac ischemia, which can be combined with cardiac troponin measurement for the early exclusion of acute coronary syndrome. IMA is an independent predictor of short and long-term adverse outcomes in patients with acute chest pain [13b].

Our study aimed to validate IMA assay when used together with ECG and standard cardiac markers of myocardial necrosis for the diagnosis and early detection of patients with IHD,

2. MATERIAL AND METHODS:

Study designs and setting: This is hospital- based cross-sectional study conducted at AL Shab Hospital, Khartoum, Sudan, During 1st of February 2015 to October 2015.

Study population: Patients who arrived to the Emergency Department suffering from acute chest pain within two to four hours.150 patients as study group.

Control group selection: One hundred healthy volunteers individuals' age and sex matched who didn't have any evidence of coronary artery disease were taken as the control group.

Data and sample collecting: Well-structured questioner was created to take demographic and clinical information (Cardiologist was interview and questionnaire the test group and control group to assessment and obtain clinical data. The data include a thorough history taking including (age, sex, duration of chest pain, and presence of risk factors for ACS as diabetes mellitus and hypertension), full physical examination, family history considering DM, hypertension and ischemic heart), , biochemical data levels Ischemia Modified Albumin, isozyme of Creatinine Kinas , Cardiac Troponin I , Lactate dehydrogenase , aspartate aminotransferase , manifestations suggestive of acute myocardial ischemia, including those such as chest pain dyspnea, chest pain, palpitations, syncope, edema, cyanosis, and fatigue[19]. The ECG measured in the ED as part of the standard of care at the AL Shab Hospital.

Inclusion criteria:

Test group: Standardized clinical data were collected for each patient, which included time of presentation at the emergency department, approximate duration of symptoms of the acute chest pain.

Exclusion criteria:

Patients with liver disorders, autoimmune disorders, pregnant women, patients with symptoms and signs suggestive of acute mesenteric ischemia, acute renal failure, peripheral vascular disease, or brain ischemia were not enrolled in the study.

Samples processing

Blood samples collected in tubes containing lithium heparin at the time of the patient's presentation to the emergency department, centrifuge for 5 minutes and preserve at -70^0 C

Biochemical measurement

Ischemic Modified Albumin (IMA): that assayed in intervals at 2 - 4 hours and 6 - 8 hours. The microtiter plate provided in this kit has been pre-coated with an antibody specific to IMA. Standards or samples are then added to the appropriate microtiter plate wells with a biotin-conjugated antibody preparation specific for IMA and Avidin conjugated to Horseradish Peroxidase (HRP) is added to each microplate well and incubated.Then a TMB (3,3',5,5′ tetramethyl-benzidine) substrate solution is added to each well. Only those wells that contain IMA, biotin-conjugated antibody and enzyme-conjugated Avidin will exhibit a change in color. The enzyme-substrate reaction is terminated by the addition of a sulphuric acid solution and the color change is measured spectrophotometrically at a wavelength of 450 nm ± 2 nm. The concentration of IMA in the samples is then determined by comparing the O.D. of the samples to the standard: reference value that is reported by the manufacturer (0.21+ 0.65) by EISA the microtiter plate provided kit has been pre-coated with an antibody specific to IMA.

Troponin (I):) cardiac Troponin I (cTnI) measure with Fluorescence Immunoassay Quantitative detection method by ichro. Reference value (< 0.3 ng/ml.

Creatinine Kinas: CK-MB was measured by spectrophotometer by specific antibody inhibits both M subunits of CK-MM (CK-3) and the single M subunit ofCK-MB (CK-2) and thus allow determination of the B subunit of CK-MB 1. Reference value (up to 25 U/L).

Lactate dehydrogenase (LDHLDH was measured by spectrophotometric assay L-lactate substance): Reference value (207 - 414 U/L). Aspartate aminotransferase(AST): AST was measured by spectrophotometric assay catalyzes the transfer of the amino group from aspartate to 2-oxoglutarate, forming oxalacetate and glutamate. Reference value (up to 40 U/L).

Statistical Analysis:

SPSS software (version 16) was used for analysis of clinical variables. Descriptive statistics used to analyze all variable studies such as the demographic characteristics. Data were summarizing as mean ± SD. Variables were compare between study group (with acute chest pain) and control group (without chest pain) by Student's *t* test and ANOVAs method, p value of < 0.05 was considered significant. Liner regression analysis was used to assess correlation between Ischemic Modified Albumin (IMA) concentration, Cardiac enzyme markers, cTnI and the duration of chest pain.

Ethical consideration

The study protocol was approved by ethical committee for medical and health research at Omdurman Islamic University and local ethics committee of Medical Director of Khartoum Al Shab hospital in Sudan.

3. RESULTS:

Clinical Characteristics

This study was conducted on 150 patients who arrived at the emergency department of Alshab Hospital, Sudan, Khartoum state, within two hours of acute chest pain as test group and 100 apparently healthy subjects' volunteers who didn't have any evidence of coronary artery disease. Age and sex for both groups were matched. (Table 1) that shows the results study group 150 patients 105 male (70%) and 45 females (30%) and the100 healthy control group 69 male (69%) and 31 females (31%). When compare ages in test group and control group find no significant difference Mean ±SD: was (57.5 ±17.6) versus (59.4±18.5) years (p =0.992), respectively.

IMA result

We estimated IMA in test group 127 have IMA elevated (84.7%) and 23 have IMA non-elevated (15.3%) after the onset of acute chest pain with sensitivity (84.6%) and specificity (81%) .Serum levels of IMA were significantly higher in (IHD) patients than in healthy controls (p value = 0.000, significance <0.001), The comparison between test and control group show that there was a highly statistically significant increase the mean of plasma IMA levels of the test group when compare with the mean of control group Mean± SD: (88.16± 57.37) versus control group Mean± SD: (38.43±6.22) U/ml. (p=0.000)(Tables 2,3).

IMA and ECG Results

Among these 127 patients with IMA elevated, only 96 (75.5%) had evidence on the ECG for Myocardial Infarction (MI) with ST segment elevated Myocardial Infarction (STEMI) and 31(24.5%) with no evidence of (MI) with non-ST segment elevated Myocardial Infarction (NSTEMI).

IMA & CTnI Results

Number of positive CTnI within first 2-4 hour show that from the 127 patient which have elevated IMA only 36 patients have raised cTnI (28.3 %) and 91 patients with non-raised cTnI (71.1%). (Table 4).

IMA and other Cardiac Enzymes Biomarker Results

when demonstrate the percentage numbers of elevated each cardiac enzyme markers (CK-MB, LDH and AST) Among these 127 patients with elevated IMA, there was a statistically significant difference between the means of plasma IMA levels (88.16+57.3) and cardiac enzymes markers levels CK-MB (19.81+11.31), LDH (315.60+126.05) and AST (43.17+58.77) with (P.value 0.000), (P.value 0.009) and (P.value 0.003) respectively at (2 – 4 hrs) of the onset of acute chest pain.{Figure1} and (Table 6).

Table 6 shows the clinical performance of IMA with cutoff value 88.16 U/L from Receiver operating characteristic (ROC) curve show that it is highly sensitive and somewhat moderate specific (area under the

ROC curve, 0.88; P = 0.00) for the detection of cardiac ischemia when compare with others cardiac markers and ECG. The negative predictive value for the IMA assay at this cut point was 77.9% for excluding the diagnosis of ischemic heart disease.

Table (1) Baseline demographic and clinical characterizations of the test group and the control group

Group		Frequency	Percent	Cumulative frequency
case	Female	45	30.0	30.0
	Male	105	70.0	100.0
	Total	150	100.0	
control	Female	31	31.0	31.0
	Male	69	69.0	100.0
	Total	100	100.0	

Table (2) from 150 patients suffering from chest pain 127 have increase level IMA (84.7%) and 23 have non-elevated IMA (15.3%).

IMA	Frequency	Percent (%)	Cumulative Percent (%)
Increase (IMA) (88.16+ 57.3)	127	84.7	84.7
Normal (IMA) (0.43+ 0.22)	23	15.3	15.3
Total	150	100.0	100.0

IMA: Ischemia Modified Albumin

Table (3) Comparison means of plasma (IMA) test group and control group.

	Group	N	Mean	Std. Deviation	P value
IMA	Case	150	88.16	57.3	0.000
	Control	100	38.43	6.22	

IMA: Ischemia Modified Albumin

Table (4) shows the percentage number of CTnI positive and negative in case group with IMA elevated (n=127).

CTnI with IMA elevated		Frequency	Percent
Case	Raised	36	28.3
	Normal	91	71.7
total		127	100

cTnI: Cardiac Troponin I **IMA**: Ischemia Modified Albumin

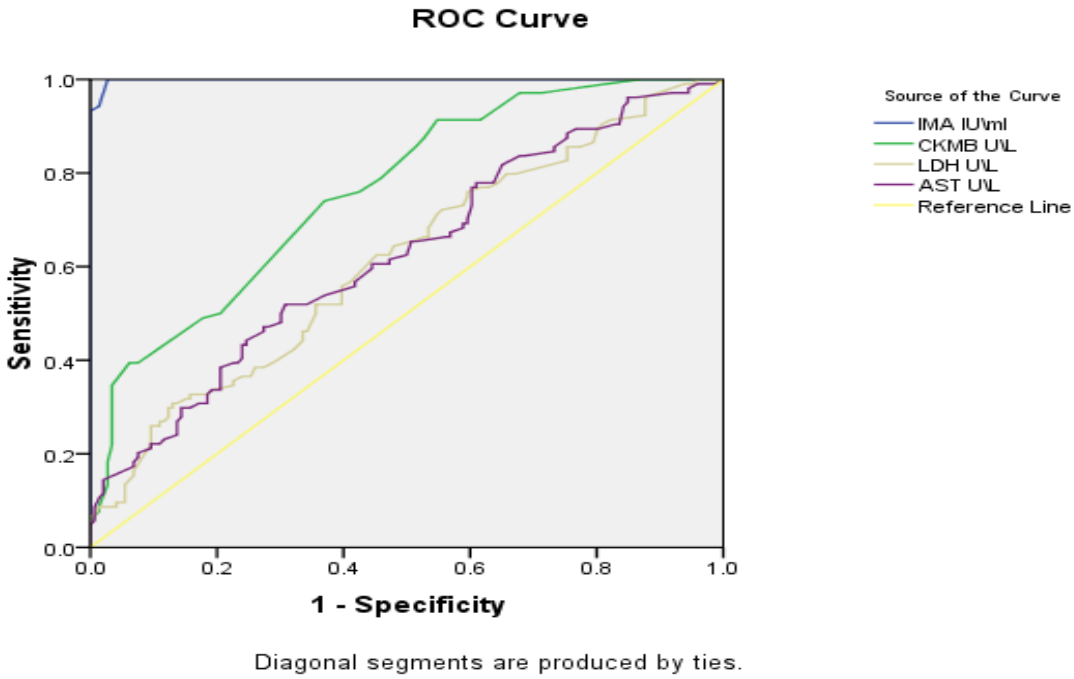

Figure 1: Receiver operating characteristic (ROC) analysis for the assay for ischemia-modified albumin. Although highly sensitive with moderate specific. The area under the ROC curve was 0.878 (P = 0.00). When use IMA >88.16U/L as rule for chest pain diagnosis the area Under the Curve for CKMB U\L=0.763 LDH U\L=0.614 and AST U\L=0.625.

Table (5) Comparison of Sensitivity, specificity, PPV and NPV of IMA, ECG, cTnI and cardiac enzyme markers for diagnosis of Ischemic Heart Disease

Test	Sensitivity (%)For IHD	Specificity (%) For IHD	PPV (%) For IHD	NPV (%) For IHD
IMA	84.6	81	87	77.9
ECG	64	98	98	64.5
CTnI	24	99	97.3	46.5
CK-MB	20	98	83.8	44.5
LDH	22	84	68	42
AST	32	82	75	44.57

ECG: electrocardiogram **IMA:** Ischemia Modified Albumin **CK-MB:** isozyme of Creatinine Kinas **cTnI:** Cardiac Troponin I **LDH:** Lactate dehydrogenase **AST:** aspartate aminotransferase

Table (6)IMA in combination with ECG, cTnI, and cardiac enzymes Markers, for diagnosis of cardiac ischemia.

Clinical performance in combination	Sensitivity (%) For IHD	Specificity (%) For IHD
IMA+ECG	94.5	99.6
IMA+CTnI	88.3	99.8
ECG+CTnI	72.6	99.9
IMA+ECG+CTnI	95.8	99.9
IMA+ECG+CTnI+Enzymes	98.2	99.9

4. DISCUSSION:

The IMA measurement as a marker of myocardial ischemia without myocardial necrosis and/or preceding myocardial necrosis has introduced the hope for improved diagnosis in patients with IHD without or with non-specific ECG changes [20, 21].

in the cases with cardiac ischemia, it may be more difficult to reach at a diagnosis when the patient has acute chest pain with a non-diagnostic 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. According to (Sinha MK,et al) [22], IMA sensitivity for the diagnosis of acute ischemic chest pain is significantly higher than that of ECG and cTnT, these results accords with the findings of (Christenson RH, et al)[23], who also observed high sensitivity and high negative predictive values of IMA, demonstrating that the ACB test could be used to safely identify low-risk patients, and therefore, reduce the admission of patients in emergency hospitals. However, the presence of IMA may not confirm myocardial ischemia but other medical conditions such as diabetes mellitus, peripheral vascular disease, glaucoma, skeletal muscle ischemia and systemic sclerosis [24].

In this study, we evaluated IMA for the diagnosis of cardiac ischemia in 150 patients attending emergency department within 2 – 4 hours after the onset of acute chest pain and compare with normal control subjects; the result presented that the IMA level in the patients with acute chest pain was significantly greater (88.16± 57.37) as compared to that of the control group (38.43±6.22) U/ml (p=0.000).These findings accords to other studies that confirmed the efficiency of IMA as an early marker in the diagnosis of myocardial ischemia.[25, 23, 24].There is an increase in the IMA levels, which remain high at 12 – 24 hours after onset of chest pain, this also reported by (Ertekin B, et al)[26]which reported that in early ischemia there is an increase in the IMA levels, which remain high.

IMA, ECG& Cardiac Markers:

In this current study 127 have elevated IMA level only 96 patients of them have ECG changes (75.5%), 36 patients (28.3%) have elevated cTnI with cutoff value (0.35 ng/ml) and elevated cardiac enzymes biomarkers(CK-MB, LDH and AST). The diagnostic performers of IMA only to detect cardiac ischemia have

a highlysensitivity (84.6%) andspecificity (81%) when compare with the sensitivity of traditional ECG(64%) and cTnI (24%).The cardiac enzyme markers have poor sensitivity CK-MB (20%), LDH (22%) and AST (32%)with a highly specificity (98%), (84%) and (82%) respectively to detect IHD (Table6).In addition, (ChristensonRH, et al) [23] demonstrated that IMA can be an early predictor of cTnI results after 6-24 hours in patients with ACS, suggesting an association between IMA and cTnI. In contrast, our results show an association between IMA and the cardiac markers CK-MB, LDH and AST analyzed in this study. However,our results confirmed those found in previous studies[27, 28] that showed that the IMA test does not differentiate ischemic from non-ischemic patients, although there is an increase in IMA levels before the cTnI levels increase in patients with myocardial ischemia[11] .

Among these 127 patients have elevated IMA there is only 36 patients(28.3%) have elevated cTnI and standard cardiac markers with ECG changes finally diagnosed they have stable angina myocardial infraction (MI), and the others 91patients(71.3%) have elevated IMA without increase cTnI level they diagnostic have unstable angina cardiac ischemia .This study shows that the sensitivity of IMA to detection of IHD was greater than those of ECG, cTnI and cardiac enzyme markers assay with low specificity. Our results confirmed those found in previous studies done by (Keating L,et al.& Collinson PO,et al)[29, 21].

In this study clinical performance of the combination IMA and ECG results improved the sensitivity 94.5 % and specificity 99.6% of the detection of IHD this also agree with study done by (Chawla R, et al.& Liyan C, et al.)[30, 31] .A higher sensitivity along with a higher positive and negative predictive value for IMA as compared to the cardiac enzyme markers (CK-MB, LDH and AST) for the detection of ischemic heart condition reinforces the postulate that the two tests have different roles to play in the management of patients with ACS where IMA appears to establish itself as sensitive marker for cardiac ischemia by (Anwaruddin S, et al.)[32].

Whereas cardiac enzyme markers have high specificity with cTnI and should be used to follow up the cases with overt infraction, the sensitivity, specificity, PPV and NPV of cTnI for the diagnosis of ACS for patients with acute chest pain are 24%, 99%, 97.3% and 46.5% respectively (Mohamed M, et al.)[33] Furthermore, the sensitivity was additionally improved by adjusting the IMA measurement with ECG of the patient. For the screening of IHD, the sensitivity and negative predictive value of IMA were higher than those of the conventional cardiac markers and cTnI, and its specificity was lower, which were similar to the results of previous studies (sensitivity, 80–90%; negative prediction rate, 85–92%; specificity, 31–49%)[22b]. The increase of IMA sensitivity could be explained by its theoretical increase under ischemic condition prior to the development of tissue necrosis.

When we used the IMA in a combination with ECG will improve our sensitivity (94.5%), specificity (99.6%) and negative predictive (77.9%) value for IHD. When we used the IMA in a combination with ECG and cTnI resulted in superior sensitivity (95.5%), specificity (99.9%) and positive predictive (97.3%) value for IHD (Chawla R, et al., 2006 & Sbarouni E, et al., 2008) [30, 34].

Limitations

Study was conducted in a single center, which may limit the generalizability of our results, used a standard troponin I test because our institution did not have a high-sensitivity troponin I test. We could not make a comparison with the cut-off values of the other studies.

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