Assessment of Ischemic Modified Albumin levels as a Predictor Marker for Acute Coronary Syndrome

Inaam Kadhoum Mohamad[1], Rana Majeed Hameed[2], Saleh Yahya Saleh Al jawad[3]

[1]Postgraduate Student/ College of Medicine/ University of Karbala

[2]PhD Biochemistry/ Department of Chemistry and Biochemistry- College of Medicine /University of Kerbala

[3]Consultant cardiologist /karbala heart centre/ Al Hussein Teaching Medical Hospital

Abstract

Background: Acute coronary syndrome (ACS) is the clinical manifestation of the critical phase of coronary artery disease. Based on ECG and biochemical markers it is distinguished from ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and unstable angina. The aim of this study was to Investigate the role of biochemical markers; Ischemia modified albumin (IMA) as an early diagnostic tool of ACS also, to Identify the cutoff values of these biochemical markers in early diagnosis of ACS. Methods: Case - control study approach was conducted on four groups of participants, MI- , MI+ , UA and healthy Control in Kerbala and Baghdad Governorates. All groups were exposed to medical examination for signs and symptoms of any cardiac disorders manifest such as Troponin with electrocardiographic patterns by specialized doctor. Serum biomarkers level were measured for the following parameter: IMA levels were measured using ELISA technique.; Measurement of lipid profile levels in Human serum was performed using Spectrophotometric Technique; biochemical analyser for Complete blood count was done by XP-300™ Automated hematology analyzer Sysmex. The association between biochemical markers and disease severity was evaluated. The efficiency of the predicting value was assessed using receiver operating characteristic (ROC) curve. Results: Results were indicated that IMA levels were shown a significant increased range levels in the negative troponin MI cases compared to the positive troponin MI and unstable angina. The range levels were (3.12-6.41); (3.1-5.66) and (3.17-5.56) respectively. On the other hand, unstable angina cases were shown a decreasing level of Albumin and increasing levels of IMA/ Alb ratio. Results were also illustrated the receiver operating curve (ROC) and AUC analysis for the Ischemic Modified Albumin, IMA/Albumin ratio as possible diagnostic parameters. IMA level was shown a good diagnostic performance for prediction ACS Patients compared to control group. the optimal diagnostic points for predicting ACS by IMA were (sensitivity = 90%, specificity = 80%) at a level = 3.59, while IMA/ Alb ratio levels: (sensitivity = 0.92%, specificity = 0.67%) at a level = 0.072. Only p-values of the AUC for IMA were <0.001 and statistically significant. Conclusion: Serum IMA appears to be a sensitive biomarker of myocardial ischemia in MI patients. Data analysis confirmed the ability to detect ischemia before myocyte destruction. Also, results were indicated that assessment of concentrations

1. Introduction

Albumin is one of the most abundant proteins in the human body, with about 40% circulating in the bloodstream. It is also a significant component of most extracellular fluids, including lymph, interstitial, and cerebrospinal fluids (1). Constant redistribution of the protein is achieved through the dynamic exchange of its intravascular and extravascular pools (2).Albumin is synthesized in the liver at a rate of 10-12 g/day, accounting for about 25% of total proteins (3).In addition, smaller amounts of albumin can be produced in extrahepatic tissues, such as kidneys, pancreas, intestines, lymph, mammary glands, reproductive tissues, and brain (4).This multifunctional globular protein has a molecular weight of approximately 66-69,000 Da, with minor variations among species. There is 83% to 88% amino acid homology among albumin molecules of many veterinary species (5).

The single polypeptide chain of human serum albumin (HSA) comprises 585 amino acid residues that form nine loops connected by 17 intramolecular disulfide bonds. HSA contains three homologous domains (I, II, and III), each split into A and B subdomains. The multifunctionality of albumin results from the presence of multiple binding sites. HSA contains Sudlow sites 1 and 2 that play a significant role in transporting hydrophobic molecules seven fatty acid-binding sites (FA1-7), heme-binding site, numerous small ligand-binding sites, and four metal-binding sites, including sites A and B, N-terminal site (NTS), and Cys34 (6).

IMA has been proposed as an early biomarker for various diseases associated with ischemia and oxidative stress, including myocardial infarction and cerebrovascular accidents, diabetes mellitus and renal failure, and hypothyroidism and

doi.org/10.31838/hiv22.02.750 Received: 11.07.21, Revised: 24.08.21, Accepted: 09.09.21

hyperthyroidism (7) Mounting experimental data suggest that this marker is ambiguous and that its values depend on the type and stage of the pathological process and methods used. Cardiovascular diseases, especially acute coronary syndromes (ACS), are the leading causes of morbidity and mortality in humans worldwide. According to the World Health Organization (WHO), an estimated 17.5 million people die from cardiovascular diseases annually, and about 42% of these deaths are due to ACS (8).The advances in the study of heart diseases have led to the discovery of a broad range of novel biomarkers associated with cardiovascular risks, including cTnI and IMA (9)Although these biomarkers have a prognostic value independent of the previous traditional risk factors, they have some limitations as early markers for ACS, including unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) (10).

Christenson et al. showed in a multicenter study that IMA was a potential earlier ACS predictor than cTnI. They examined 226 patients who arrived at the emergency departments (ED) within 3 hours of the onset of signs and symptoms suggestive of ACS. All the patients had negative cTnI at presentation, and this marker for necrosis started to increase within 6-24 hours of hospitalization. Findings showed that sensitivity and specificity for the ACB test were 70% and 80%, respectively, with a negative predictive value of 96% (11).

Other studies have supported these results. Chawla et al. found IMA's sensitivity and specificity for detecting ACS to be 78.0% and 82.7%, respectively, compared to 58.0% and 60.0% for the CK-MB assay (12).

Lee et al. obtained other results, finding the sensitivity and specificity of IMA for identifying ACS to be 93% and 35.6%, respectively, and the negative and positive predictive values to be 91.8% and 39.6%, respectively. The combination of myoglobin, CK-MB, and TnT demonstrated 80.2% of sensitivity and 57% of specificity for ACS diagnosis. Sensitivity increased to 94.5%, and specificity fell to 45.1% when IMA was included in the cardiac marker panel (13).

Many other authors find IMA a more sensitive indicator of ACS than TnI, myoglobin, and CK-MB. These latter markers are informative only within 2-6 hours of the onset of chest pain and acute cardiac events, whereas IMA rises within 30 min and continues to increase for the next 6-12 hours (14). IMA measurements allow for ACS speculations in the absence of changes in the electrocardiogram and unchanged cardiac markers (15). Evaluation of serum IMA is recommended not only for early detection of myocardial ischemia but also as a prognostic indicator of the disease severity. People with higher IMA showed longer hospitalization days and had more readmissions as compared to patients with high troponin. However, top high-level IMA did not predict negative cardiovascular events during the hospital stay, while the cTnT test predicted arrhythmia more often than the ACB test (16).

Methodology: Case - control study approach was conducted on four groups of participants, Myocardial infraction with troponin negative test [MI-], Myocardial infraction with troponin positive test [MI+] ,un stable angina [UA] and Control group in Kerbala and Baghdad Governorates. Participants were ensured on the confidentiality and privacy of their responses. They were also exposed to medical examination for signs and symptoms of any cardiac disorders manifest such as Troponin with electrocardiographic patterns by specialized doctor. Serum biomarkers level were measured for the following parameter: IMA levels were measured using ELISA technique.; Measurement of Lipid profile levels in Human serum was performed using Spectrophotometric Technique; biochemical analyser for Complete blood count was done by XP-300™ Automated hematology analyzer Sysmex. The association between biochemical markers and disease severity was evaluated. The efficiency of the predicting value was assessed using receiver operating characteristic (ROC) curve.

2. Result

Association between ischemia-modified albumin and ACS subgroups

Knowledge about the role of oxidative stress in human diseases, including cardiovascular system disorders, emphasizes the need for reliable markers of oxidative stress. Evaluation the levels of the novel marker ischemia-modified albumin (IMA) was highlighted in the updated research. Serum IMA levels as an oxidative stress index, their ratio to Albumin and total albumin were estimated in this study among three subgroups of ACS patients. Results were indicated that IMA levels were shown a significant increased range levels in the negative troponin MI cases compared to the positive troponin MI and unstable angina. The range levels were (3.12-6.41); (3.1-5.66) and (3.17-5.56) respectively. On the other hand, unstable angina cases were shown a decreasing level of Albumin and increasing levels of IMA/ Alb ratio. Figure (1) demonstrated the distribution of Ischemic Modified Albumin, IMA/Albumin ratio and Albumin Levels in Acute coronary syndrome groups

Examination the sampling time of ischemia-modified albumin in ACS subgroups.

The timing of the IMA sampling was also looked at in this study. The sampling period was separated into two subgroups: samples that left the CCU in excess of 90 minutes and samples that left less than 90 minutes after their arrival. Even within the normal range, the effect of serum albumin on IMA levels is

still a significant issue. It has been established that there is a negative connection between changes in albumin levels of 1 g/dl and changes in IMA levels of 2.6%. This suggests that in order to prevent any false-positive or false-negative findings, it is necessary to compare IMA values with those of albumin using their ratio.

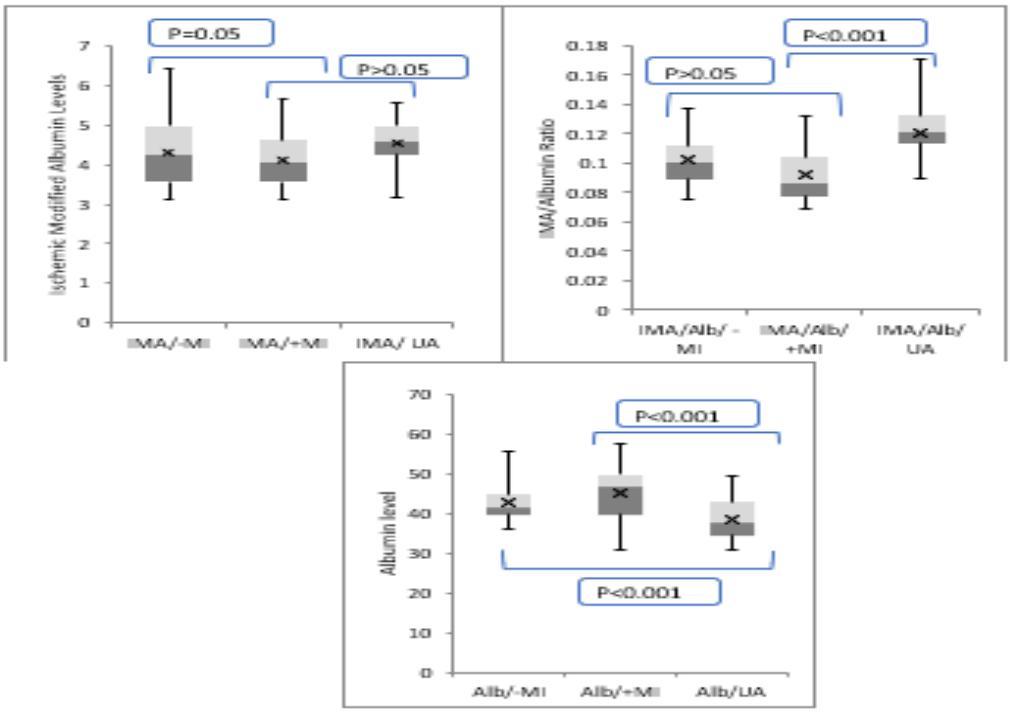

Figure (1) Boxplot of Distribution Ischemic Modified Albumin, IMA/Albumin ratio and Albumin Levels in Acute coronary syndrome groups

Results showed that serum IMA and its ratio to albumin assessed in ACS patients who were sent to CCU in less than 1.5 hours of chest pain had higher levels and suggested their capability in differentiating the early ischemia episode. The mean levels of IMA recorded within the first 90 minutes following an attack were (4.79), while the mean levels measured after more than 90 minutes were (2). Additionally, early measurement resulted in a good increase in the IMA/Alb ratio.

Figure (3.5) illustrated the mean Levels of IMA and Ischemic Modified Albumin/ Albumin ratio) in Acute coronary syndrome patients based on the sampling time of their duration staying in emergency and CCU.

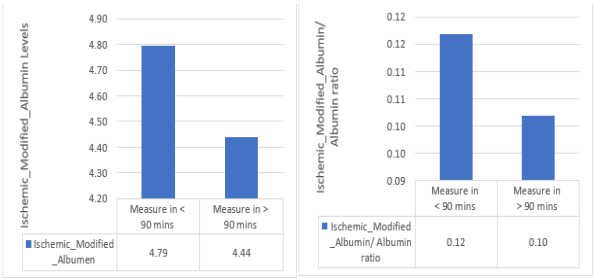

Figure (2): Biomarkers Levels (IMA and Ischemic_Modified_Albumin/ Albumin ratio) in Acute coronary syndrome patients based on the sampling time of their duration staying in emergency and CCU

Considering the important role of the measured biomarkers in the progression of ACS, the multivariable linear regression model was used to analyze the response relationship between parameters.

Serum IMA levels was positively significant correlated to their ratio with albumin. In addition, IMA was significantly associated with TG & LDL levels as presented in Table (1) . On the other hand, serum IMA/Alb ratio was highly significant positively related to Albumin levels and TG (all P < 0.05), as shown in Table (2).

Table (1) Correlation coefficients by Spearman rank test for Ischemic Modified Albumin, IMA/Albumin ratio with the lipid profile and Albumin in ACS patients

Variables	IMA	
	Correlation coefficient (r)	P value
IMA/Alb	0.8	<0.001
Albumin	0.2	0.103
HDL	0.3	0.47
TG	0.4	0.01
LDL	0.4	0.026
Cholesterol	0.32	0.14

Table (2) Correlation coefficients by Spearman rank test for Ischemic Modified Albumin, IMA/Albumin ratio with the lipid profile and Albumin levels in ACS patients

Variables	IMA/Alb ratio	
	Correlation coefficient (r)	P value
IMA	0.8	<0.001
Albumin	0.5	<0.001
HDL	0.3	0.9
TG	0.4	0.04
LDL	0.2	0.128
Cholesterol	0.41	0.698

Results of the receiver operating curve (ROC) and AUC analysis for the Ischemic Modified Albumin, IMA/Albumin ratio as possible diagnostic parameters was also performed. IMA level was shown a good diagnostic performance for prediction ACS Patients compared to control group, data are presented in Figure (3) and Table (3).

For IMA levels: (sensitivity = 90%, specificity = 80%) at a level = 3.59, while IMA/ Alb ratio levels: (sensitivity = 0.92%, specificity = 0.67%) at a level = 0.072. Only p-values of the AUC for IMA were <0.001 and statistically significant.

Table (3) AUC, optimal threshold, Sensitivity and specificity of Ischemic Modified Albumin, IMA/Albumin ratio obtained by the ROC curves for prediction of ACS compared to control group

Test Variable	AUP	Sensitivity %	Specificity %	Cut-off points	P vale	CI (95%)
IMA	0.703	0.9	0.8	3.59	0.006	0.568-0.837
IMA/ Albumin	0.62	0.9	0.6	0.072	0.111	0.481-0.754

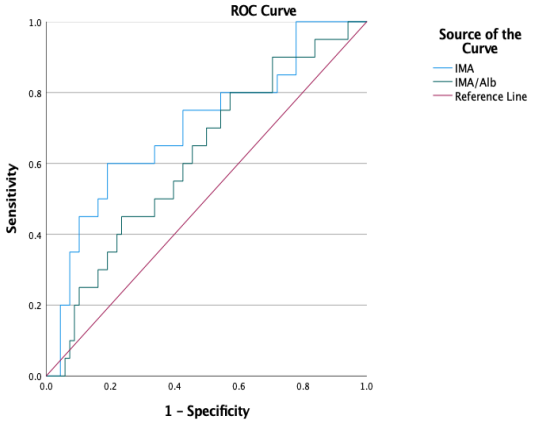

Figure (3) ROC curves for Ischemic Modified Albumin, IMA/Albumin ratio in ACS patients to analyse the optimal diagnostic points for predicting ACS cases compared to control group.

3. Discussion

Albumin synthesis or changes of functional activity can destabilize oncotic blood pressure. Albumin properties incur some changes under ischemic attacks associated with oxidative stress, production of reactive oxygen species (ROS), and development of acidosis

The mechanism of A production during ischemia is fueled by oxidative stress. Acidosis is brought on by tissue hypoxia and anaerobic glycolysis, which also cause the release of Cu2+ ions from copper-containing proteins such ceruloplasmin. Cu2+ is converted to Cu+ in the presence of reducing chemicals, which is followed by the production of the superoxide anion O2. The enzyme superoxide dismutase (SOD) catalyzes the dismutation of superoxide O2 to hydrogen peroxide H2O2, which then undergoes the Fenton reaction and produces hydroxyl radicals (OH) when Cu2+ is present. The degradation of NTS and IMA production is facilitated by these radicals (17).

Also many studies reported that , IMA has been proposed as an early biomarker for various diseases associated with ischemia and oxidative stress (18).

The N-terminal sequence of HSA (Asp1-Ala2- His3-Lys4) is very susceptible to biochemical modifications and degradation induced by oxidative stress. Consequently, the affinity of NTS to transition metals, especially to cobalt, is reduced. This variant of albumin was called ischemia- modified albumin (IMA) (19).

It seems to be in case of negative troponin, as an early stage of ischemia, IMA could be used as an early diagnostic marker better than even troponin. The Posttranslational changes might be result in a wide range of albumin variants that appear or become more abundant in the blood as a result of metabolic changes associated with various diseases (20).

serum IMA appears to be a sensitive biomarker of myocardial ischemia in MI patients. Research was confirmed the ability to detect ischemia before myocyte destruction. Furthermore, it was also indicated that assessment of concentrations of IMA were vastly superior to the assessment of cTn concentrations within the same time frame for early diagnosis of MI. In myocardial ischemia, a structural change in the N-terminus of albumin occurred, and this albumin showed lower metal-binding capacity with cobalt on the albumin–cobalt binding test. IMA rise can be detected by this test 3 hours after the appearance of ACS symptoms (21).

It is well known that within minutes of onset of myocardial ischemia, there is hypoxia, free radical damage and acidosis followed by disruption of membrane sodium/calcium ion pumps. Also, it has been indicated that mechanisms involved in ischemia / reperfusion are induced changes in albumin and may include exposure to endothelial and extracellular hypoxia, acidosis, free radical damage, ATP dependent sodium and calcium pump disruption resulting in exposure to free iron and copper ions (22).

An early study was shown that IMA levels rise within minutes after ischemia and return to baseline within 6 h (23). It has been reported that the sensitivity of IMA for the diagnosis of acute ischemic chest pain is significantly greater than that of ECG and cTn. In addition, in a human model of ischemia induced by balloon angioplasty, IMA rises early after balloon inflation and levels returns to baseline within 6–12 hours (24).

On the other hand, utilization of IMA measurements in ACS patients was start to rise in the blood after a few minutes following ischemia when investigated in a number of trials. The results of trials indicate that the IMA levels show an early increase shortly after the onset of ischemia and maintain these high levels for 6-12 hours following ischemia (25).

there correlations would be confirmed the post translation modification of albumin due to oxidative

stress process and accumulation of lipid, since Several works suggested the release of fatty acids in myocardial ischemia results in the binding of fatty acid to albumin, inducing a conformational change in albumin (26).

Previously, it has been demonstrated by Ertekin et al., 2013 that the high sensitivity and specificity rates of IMA make it the safe and promising method in diagnosing ACS at the emergency department along with its advantages in low cost, rapid results and easy measured indicate that this test may be used as a powerful marker in clinical practice in the near future (27).

Also, Abdel Wahab. (2017) revealed that the diagnostic performance of the IMA level in the ACS patients was greater as compared to that of the TnI assay. The sensitivity and the specificity of IMA were significantly greater than those of TnI. The combination of the IMA and the TnI results improved the sensitivity of the detection of ACS to 98% with a negative predictive value of 92%. These authors also revealed that 71% of troponin negative patients have significant obstructive coronary artery disease while IMA could predict significant obstructive CAD in those troponin negative patients with sensitivity of 96.3%, specificity of 72.7%, PPV of 89.7%, NPV of 88.9% and accuracy 89.5% (28).

The determination of biomarkers for myocardial injuries plays an important role in the diagnosis and the treatment of ACS. In the clinical practice, more attention has been paid to the determination of myocardial markers for the diagnosis of acute myocardial Ischemia, stratification of the ACS risk and the differential diagnoses of reversible versus irreversible myocardial ischemia and acute chest pain. The quantitative or qualitative determination of cardiac TnI has been well accepted as a marker of the myocardial damage. However, most of the biomarkers of Acute Myocardial Infarction (AMI) are the products of myocardial necrosis and thus are detected typically at a later stage of the myocardial damage (29). Therefore, rapidly detectable, highly sensitive markers would be desirable for myocardial ischemia, to identify the patients with only ischemia and those who are early in the course of an acute coronary syndrome without the evidence of any myocardial necrosis.

The core of this study lay in the fact that the measurements of the serum IMA levels could aid in a diagnosis of ACS in patients with ongoing ischaemic pain, who presented to the emergency department. IMA can be used as an independent point of care test or an additional parameter along with TnI, to boost the confidence of the clinicians in ruling out cardiac ischaemia. This combination seems to have clear potentials of time saving, an early intervention and a shortened stay in the emergency department (30).

Also, IMA has confirmed to provide a valuable information regarding the duration of diseases and possible complications, and it can be used in the differential diagnosis of certain pathological conditions. IMA's advantage as a biomarker over other markers is its ability to detect ischemic conditions at earlier stages. The simplicity and availability of the techniques for its determination provide an opportunity to stratify patients and determine risk groups for adverse events after a stroke, heart attack, traumatic brain injuries, and spinal injuries and assess the state of patients with neurological disorders, diabetes, pregnancy complications, and with gynecological and other ischemic-associated pathologies (31).

References

S. M. Ahn and R. J. Simpson, "Body fluid proteomics: prospects for biomarker discovery," *Proteomics – Clinical Applications*, vol. 1, no. 9, pp. 1004–1015, 2007.

M. Ellmerer, L. Schaupp, G. A. Brunner et al., "Measurement of interstitial albumin in human skeletal muscle and adipose tissue by open-flow microperfusion," *American Journal of Physiology-Endocrinology and Metabolism*, vol. 278, no. 2, pp. E352–E356, 2000.

T. Peters, *"All about Albumin," Biochemistry, Genetics, and Medical Applications*, Academic Press, Inc., San Diego, California, 1996.

S. M. Ahn, K. Byun, K. Cho et al., "Human microglial cells synthesize albumin in brain," *PLoS One*, vol. 3, no. 7, article e2829, 2008.

R. Nurdiansyah, M. Rifa'i, and Widodo, "A comparative analysis of serum albumin from different species to determine a natural source of albumin that might be useful for human therapy," *Journal of Taibah University Medical Sciences*, vol. 11, no. 3, pp. 243–249, 2016.

S. Al-Harthi, J. I. Lachowicz, M. E. Nowakowski, M. Jaremko, and Ł. Jaremko, "Towards the functional high-resolution coordination chemistry of blood plasma human serum albumin," *Journal of Inorganic Biochemistry*, vol. 198, article 110716, 2019.

V. S. Reddy, S. Bukke, K. Mahato et al., "A meta-analysis of the association of serum ischaemia-modified albumin levels with human hypothyroidism and hyperthyroidism," Bioscience Reports, vol. 37, no. 1, 2017.

N. A. Lashari, N. I. Lakho, S. Ahmed, and A. Ahmed, "Acute coronary syndrome; frequency, contributing factors and types in patient with typical chest pain," The Professional Medical Journal, vol. 24, no. 3, pp. 409–413, 2017

Y. Huang, K. Gulshan, T. Nguyen, and Y. Wu,"Biomarkers of cardiovascular disease," Disease Markers, vol. 2017, Article ID 8208609, 2 pages, 2017

K. A. Hashmi, H. Y. Saeed, M. S. Farid, J. Najam, M. Irfan, and A. A. Hashmi, "Frequency of multivessel severe coronary artery disease in patients with non-ST segment elevation myocardial infarction having markedly raised cardiac troponin T," Cureus, vol. 12, no. 8, article e9571, 2020.

. H. Christenson, S. H. Duh, W. R. Sanhai et al., "Characteristics of an albumin cobalt binding test for assessment of acute coronary syndrome patients: a multicenter study," Clinical Chemistry, vol. 47, no. 3, pp. 464–470, 2001

R. Chawla, N. Goyal, R. Calton, and S. Goyal,"Ischemia modified albumin: a novel marker for acute coronary syndrome," Indian Journal of Clinical Biochemistry, vol. 21, no. 1, pp. 77– 82, 2006.

Y. W. Lee, H. J. Kim, Y. H. Cho, H. B. Shin, T. Y. Choi, and Y. K. Lee, "Application of albumin-adjusted ischemia modified albumin index as an early screening marker for acute coronary syndrome," Clinica Chimica Acta, vol. 384, no. 1–2, pp. 24–27, 2007.

X. Su, K. Zhang, F. Guo et al., "Ischemia-modified albumin, a predictive marker of major adverse cardiovascular events in continuous ambulatory peritoneal dialysis patients," Clinical Biochemistry, vol. 46, no. 15, pp. 1410–1413, 2013.

C. Bhakthavatsala Reddy, C. Cyriac, and H. B. Desle, "Role of "Ischemia Modified Albumin" (IMA) in acute coronary syndromes,"Indian Heart Journal, vol. 66, no. 6, pp. 656–662, 2014

M. Nepal, S. Jaisawal, M. Guragain et al., "Ischemic modified albumin (IMA) as a novel marker for ischemic heart disease and surrogate marker for other high oxidative -ischemic conditions," Journal of Cardiovascular Disease Research, vol. 8, no. 4, pp. 112–116, 2017.

Shevtsova, A., Gordiienko, I., Tkachenko, V. and Ushakova, G., 2021. Ischemia-modified albumin: origins and clinical implications. Disease Markers, 2021.

LEE, Philbert; WU, Xiaoyang. Modifications of human serum albumin and their binding effect. *Current pharmaceutical design*, 2015, 21.14: 1862-1865.

WATANABE, Hiroshi, et al. Clinical implications associated with the posttranslational modification–induced functional impairment of albumin in oxidative stress–related diseases. *Journal of pharmaceutical sciences*, 2017, 106.9: 2195-2203.

CHUBAROV, Alexey, et al. Reversible dimerization of human serum albumin. *Molecules*, 2020, 26.1: 108.

AYDIN, Suleyman, et al. Biomarkers in acute myocardial infarction: current perspectives. *Vascular health and risk management*, 2019, 15: 1.

BERENSHTEIN, Eduard, et al. Patterns of mobilization of copper and iron following myocardial ischemia: possible predictive criteria for tissue injury. *Journal of molecular and cellular cardiology*, 1997, 29.11: 3025-3034.

BAR-OR, David, et al. Reduced albumin-cobalt binding with transient myocardial ischemia after elective percutaneous transluminal coronary angioplasty: a preliminary comparison to creatine kinase-MB, myoglobin, and troponin I. *American heart journal*, 2001, 141.6: 985-991.

SINHA, M. K., et al. Role of "Ischemia modified albumin", a new biochemical marker of myocardial ischaemia, in the early diagnosis of acute coronary syndromes. *Heart*, 2004, 90.6: 644-644.

LIYAN, Cui, et al. Assay of ischemia-modified albumin and C-reactive protein for early diagnosis of acute coronary syndromes. *Journal of clinical laboratory analysis*, 2008, 22.1: 45-49.

DOMINGUEZ-RODRIGUEZ, Alberto, et al. Association of ischemia-modified albumin and melatonin in patients with ST-elevation myocardial infarction. *Atherosclerosis*, 2008, 199.1: 73-78

ERTEKIN, Birsen, et al. Diagnostic value of ischemia-modified albumin in acute coronary syndrome and acute ischemic stroke. *Pakistan journal of medical sciences*, 2013, 29.4: 1003

WAHAB, Mohamed Abdel Kader Abdel. Ischemia modified albumin (IMA) in acute coronary syndrome (ACS) and left bundle branch block (LBBB). Does it make the difference? *The Egyptian Heart Journal*, 2017, 69.3: 183-190.

TAKHSHID, M. A., et al. Early diagnosis of acute coronary syndrome with sensitive troponin I and ischemia modified albumin. 2010.

PATIL, Sangita M., et al. The clinical assessment of ischaemia modified albumin and troponin I in the early diagnosis of the acute coronary syndrome. *Journal of clinical and diagnostic research: JCDR*, 2013, 7.5: 804.

Shevtsova, A., Gordiienko, I., Tkachenko, V. and Ushakova, G., 2021. Ischemia-modified albumin: origins and clinical implications. Disease Markers, 2021.