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ARAŞTIRMA / RESEARCH

Ischemia modified albumin levels in distinguishing NSTEMI patients from non-ischemic controls and correlation with disease severity

İskemi modifiye albümin düzeylerinin NSTEMI hastalarını iskemik olmayan kontrollerden ayırt etmedeki rolü ve hastalık şiddeti ile ilişkisi

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Abstract

Purpose: The aim of this study was to investigate the diagnostic value of ischemia modified albumin (IMA) in early non-ST elevation myocardial infarction (NSTEMI) patients diagnosed with high-sensitive cardiac troponin (hs-cTn)assays.

Materials and Methods: In the first three hours of symptom onset, one hundred sixty-two patients without cardiovascular disease history admitted to our hospital with NSTEMI were enrolled between March 2018 and August 2019. The patients' IMA levels were compared with IMA levels of randomly selected, age and the sex-matched control group comprised of 61 subjects with normal coronary angiography results.

Results: IMA levels of NSTEMI patients were higher than the control group. In receiver operating characteristic (ROC) curve analysis, a value equal or greater than 0.3855 ABSU has an 82% sensitivity and a 99.4% specificity for diagnosing NSTEMI (AUC: 0.962, 95% CI: 0.937 – 0.986,). In addition, ROC curve analysis revealed moderate predictive power for distinguishing three-vessel disease (cut-off value: 0.4290 ABSU, sensitivity 78.4% and specificity 56.3%, AUC: 0.696, 95% CI: 0.616 – 0.776,). IMA levels were positively correlated with Gensini scores of the patient group.

Conclusion: Ischemia-modified albumin, when used alone, was very useful in distinguishing NSTEMI from non-ischemic controls. Besides, IMA levels were positively correlated with CAD severity.

Keywords:. Myocardial infarction; sulfhydryl compounds; atherosclerosis

Öz

Amaç: Bu çalışmada yüksek duyarlılığa sahip kardiyak troponin (hs-cTn) testleri ile tanı konulan erken dönem ST yükselmesiz miyokard infarktüsü (NSTEMI) hastalarında iskemi modifiye albümin (İMA) 'nın tanısal değerini araştırmayı amaçladık.

Gereç ve Yöntem: Mart 2018 ve Ağustos 2019 tarihleri arasında hastanemize NSTEMI ile başvuran kardiyovasküler hastalık öyküsü olmayan 126 hasta kaydedildi. Hastaların IMA düzeyleri rastgele seçilen, yaş ve cinsiyet eşleştirilmiş koroner anjiyografi sonuçları normal olan 61 deneğin IMA düzeyleri ile karşılaştırıldı.

Bulgular: NSTEMI hastalarının IMA seviyeleri kontrol grubuna göre daha yüksekti. İşlem karakteristiği (ROC) eğri analizinde, 0,3855 ABSU' ya eşit veya daha büyük bir değer, NSTEMI tanısı için %82 duyarlılığa ve%99,4 özgülüğe sahiptir (EAA: 0,962, %95 CI: 0,937 – 0,986). Ek olarak, ROC eğrisi analizi, üç damar hastalığını ayırt etmek için orta düzeyde tahmin gücü ortaya koydu (sınır değeri: 0,4290 ABSU, duyarlılık %78,4 ve özgüllük %56,3, EAA: 0,696, %95 CI: 0,616 – 0,776). İMA düzeyleri ile hasta grubunun Gensini puanları arasında pozitif korelasyon vardı.

Sonuç: İskemi modifiye albümin tek başına kullanıldığında, NSTEMI' yi iskemik olmayan kontrollerden ayırt etmede oldukça yararlı olmuştur. Ayrıca, IMA seviyeleri KAH şiddeti ile pozitif korelasyon gösteriyordu.

Anahtar kelimeler: Miyokard enfarktüsü; sülfhidril bileşikleri; ateroskleroz

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INTRODUCTION

Despite advances in patients' health care with atherosclerotic cardiovascular disease, myocardial infarction (MI) remains the most critical public health problem globally. In the past decades, while coronary artery disease (CAD) mortality decreases, the prevalence of non-ST segment elevation myocardial infarction (NSTEMI) tends to increase[1].

High sensitive cardiac troponin (hs-cTn) assays have consistently improved diagnostic accuracy for MI compared to traditional assays, notably in patients presenting early after chest pain start, allowing for a more fast rule-in or rule-out[2,3]. Usage of hs-cTn assays reduced the troponin blind interval, resulting in earlier acute MI detection. Besides, hs-cTn use resulted in approximately 4% absolute and a 20% relative increase in the diagnosis of type 1 MI and a parallel decrease in unstable angina diagnosis[4].

Ischemia-modified albumin (IMA) occurs when albumin, the most abundant circulating protein in the blood, is exposed to ischemic tissue and undergoes chemical changes. Ischemia causes a conformational change in the N terminal part of albumin, resulting in decreased metal-binding capacity, mainly cobalt[5]. Ischemia-modified albumin is a new biomarker proposed for early acute coronary syndromes[6]. Contrary to other cellular cytoplasmic markers like troponins, IMA can be detected early in ischemic conditions, rises in 30 minutes after symptom onset or percutaneous interventions, and returns to baseline levels 12 hours[5]. Although some studies failed to show such a relationship[7,8], several have shown that IMA can help exclude non-cardiac chest pain when used alone or combined with troponin levels and electrocardiograms[9-11]. However, IMA's diagnostic role has been widely studied, conventional troponin assays were used exclusively in these studies, and the IMA's diagnostic value in the hs-cTn era is unknown. We conducted a study to determine the diagnostic value of IMA levels in NSTEMI patients and the relationship between IMA levels and CAD severity.

MATERIALS AND METHODS

Study population

In the first three hours of symptom onset, one hundred sixty-two patients admitted to our hospital with NSTEMI were enrolled between March 2018 and August 2019. Patients with any previous atherosclerotic disease (CAD, embolic and hemorrhagic stroke, peripheral artery disease, aortic diseases), moderate to severe valvular heart disease, uncontrolled hypertension, chronic inflammatory diseases (inflammatory bowel diseases, rheumatologic diseases), renal or hepatic insufficiency, nephrotic syndrome, and cancer were excluded from the study. Patients with symptom onset more than three hours were also excluded because IMA's early peak in acute coronary syndromes. All patients carefully read and understood the study protocol and gave informed consent. The study protocol was approved by the local ethics committee of Çukurova University on 13 January 2017 (meeting no: 60). The research was carried out in accordance with the Helsinki Declaration's guidelines.

Patients undergoing elective coronary angiography due to suspicion of CAD were chosen as the control group. Subjects in the control group were selected randomly; only age and sex match with the patient group was arranged. In the control group, patients were evaluated for CAD by exercise treadmill test and myocardial perfusion scintigraphy and revealed normal. Since slow coronary flow has been shown to alter IMA levels significantly, patients with the slow coronary flow were also excluded from the control group [12]. Coronary angiography was performed due to ongoing symptoms and suspicion of CAD. The authors of this article did not decide to perform coronary angiography for the control group. Control subjects were randomly chosen from a subset of 75 patients with normal coronary angiography, age extremes were excluded one by one until age, and a sex match was established with the patient group. Sixty-one subjects remained in the control group after matching. The authors did not know the variables other than age and gender to prevent any selection bias.

Diagnosis

The diagnosis of NSTEMI was made according to the latest ESC NSTEMI guidelines. High-sensitive troponin I was measured with a new high-sensitive assay (Access 2, Beckman Coulter, Inc. Brea, CA 92821, USA). The limit of blank, detection, functional sensitivity of this assay were 0.14, 0.34, and 1.35 ng/L. The within-run, between-run, and total imprecision were 2.2%–2.9%, 4.6%–5.4%, and 5.4%–6.1%, respectively. The linearity was excellent

in the range of cTnI values between 0.95 and 4195 ng/L (r=1.00). The 99th percentile upper reference limit was 15.8 ng/L[13].

Coronary angiography

Coronary angiography was performed using the femoral artery with standard Judkins catheters. All patients were treated under the latest NSTEMI guideline. Glycoprotein IIb/IIIa inhibitors were only used in no-reflow or significantly high thrombus burden [14]. Two experienced interventional cardiologists assessed all coronary angiographies, and Syntax and Gensini scores were calculated by both of them separately. In the case of unanimity, scores were averaged. Patients were compared with sixty-one age and sex-matched healthy controls with normal coronary angiograms.

Measurement of serum IMA levels

Bar-Or et al. developed a fast, colorimetric assay for measuring human serum IMA levels based on diminished cobalt binding to albumin. The novel assay method begins with adding 50 L of m 0.1% cobalt chloride (Sigma, CoCl2.6H2O) in H2O to 200 μL of serum, delicately mixing and holding up 10 minutes for fine cobalt-albumin binding. Fifty microliters of dithiothreitol (DTT) (Sigma, 1.5 mg/ml H2O) were added as a colorizing agent, and the reaction was extinguished 2 minutes afterward, adding 1.0 mL of 0.9% NaCl to the solution.

Utilizing a spectrophotometer at 470 nm (Shimadzu, model UV160U), color occurrence with DTT was compared to a serum-cobalt blank without DTT and calculated in absorbance units (ABSU). The colorimetric assay measures the remaining free cobalt after cobalt-albumin binding has happened. Therefore, with diminished cobalt-albumin binding, more accessible cobalt is identified, resulting in elevated IMA levels [15]. The authors confirmed the colorimetric assay with experiments using radioactive ^{57}Co (unpublished observation by Bar-or et al.).

Statistical analysis

For statistical analysis, SPSS 20.0 software (SPSS Inc., Chicago, IL) was utilized. Shapiro-Wilk test was used to analyze the normality of continuous variables. Continuous variables with normal distribution were reported as mean ± standard deviation and non-normally distributed variables as median (minimum-maximum). Student's t-test and Mann-Whitney U tests compared normally and non-normally distributed continuous variables between two groups. One-way ANOVA and Kruskal Wallis tests were used to compare continuous variables between three or more groups. Chi-square tests were used to compare categorical variables. Pearson and Spearman correlation coefficients were reported for bivariate analysis. Patient and control groups were analyzed by using the Students' t-test and Mann-Whitney U tests.

Linear regression analysis was used to determine the independent relation of variables with IMA levels. Variables with a p-value of less than 0.25 in bivariate analysis were included in the model as covariates and cofactors of IMA levels [16]. Syntax and Gensini scores were not included in the same regression model due to multicollinearity ($r= 0.85$, $p<0.001$). A p-value of less than 0.05 was considered statistically significant.

We applied receiver operating characteristic (ROC) curve analysis to determine the IMA cut-off value for discriminating patients from controls and distinguishing three-vessel disease from other NSTEMI patients. We examined the ROC curve analysis output to select a cut-off value, the youden index, and the index of union methods were used. The decision was made after interpreting the results. We reported the analysis outcome in detail in the results and discussion sections.

RESULTS

The patient group was comprised of 162 NSTEMI cases, and the control group was composed of 61 healthy subjects with normal coronary arteries (age 58.02 ± 9.56 vs. 60.51 ± 11.09, p=0.122 and female gender 64 (39.50%) vs. 26 (42.62%), p=0.678 respectively). Age, gender, lipid profile, white blood cell counts were similar between groups ($p>0.05$ for all). Only the patient group's hemoglobin levels were higher than the control group (13.58 ± 1.68 gr/dl vs. 12.84 ± 1.90 gr/dl, p = 0.008). As expected, the patient group had higher troponin levels than the control group (9.0 (0-16) v.s 1348 (29-2768) ng/L). Patients' group had higher levels of IMA than the control group (0.47 ± 0.10 vs. 0.28 ± 0.04 ABSU, $p<0.001$) (Table 1).

In bivariate correlation analysis, IMA was positively correlated with the Gensini score in the patient group ($r = 0.31$, $p= 0.040$) (Table 2). There was no correlation between the Syntax score and IMA. Multivariate analysis did not reveal any independent relationship.

Table 1. Comparison of the control group with the patient group

	N=162	N=61	p
Age, years	58.02 ± 9.56	60.51 ± 11.09	0.122
Creatinin, mg/dl	0.87±0.36	0.91 ± 0.44	0.485
Gender, female, n (%)	64 (39.5%)	26 (42.62%)	0.678
Haemoglobin, (gr/dl)	13.58 ± 1.68	12.84 ± 1.90	0.008
White blood cell count, (n/mm^3)	8954 ± 3125	9876.66 ± 3359.06	0.064
Total cholesterol, (mg/dl)	177.13 ± 56.42	192.14 ± 59.78	0.084
High density lipoprotein, (mg/dl)	36.79 ± 11.72	39.49 ± 10.15	0.115
Low density lipoprotein, (mg/dl)	131.24 ± 49.92	126.04 ± 48.57	0.485
Triglycerides, (mg/dl)	210.77 (10 – 520)	190.54 (0 – 485)	0.257
Systolic blood pressure, (mmHg)	133.75 ± 25.24	132.09 ± 22.10	0.653
Diastolic blood pressure, (mmHg)	77.19 ± 13.68	76.85 ± 12.12	0.864
IMA, (ABSU)	0.47 ± 0.10	0.28 ± 0.04	<0.001
Gender, female, n (%)	32 (52.5%)	64 (39.5%)	0.096
Diabetes mellitus, n (%)	20 (32.7%)	70 (43.5%)	0.147
Hypertension, n (%)	29 (47.5%)	95 (59%)	0.079
Hyperlypidemia, n (%)	6 (9.83%)	8 (5%)	0.217
ACE inhibitor usage, n (%)	21 (34.4%)	44 (27.16%)	0.287
ARB usage, n (%)	12 (19.67%)	25 (15.43%)	0.575
Beta blocker usage, n (%)	14 (22.95%)	27 (16.66%)	0.287
Statin usage, n (%)	8 (13.11%)	15 (9.25%)	0.398
Troponin (ng/L)	9 (0-16)	1348 (29-2768)	<0.0001

ABSU: Absorbance units, ACE: Angiotensin-converting enzyme, ARB: Angiotensin receptor blocker, IMA: Ischemia modified albumin. Students t-test, Chi-square test, Kruskal Wall's tests were used.

Table 2. Correlations between IMA and Gensini and Syntax scores.

	Gensini score		Syntax score	
	r	p	R	p
IMA	0.31	0.040	0.139	0.096

IMA: Ischemia modified albumin. Pearson and Spearman correlation tests were used

Receiver operating characteristic curve analysis showed nearly a perfect result for IMA levels for discriminating NSTEMI patients from healthy controls. Area under the curve was 0.962 (95% CI: 0.937 – 0.986, p< 0.001). A value equal to or greater than 0.3855 ABSU has an 82% sensitivity and a 99.4% specificity for diagnosing NSTEMI (positive likelihood ratio: 50.02, negative likelihood ratio: 0.18). A cut-off value of 0.3725 has an 87,3% sensitivity and 96.7% specificity (positive likelihood ratio: 26.63, negative likelihood ratio: 0.13). (Figure 1). When we used the youden index and the index of union methods to determine the best cut-off value for IMA in ROC curve analysis, we found a cut-off value of 0.3685 ABSU with a sensitivity of 88.7% and specificity of 96.1%. However, this value slightly improved the sensitivity (96.1% vs. 87.3%), the specificity was decreased from 99.4% to 96.1%. When we consider the nature of the acute coronary syndromes ruling out is more critical than ruling in;

therefore, higher specificity has to be targeted when the loss of sensitivity is mild. We advocate using the cut-off value, which has a higher specificity, rather than found by using the indexes above.

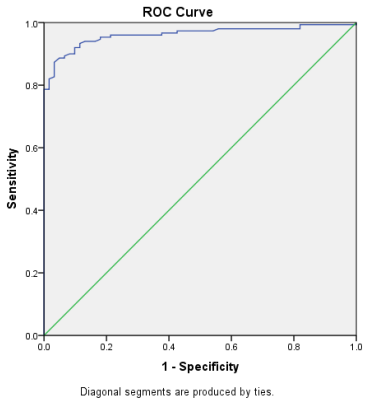

Figure 1. IMA cut-off value for discriminating NSTEMI patients from healthy controls.

A value equal or greater than 0.385 U has 82% sensitivity and 99.4% specificity for diagnosing NSTEMI (AUC: 0.962 95% CI: 0.937 – 0.986, p< 0.001).

In our study, IMA also was useful in discriminating three-vessel disease from non-three-vessel disease. A cut-off value 0.4290 ABSU has a sensitivity of 78.4% and a specificity of 56.3% for discriminating three-vessel disease (AUC: 0.696 95% CI: 0.616 – 0.776, p<0.001) (Figure 2).

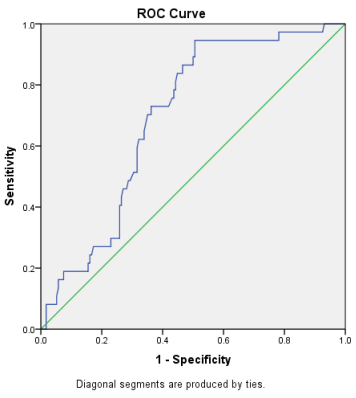

Figure 2. IMA cut-off value for discriminating three-vessel disease from non-three-vessel disease among NSTEMI patients.

A cut-off value 0.4290 ABSU has a sensitivity of 78.4% and a specificity of 56.3% for discriminating three-vessel disease (AUC: 0.696 95% CI: 0.616 – 0.776, p<0.001).

DISCUSSION

In ischemic conditions circulating albumin detoxifies free reactive oxygen species by binding with its N-terminal region. As a consequence of this reaction, it loses its metal binding capacity and converts into ischemia-modified albumin. Previous studies showed that IMA elevation was associated with the extent of reactive oxygen species formed during ischemia[5]. Ischemia-modified albumin levels increase in acute coronary syndromes, probably have a protective role for cardiomyocytes by antagonizing reactive oxygen species prevents oxidative damage. Studies show that IMA levels, when combined with electrocardiographic findings, troponin, and CK-MB levels, help diagnose MI with high sensitivity and high specificity in patients admitted to the emergency department with chest pain[9-11]. It has also been shown that higher IMA levels are associated with the extent of ischemia[17], left ventricular systolic dysfunction in patients with STEMI treated with primary PCI [18], and with major cardiac adverse events in NSTEMI patients[19]. Ischemia-modified albumin has been introduced as a novel diagnostic marker for acute coronary ischemia[10]. Our study found that IMA levels were higher in NSTEMI patients than control subjects, consistent with previous studies[9,20].

Receiver operating characteristic curve analysis revealed that IMA levels have high sensitivity and specificity for discriminating NSTEMI patients from control subjects (AUC: 0.962 95% CI: 0.937 – 0.986, p< 0.001). In our study, a cut-off value of 0.385 U for IMA has 82% sensitivity and 99.4% specificity for diagnosing NSTEMI (positive likelihood ratio: 50.02, negative likelihood ratio: 0.18). In previous studies, IMA levels combined with electrocardiogram and troponin levels were useful in discriminating MI from non-ischemic diseases or stable CADs in emergency departments[10,21-23]. In a study by Kazanis et al., stable CAD patients had higher IMA levels than the control group comprised of subjects with normal coronary angiography results. In this study, 114 stable patients were enrolled, and in ROC curve analysis, a cut-off value of 101.5 U/ml had an 87.7% sensitivity and 87.7% specificity for diagnosıng CAD (AUC: 0.901, 95% CI: 0.86-0.94). In a study by Bhagavan et al., the IMA level was highly sensitive and specific for discriminating acute ischemic events from non-ischemic chest pain in the emergency department. In this study, a cutoff value of 0.50 ABSU was 88% sensitive and 94% specific (AUC: 0.95, 95% CI: 0.92-0.99) for ischemia diagnosis[20].

The study population consisted of 167 subjects (75 patients and 92 controls). Our study found a similar powerful relationship between IMA levels and NSTEMI in a relatively large number of patients with a slightly higher area under the curve (0.950 vs. 0.962). In the study by Bhagavan et al., ischemia diagnosis was made using criteria; typical chest pain, any ischemic ECG changes, rise or fall of CK-MB or troponin levels, or undergoing any percutaneous intervention. Meeting one or more criteria was considered diagnostic, and the other patients admitting to the emergency department were considered non-ischemic[20]. In our study, the diagnosis of NSTEMI was clearly defined with a positive troponin test, and the control group was more clearly free of ischemic heart disease. Our study asserts that the clinical distinction between ischemic and non-ischemic individuals was more successfully demonstrated. In the emergency department, there would have been ischemic patients without obvious evidence of an acute disease. In this subset of patients, ischemia can be diagnosed or ruled out by further testing. Also, we used hs-cTn I assay to exclude NSTEMI, which is shown to better rule in or rule out NSTEMI patients than conventional troponin assays[4]. New generation hs-cTn assays report nanograms in liters, whereas conventional assays report in micrograms in liters. This improvement resulted in higher accuracy in the diagnosis of MI.

In our study, IMA also was useful in discriminating three-vessel disease from non-three-vessel disease. A cut-off value 0.4290 ABSU has a sensitivity of 78.4% and a specificity of 56.3% for discriminating three-vessel disease (AUC: 0.696 95% CI: 0.616 – 0.776, $p<0.001$). In another study by Demirtas et al., IMA levels were useful in distinguishing obstructive CAD from non-obstructive CAD in NSTEMI patients with a moderate sensitivity and specificity(24). We also found a weak but significant correlation between the Gensini score, which is a marker of the total coronary atherosclerotic burden of NSTEMI patients, and IMA levels ($r = 0.31$, $p= 0.040$). Demirtaş et al. reported a similar correlation coefficient ($r=0.25$, $p=0.05$) to our study[24]. Our findings confirm these results. These results suggest that in patients with NSTEMI diagnosis, measuring IMA levels can give valuable information about CAD severity, thus help to determine the patients who can benefit from more aggressive therapy.

In previous studies, IMA levels were related to markers of hyperlipidemia and inflammation such as cholesterol levels, oxidized LDL, hs-CRP in healthy populations, and diabetics, which are also classical risk factors for developing CAD[25,26]. The sophisticated relationship between atherosclerosis and classical risk factors and IMA may have accounted for the weak correlation and the lack of independent relationships in the multivariate analysis.

Increased IMA levels are associated with several non-cardiac pathologies like ischemic and hemorrhagic strokes, peripheral vascular diseases, advanced liver, and renal insufficiency, acute infections, malignancies, normal or complicated pregnancies, and prostate diseases[5,27]. Increased IMA levels have been reported in non-ischemic cardiac disorders such as radiofrequency ablation of arrhythmias and pacemaker implantation[28]. These findings show that IMA is not specific to cardiac ischemia. However, recent data propose that IMA release may result from reperfusion-induced events rather than ischemia[29]; several studies have shown a strong correlation between objective markers of ischemia, such as lactate and isoprostane concentrations and IMA levels[30,31]. During balloon angioplasty, serum IMA levels were directly proportional to the pressure, duration, and the number of inflations[32]. These findings suggest that IMA reflects the magnitude of ischemia during angioplasty. The mechanisms described above may be responsible for our results showing an association between IMA levels and CAD severity.

Ischemia-modified albumin levels are beneficial in distinguishing NSTEMI patients from non-ischemic healthy subjects. At the same time, IMA correlates with the Gensini score, an indicator of CAD severity, and was found to be moderately helpful in distinguishing three-vessel patients from other NSTEMI patients. Ischemia-modified albumin levels may be used to determine high-risk patients diagnosed with NSTEMI.

Yazar Katkıları: Çalışma konsepti/Tasarımı: SÖ, GYK; Veri toplama; ODU. SN, ÖE; Veri analizi ve yorumlama: SÖ, GYK, ODU; Yazı taslağı: SÖ, İçeriğin eleştirel incelenmesi: SÖ; Son onay ve sorumluluk: SÖ, GYK, ÖDU, SN, ÖE; Teknik ve malzeme desteği: ODU, SN, ÖE; Süpervizyon: SÖ; Fon sağlama (mevcut ise): yok.
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REFERENCES

1. Puymirat E, Simon T, Cayla G, Cottin Y, Elbaz M, Coste P et al. Acute myocardial infarction: changes in patient characteristics, management, and 6-month outcomes over a period of 20 years in the FAST-MI Program (French Registry of Acute ST-Elevation or Non-ST-Elevation Myocardial Infarction) 1995 to 2015. Circulation. 2017;136:1908-19.
2. Twerenbold R, Badertscher P, Boeddinghaus J, Nestelberger T, Wildi K, Puelacher C et al. 0/1-Hour Triage algorithm for myocardial infarction in patients with renal dysfunction. Circulation. 2018;137:436-51.
3. Boeddinghaus J, Twerenbold R, Nestelberger T, Koechlin L, Wussler D, Meier M et al. Clinical use of a new high-sensitivity cardiac troponin i assay in patients with suspected myocardial infarction. Clin Chem. 2019;65:1426-36.
4. Collet JP, Thiele H, Barbato E, Barthelemy O, Bauersachs J, Bhatt DL et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2020.
5. Sbarouni E, Georgiadou P, Voudris V. Ischemia modified albumin changes – review and clinical implications. Clin Chem Lab Med. 2011;49:177.
6. Collinson PO, Gaze DC. Biomarkers of cardiovascular damage and dysfunction--an overview. Heart Lung Circulation. 2007;16:71-82. .
7. Keating L, Benger JR, Beetham R, Bateman S, Veysey S, Kendall J et al. The PRIMA study: presentation ischaemia-modified albumin in the emergency department. Emerg Med J. 2006;23:764-8.
8. Hjortshoj S, Kristensen SR, Ravkilde J. Diagnostic value of ischemia-modified albumin in patients with suspected acute coronary syndrome. Am J Emerg Med. 2010;28:170-6.
9. Christenson RH, Duh SH, Sanhai WR, Wu AH, Holtman V, Painter P et al. Characteristics of an Albumin Cobalt Binding Test for assessment of acute coronary syndrome patients: a multicenter study. Clin Chem. 2001;47:464-70.
10. Peacock F, Morris DL, Anwaruddin S, Christenson RH, Collinson PO, Goodacre SW et al. Meta-analysis of ischemia-modified albumin to rule out acute coronary syndromes in the emergency department. Am Heart J. 2006;152:253-62.
11. Sinha MK, Roy D, Gaze DC, Collinson PO, Kaski JC. Role of "Ischemia modified albumin", a new biochemical marker of myocardial ischaemia, in the early diagnosis of acute coronary syndromes. Emerg Med J. 2004;21:29-34.
12. Koc F, Erdem S, Altunkas F, Ozbek K, Gul EE, Kurban S et al. Ischemia-modified albumin and total antioxidant status in patients with slow coronary flow: a pilot observational study. Anadolu Kardiyol Derg. 2011;11:582-7.
13. Lippi G, Ferrari A, Gandini G, Gelati M, Lo Cascio C, Salvagno GL. Analytical evaluation of the new Beckman Coulter Access high sensitivity cardiac troponin I immunoassay. Clin Chem Lab Med. 2017;56:157-61.
14. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Rev Esp Cardiol (Engl Ed) 2015;68:1125.
15. Bar–Or D, Lau E, Winkler JV. A novel assay for cobalt-albumin binding and its potential as a marker for myocardial ischemia—a preliminary report. J Emerg Med. 2000;19:311-15.
16. Hosmer DW, Lemeshow S. Applied Logistic Regression. New York, Wiley, 2008.
17. Chek J, Dusek J, Stasek J, Vojacek J, Bis J, Ulrychova M et al. Role of ischemia-modified albumin in estimating the extent and scope of cardiac ischemia in patients with ST elevation myocardial infarction. Heart and vessels. 2011;26:622-7.
18. Dominguez-Rodriguez A, Abreu-Gonzalez P, Garcia-Gonzalez MJ, Samimi-Fard S, Kaski JC. Relation of ischemia-modified albumin levels and left ventricular systolic function in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. Clin Chim Acta. 2008;388:196-99.
19. Bali L, Cuisset T, Giorgi R, Monserrat C, Quilici J, Carrega L et al. Prognostic value of ischaemia-modified albumin in patients with non-ST-segment elevation acute coronary syndromes. Arch Cardiovasc Dis. 2008;101:645-51.
20. Bhagavan NV, Lai EM, Rios PA, Yang J, Ortega-Lopez AM, Shinoda H et al. Evaluation of human serum albumin cobalt binding assay for the assessment of myocardial ischemia and myocardial infarction. Clin Chem. 2003; 49:581-5.
21. Roy D, Quiles J, Aldama G, Sinha M, Avanzas P, Arroyo-Espliguero R et al. Ischemia Modified Albumin for the assessment of patients presenting to the emergency department with acute chest pain but normal or non-diagnostic 12-lead electrocardiograms and negative cardiac troponin T. Int J Cardiol. 2004;97:297-301.

22. Collinson PO, Gaze DC, Bainbridge K, Morris F, Morris B, Price A et al. Utility of admission cardiac troponin and "ischemia modified albumin" measurements for rapid evaluation and rule out of suspected acute myocardial infarction in the emergency department. Emerg Med J. 2006;23:256-61.
23. Anwaruddin S, Januzzi JL, Jr., Baggish AL, Lewandrowski EL, Lewandrowski KB. Ischemia-modified albumin improves the usefulness of standard cardiac biomarkers for the diagnosis of myocardial ischemia in the emergency department setting. Am J Clin Pathol. 2005;123:140-5.
24. Demirtas AO, Karabag T, Demirtas D. Ischemic modified albumin predicts critical coronary artery disease in unstable angina pectoris and non-st-elevation myocardial infarction. J Clin Med Res. 2018;10:570-75.
25. Duarte MM, Rocha JB, Moresco RN, Duarte T, Da Cruz IB, Loro VL et al. Association between ischemia-modified albumin, lipids and inflammation biomarkers in patients with hypercholesterolemia. Clin Biochem. 2009;42:666-71.
26. Piwowar A, Knapik-Kordecka M, Warwas M. Ischemia-modified albumin level in type 2 diabetes mellitus - Preliminary report. Dis Markers. 2008;24:311-7.
27. Baydin A, Amanvermez R, Tuncel Ö K, Ocak M, Meric M, Cokluk C. Ischemia-modified albumin is not better than creatine kinase-MB and cardiac troponin I in predicting a cardiac injury in nontraumatic subarachnoid hemorrhage. Am J Emerg Med. 2015;33:488-92.
28. Sbarouni E, Georgiadou P, Panagiotakos D, Livanis EG, Theodorakis GN, Kremastinos DT. Ischaemia modified albumin in radiofrequency catheter ablation. Europace. 2007;9:127-9.
29. Hjortshøj S, Dethlefsen C, Kristensen SR, Ravkilde J. Kinetics of ischaemia modified albumin during ongoing severe myocardial ischaemia. Clin Chim Acta. 2009; 403: 114-20.
30. Sinha MK, Gaze DC, Tippins JR, Collinson PO, Kaski JC. Ischemia modified albumin is a sensitive marker of myocardial ischemia after percutaneous coronary intervention. Circulation. 2003;107:2403-5.
31. Sinha MK, Vazquez JM, Calvino R, Gaze DC, Collinson PO, Kaski JC. Effects of balloon occlusion during percutaneous coronary intervention on circulating ischemia modified albumin and transmyocardial lactate extraction. Heart. 2006;92:1852-3.
32. Quiles J, Roy D, Gaze D, Garrido IP, Avanzas P, Sinha M et al. relation of ischemia-modified albumin (IMA) levels following elective angioplasty for stable angina pectoris to duration of balloon-induced myocardial ischemia. Am J Cardiol. 2003;92:322-4.