DOI: 10.47799/pimr.1102.04

Ischemia-Modified Albumin (IMA) for early detection of myocardial ischemia in acute coronary syndrome with type 2 diabetes mellitus: a case control study

Mehraj A Junedi*, Abdulazim A Junaidi

Assistant professor, Department of Biochemistry, Ashwini Rural Medical College, Hospital & Research Centre, Kumbhari, Maharashtra, India

Corresponding Author
Mehraj A Junedi, Assistant professor, Department of Biochemistry, Ashwini Rural Medical College, Hospital & Research Centre, Kumbhari, Maharashtra, India

Date of Submission: 27/03/2023 **Date of Review: 24/05/2023** **Date of Acceptance: 30/07/2023**

ABSTRACT

Introduction: Evaluation of the patients who present to the hospital with a complaint of chest pain or other signs suggestive of acute coronary syndrome (ACS) is time-consuming, expensive, and difficult. Most of the biochemical markers are negative in early phase acute myocardial ischemia. Recent literature reports have shown more interest in a new biochemical marker which is Ischemia-modified albumin for the detection of myocardial injury. Objective: to estimate the level of ischemia-modified albumin (IMA) as a risk factor for cardiovascular disease in diabetes mellitus patients.

Materials and methods: A case-control study was undertaken with sixty Type-2 diabetic patients as cases and sixty non-diabetic healthy subjects as controls. Demographic data (sex, age), an ECG and Biochemical data were collected. Blood for IMA and HbA1C levels was collected within two hours of arrival, and IMA risk marker testing was performed before any heparin/thrombolytic treatment was started. Controlled and uncontrolled diabetic patients were determined by the level of their HBA1c and comparison with the means of IMA level in their serum.

Results: The IMA was significantly increased in diabetic patients compared to healthy controls, with cut off value (0.92 IU/L), and there is also a significant increase in IMA level in uncontrolled diabetic patients (Mean ± SD; 240.55 + 52.5) that presented with acute chest pain and have signs and symptoms of cardiac ischemia when compared with the well-controlled diabetic patients(Mean ± SD; 159.8 ± 60.4).

Conclusion: Ischemic Modified Albumin (IMA) level was elevated significantly in uncontrolled diabetic patients with early signs of early myocardial ischemia. Additionally, IMA estimation may improve our ability to identify ischaemic patients who are missed by current diagnostic strategies, or more confidently rule out patients who do not have ACS.

KEYWORDS: acute coronary syndrome (ACS), ischemia-modified albumin (IMA), Biomarker, Diabetes Mellitus

INTRODUCTION

Evaluation of the patients who present to the hospital with a complaint of chest pain or other signs or symptoms suggestive of acute coronary syndrome (ACS) is time-consuming, expensive, and difficult. Millions of patients present annually to hospitals with complaints of chest pain, and many more with other symptoms potentially indicative of ischemia. [1] Recent literature reports have shown more interest in a new biochemical marker; ischemia-modified albumin (IMA) for the detection of myocardial injury. Special attention is focused on the estimation of IMA tests for the diagnosis and evaluation of patients with myocardial ischemia as well as another acute coronary syndrome in the emergency department. [2]

Most biochemical markers are negative in the early phase of acute myocardial ischemia, such as unstable angina (UA), but IMA is highly sensitive and can be detected in the reversible early phase of ACS. [3–6]Many clinical studies have revealed that IMA can be used for early diagnosis of acute myocardial ischemia (AMI), exclusion of ACS, and stratification of ACS risk, so the admission rate of non-ischemic patients and misdiagnosis of individuals at risk for cardiac events can be reduced. [7–9]At present, there is a lack of availability of data about the correlation between serum IMA level and cardiac function changes in patients with UA or stable angina (SA).

Recent studies show that the structure of serum albumin changes when ischemia develops in the body. [10] From this point of view, studies focusing on a new marker for myocardial ischemia have been carried out. Ischemia Modified Albumin is a new marker used to detect myocardial ischemia and it shows an early change. Myocardial ischemia and accompanying hypoxia induced the structural modifications of human serum albumin (HSA). HSA molecule represents one of the circulating the antioxidant in plasma and plays a vital role in the efficient antioxidant defence of the organism thus having a protective effect. [11]

In vivo, studies revealed that serum albumin of individuals with myocardial ischemia exhibits a reduction in its inherent affinity for metal transition ions such as Co(II), Ni(II) and Cu(II) compared to non-ischemic ones. This abnormal molecule of HSA is known as Ischemia-Modified Albumin (IMA) and it is measured by the spectrophotometric Co(II)-albumin binding assay. The concentration of IMA is determined by the addition of a known amount of exogenous Co(II) to a serum sample and measurement of unbounded Co(II) by colourimetric assay using Dithiothreitol (DTT). An inverse relationship exists between the amount of albumin-bound cobalt and the intensity of the colour formation, reported in absorbance units (ABSU). [2]

There are several data on IMA in patients with different states with ischemia of non-cardiac origin such as systemic sclerosis [12, 13] peripheral vascular disease, skeletal muscle ischemia during arthroscopic knee surgery and exercise induce, but no one concerns diabetes. [14] Hyperglycemia and oxidative stress can induce chronic ischemia in diabetic patients. It could lead to necrosis of different tissues. [15, 16] Chronic hyperglycemia is associated with long-term damage, dysfunction, and failure of the normal functioning of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels. [9]The prevalence of diabetes mellitus is rising all over the world and have been increasing rapidly recently in India reaching 1.4 million cases in 2015. [10] An uncontrolled state of hyperglycemia leads to a variety of complications including peripheral vascular diseases, nephropathy, neuropathy, retinopathy, morbidity, and/or mortality. Type 2 diabetes and its related complications of hypertension, hyperlipidemia and atherosclerotic vascular disease also demonstrated an association of metabolic syndrome with the development of cardiovascular disease (CVD), and more confirmation related to mortality rate increment was given by Type 2 diabetes and their related complications cardiovascular disease remains the leading cause of death, and myocardial infarction (MI) tend to be more extensive and have poorly survival rate than in age, weight and sex-matched in individuals without diabetes. [17]

This case control study was planned to determine IMA level for early detection of myocardial ischemia in acute coronary syndrome with Type-2 Diabetes Mellitus and correlate with control of diabetic status.

MATERIAL METHODS

Study design: A Case-control study was undertaken at GMC, Baramati from 1st of February 20121 to November 2022 with the following criteria.

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

Exclusion criteria: Patients with liver disorders, autoimmune disorders, pregnant women, and 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.

Case Selection: Sixty patients with type 2 diabetes mellitus, arrived at the Emergency unit in the hospital suffering from acute chest pain with manifestations suggestive of acute myocardial ischemia, including those such as chest pain, shortness of breath, lower jaw pain, left arm pain, epigastric pain, new or increasing lower extremity edema, palpitations, and other symptoms suggestive of an angina equivalent. The ECG was measured in the ED as part of the standard of care at the GMC & Hospital, Baramati.

Control Group: Sixty healthy volunteers age and sex-matched who didn't have any evidence of diabetes and coronary artery disease were taken as the control group.

Samples processing: Demographic data (sex, age), an ECG and Biochemical data were collected. Blood for IMA and HbA1C levels was collected within two hours of arrival, and IMA risk marker testing was performed before any heparin/thrombolytic treatment was started. Blood samples were collected in tubes containing lithium heparin at the time of the patient's presentation to the emergency department, centrifuged for 5 minutes and preserved at -70 degree.

RESULTS

There were 60 individuals in the control group (mean age 65.24 $\pm$ 13.11), and 60 patients in the diabetic group (mean age 59.86 $\pm$ 9.03). The comparison of the demographic and laboratory variables is presented inTable 1. These groups were statistically similar in terms of demographic variables ($p > 0.05$). The creatinin ($p = 0.020$) and platelet values ($p = 0.213$) were found to be insignificant predictors for CAD severity. However, the WBC and IMA levels were markedly higher in the patient groups ($p = 0.01$). The comparison of the laboratory parameters and risk scores between the three groups is presented in Tables 1 and 2.

Group	Number	Mean	S.D	Value
Cases	60	194.8	69.5	P < 0.001
Controls	60	75.8	11.3	

Table 2: Comparison means of plasma (IMA) in the case group and control group.

Values of 80.70 or greater predicted myocardial ischemia with a sensitivity of 93.3% and a specificity of 60% (AUC: 0.92).

The cut-off value for IMA in diagnosing myocardial ischemia in diabetic patients attending ED was 80.70. Values of 80.70 or greater, predicted myocardial ischemia in diabetic patients with a sensitivity of 93% and a specificity of 60% (Area under curve: 0.92, Figure 1).

Variables	Controls	Cases
Age	55.6+9.9	57.7+11.1
Sex (F/M)	35/25	32/28
Disease duration	-	14.95 ± 8.63
Mean blood pressure Systolic/Diastolic blood pressure (mmHg)	126/74 ± 9/7	142/77 ± 14/10
HbA_{1c}	5.1+0.4	6.8+0.6
Total cholesterol (mg/dl)	184.0+29.8	216.2+37.7
HDL-cholesterol (mg/dl)	40.3+6.5	34.1+5.7
LDL-cholesterol (mg/dl)	115.3+32.5	175.7+34.6
Triglycerides (mg/dl)	140.8+42.8	169.4+40.0
Uric acid(mg/dl)	5.9+0.7	8.4+2.5
AST (IU/L)	23.4+6.2	52.4+20.2

Table 1: Comparison of demographical and laboratory variables between Cases (Type II diabetes Mellitus with Acute Coronary syndrome) and Controls (Healthy subjects)

Diabetic Status of Cases (n=60)	No.	Mean	S.D	Significance*
Cases with Uncontrolled Diabeties	26	240.55	52.5	P<0.0001
Cases with Uncontrolled Diabeties	34	159.8	60.4	

*Mann-Whitney Test

Table 3: Comparison means of plasma IMA between controlled and uncontrolled diabetic patients

The IMA level was significantly higher in uncontrolled diabetic patients with acute coronary syndrome compared to controlled diabetic patients with ACS.Table 3

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. [11]IMA has been proven to be an early biochemical marker to detect ischemia in patients with myocardial infarction. [17] So, Ischemia-modified albumin has been studied primarily in selected populations to display myocardial involvement only in the absence of confounding clinical conditions. IMA increases also in brain ischemia, end-stage renal disease, liver disease, some neoplasms, and infections as well as in patients with peripheral vascular diseases and exercise-induced skeletal muscle ischemia. Recent studies indicate that structural modifications of albumin can occur as the result of endothelial and extracellular hypoxia, acidosis, reduced oxygen tension, various ion-pump disruptions, and generation of reactive oxygen species (ROS). [2]

In diabetic patients, hyperglycemia, via several mechanisms (glucose autooxidation, stimulation of the polyol pathway, imbalance between the amount of reduced and oxidized coenzymes forms, nonenzymatic glycation and formation of advanced glycation end-products-AGEs), leads to multiple biochemical sequels resulting in oxidative stress. Reactive oxygen species are well known as a factor responsible for chemical and molecular damage of many biological molecules (proteins, lipids, carbohydrates, DNA, nucleotides) and cell membrane structure. Oxidative stress is important in a variety of physiological (e.g., ageing) and pathological (e.g., atherosclerosis, diabetes) processes. It plays a significant role in pancreatic islet destruction in diabetes type 2 and leads to its late complications. This also causes oxidative protein damage, formation of advanced oxidation protein products (AOPP) and probably IMA. [2]

We estimated IMA levels in the plasma of diabetic patients and control subjects using the manual method. We found that the serum levels of IMA were significantly higher in diabetic patients when compared with normal healthy non-diabetic (p-value = 0.003) this agrees with a previous study

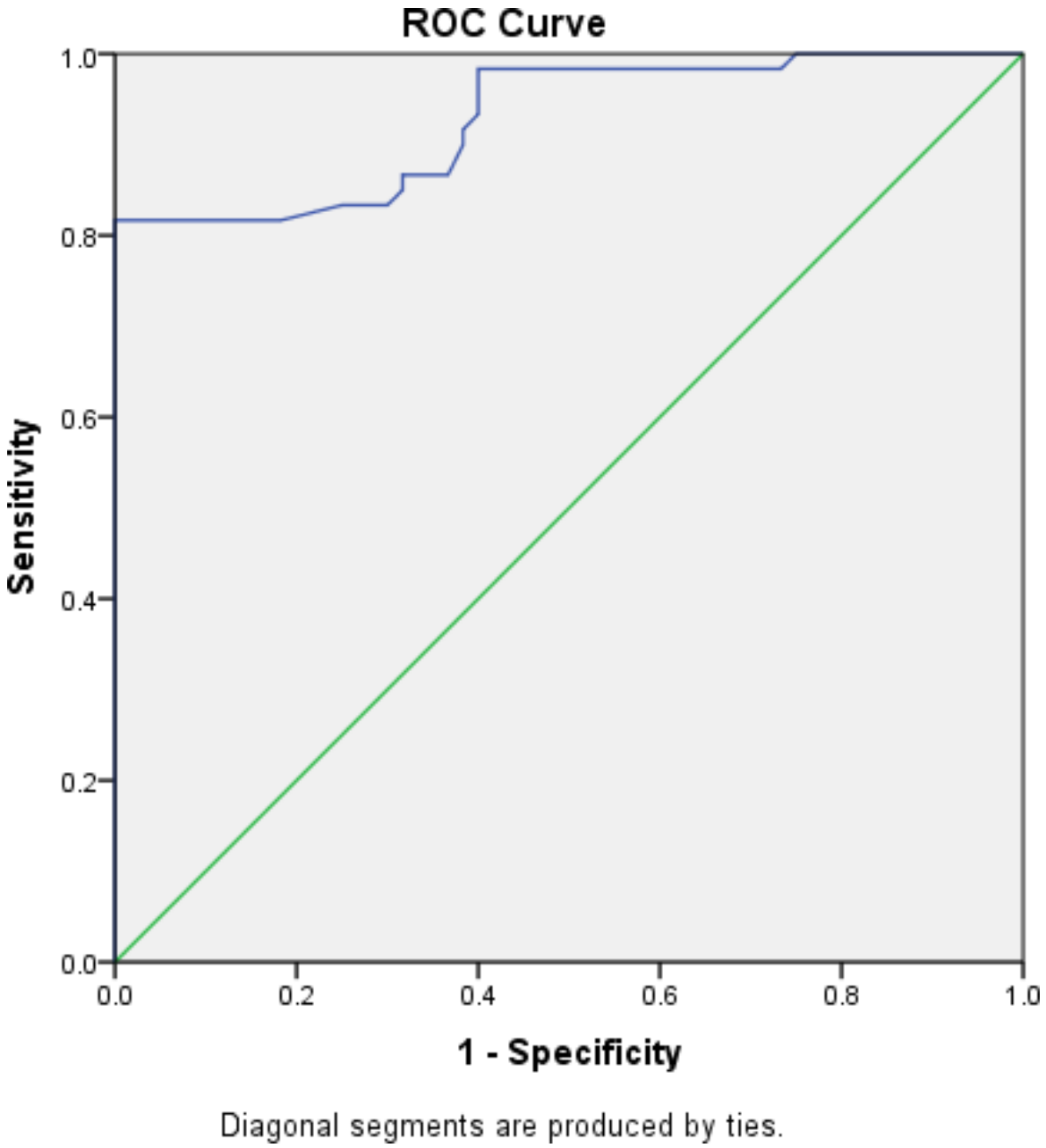

Figure 1: ROC curve showing IMA cut-off value in diagnosing critical coronary artery disease.

showing that IMA is a novel marker of tissue ischemia and is accepted as a marker of oxidative stress in type 2 diabetes patients [18] and others study report that definite and precise mechanisms for IMA production in vivo, it appears to be related to the generation of reactive oxygen species (ROS) due to ischemia-reperfusion that modifies metal binding domains of albumin molecule. [19] We observed about 75% higher levels of ischemia-modified albumin in the plasma of type 2 diabetic patients in relation to control subjects. This confirms previous, as well as our observations, that increased ROS generation, provoked by hyperglycemia, can cause oxidative protein damage. In the case of albumin decreasing ability to exogenous cobalt binding in plasma has been reported. [8, 10] IMA may indicate underlying subclinical disease or vascular dysfunction, what suggested also by Borderie et al. [12]

In diabetic patients with HbA1c level higher than 7% significant correlation between IMA and HbA1c was found. The binding of glucose to albumin typically occurs in vivo in healthy people and is known to involve the nonenzymatic covalent attachment of glucose to a lysine side chain but increases between two- to threefold in hyperglycemia. Thus, it is possible that patients with a more severe course of disease (poorly controlled diabetes compared to well-controlled diabetes as well as healthy people) could occur greater free radical production, leading to higher IMA concentration. Moreover, diabetic patients exhibit elevated

levels of iron and copper ions that, in the presence of glycated proteins, have been shown in vitro to generate ROS. [20] This indicates that IMA level should be considered in the context of well and bad compensated diabetes.

Our current findings, although preliminary, show that chronic oxidative stress provoked by hyperglycemia, in diabetic patients causes the decrease of albumin's ability to exogenous cobalt binding. It supports the hypothesis that the rise in IMA levels may be also of non-cardiac origin. We also reveal higher IMA concentrations in diabetic patients with poor long-term Glycemic control, probably with acidosis, hypertension as well as hypercholesterolemia-LDL compared with baseline.

This may have implications regarding the ability of IMA to detect myocardial ischemia in diabetics. Recently Roy et al. [21] suggested and revealed the role of reactive oxygen species, such as superoxide and hydroxyl radicals, generated during myocardial ischemia-reperfusion, on the modification of the N-terminus of albumin and formation of the IMA. A positive IMA value could also help to identify higher-risk individuals, suffering from local or systemic hypoxic conditions, such as acute ischemic stroke, peripheral vascular disease, systemic sclerosis, peripheral vascular intervention, exercise-induced calf-muscle ischemia, and end-stage renal disease.

In this current study, there was a significant difference increase in IMA levels among poorly controlled (HBA1c > 7%) diabetic patients (mean; 14.70 $\pm$ 8.66)when compared with the well-controlled (HBA1c < 7%), diabetic (mean; 3.74 $\pm$ 3.68), the patients (long-standing diabetes) duration more than 5 years had higher IMA levels than patients with less than 5 years duration.

Diabetic complications are due to various micro and microangiopathic events producing increased oxidative stress and decreased levels of antioxidants, which can lead to modification of albumin molecule of IMA than patients with less than 5 years duration of diabetes (long-stand diabetes) have a lower than the other one. [22]

CONCLUSION

We suggest that measurements of IMA in patients with chest pain or signs/symptoms suggestive of acute coronary syndrome cases even in the early phase will help to detect ACS and this is particularly important when patients have type 2 diabetes. Furthermore, there is a positive correlation between HbA1c level with IMA level thus monitoring diabetic control is an important part of the management of acute coronary syndrome. The measurements of IMA can be a very important factor in the correct diagnosis and classification of patients with coexisted diabetes who come to the emergency department with chest pain.

LIMITATIONS

1. The main limitation of our study was the limited number of cases that reduces the sensitivity and specificity of multivariate analysis.
2. Currently no reference standard exists for cardiac ischemia. A combination test of IMA with CK-MB and Troponin I can increase the sensitivity in the early diagnosis of Acute Coronary Syndrome. [23]
3. One of the limitations was that the study group was confined to patients with Non-STEMI/USAP. Therefore, our findings cannot be generalized to include all patients with ACS.

REFERENCES

1. Shaoqing J, Juan N, Jianyou S. Ischemia-Modified albumin is Increased in Patients with Unstable Angina: A new Potential Diagnostic biomarker of this Acute Coronary Syndrome. Lab Med. 2008;39(11):668–70.
2. Piwowar A, Knapik-Kordecka M, Warwas M. Ischemia-modified albumin level in type 2 diabetes mellitus - Preliminary report. Dis Markers. 2008;24(6):311–318.
3. Lee YW, Kim HJ, Cho YH, Shin HB, Choi TY, Lee YK. Application of albumin-adjusted ischemia modified albumin index as an early screening marker for acute coronary syndrome. PMID 17570353. 2007;384:24–31.
4. Lippi G, Montagnana M, Salvagno GL. Potential value for new diagnostic markers in the early recognition of acute coronary syndromes. CJEM. 2006;8(1):27–31.
5. Peacock F, Morris DL, Anwaruddin S, Christenson RH, Collinson PO, Goodacre SW. Meta-analysis of ischemia-modified albumin to rule out acute coronary syndromes in the emergency department. PMID 16875905. 2006;152:253–62.
6. Apple FS, Wu AH, Mair J, Ravkilde J, Panteghini M, Tate J. Future biomarkers for detection of ischemia and risk stratification in acute coronary syndrome. PMID 15774573. 2005;51:810–834.
7. 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(1):29–34.
8. Christenson RH, Duh SH, Sanhai WR, Wu AH, Holtman V, Painter P. Characteristics of an albumin cobalt binding test for assessment of acute coronary syndrome patients: A muticenter study. Clin Chem. 2001;47(3):464–70.
9. Adams J, Apple F. Cardiology patient page. New blood tests for detecting heart disease. Circulation. 2004;109(3):14744959–14744959.

10. Kanko M, Yavuz S, Duman C, Hosten T, Oner E, Berki T. Ischemia-modified albumin use as a prognostic factor in coronary bypass surgery. J Cardiothorac Surg. 2012;7(3):3–3.

11. 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(4):311–316.

12. Borderie D, Allanore Y, Meune C, Devaux JY, Ekindjian OG, Kahan A. High ischemia- modified albumin concentration reflects oxidative stress but not myocardial involvement in systemic sclerosis. Clin Chem. 2004;50(11):2190–2193.

13. Montagnana M, Lippi G, Volpe A, Salvagno GL, Biasi D, Caramaschi P. Evaluation of cardiac laboratory markers in patients with systemic sclerosis. Clin Biochem. 2006;39(9):913–920.

14. Refaai MA, Wright RW, Parvin CA, Gronowski AM, Scott MG, Eby CS. Ischemia- modified albumin increases after skeletal muscle ischemia during arthroscopic knee surgery. Clin Chim Acta. 2006;366(1-2):264–272.

15. Montagnana M, Lippi G, Fava C, Minuz P, Santonastaso CL, Arosio E. Ischemia-modified albumin and NT-prohormone- brain natriuretic peptide in peripheral arterial disease. Clin Chem Lab Med. 2006;44(2):16475909–16475909.

16. Laver SR, Padkin A. Does hyperglycaemia precede the clinical onset of myocardial ischaemia? Resuscitation. 2005;66(2):237–239.

17. Sadik I, Yagoub Z, Sayed N. The level of ischemic modified albumin (IMA) as risk marker for cardio vascular disease among some diabetic patients (type II) in Khartoum state- Sudan. Sudan J Med Sci. 2017;12(4):231–240.

18. Ukinc K, Eminagaoglu S, Ersoz HO, Erem C, Karahan C, Hacihasanoglu AB. A novel indicator of widespread endothelial damage and ischemia in diabetic patients: ischemia-modified albumin. Endocrine. 2009;36(3):425–457.

19. Kumar A, Sivakanesan R, Singh S. Oxidative stress, endogenous antioxidant and ischemia- modified albumin in normolipidemic acute myocardial infarction patients. J Health Sci. 2008;54(4):482–489.

20. Bar-Or D, Curtis G, Rao N, Bampos N, Lau E. Characterization of the Co(2+) and Ni(2+) binding amino-acid residues of the N-terminus of human albumin. An insight into the mechanism of a new assay for myocardial ischemia. Eur J Biochem. 2001;268(1):42–49.

21. Roy D, Quiles J, Gaze DC, Collinson P, Kaski JC, Baxter GF. Role of reactive oxygen species on the formation of the novel diagnostic marker ischaemia modified albumin. Heart. 2006;92(1):113–117.

22. Defronzo RA. Pathogenesis of type 2 diabetes: metabolic and molecular implications for identifying diabetes genes. Diabetes Rev. 1997;5(3):177–269.

23. Panimathi R, Lalitha. Ischemia modified albumin - An early marker of myocardial ischemia. JMSCR. 2016;4(7):11596–604.

How to cite this article: Junedi MA, Junaidi AA. Ischemia-Modified Albumin (IMA) for early detection of myocardial ischemia in acute coronary syndrome with type 2 diabetes mellitus: a case control study. Perspectives in Medical Research. 2023;11(2):17-22
DOI: 10.47799/pimr.1102.04