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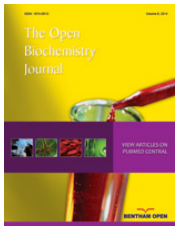

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RESEARCH ARTICLE

The Diagnostic Accuracy of Cardiac Enzymes-Lipid Profile Ratio for Diagnosing Coronary Heart Disease in Chest Pain Patients

Mohamed Kadry[1], Faten M. Zahran[2], Tarek M. Emran[3] and Mohamed M. Omran[4,*]

[1]*Department of Medical Laboratory, Gamasa Central Hospital, Gamasa, Egypt*
[2]*Department of Chemistry, Faculty of Science, Zagazig University, Zagazig, Egypt*
[3]*Department of Clinical Pathology, Faculty of Medicine, Al-Azhar University, New Damietta, Egypt*
[4]*Department of Chemistry, Faculty of Science, Helwan University, Cairo, Egypt*

Abstract:

Background:

Lipid abnormalities increase Coronary Heart Disease (CHD) risk. Our developed indexes 1,2 were reported in scientific Journals. Here, we verified and evaluated the cardiac enzymes-lipid profile ratio's diagnostic value for diagnosing CHD patients.

Methods:

Lipid profiles and cardiac enzymes were estimated in all chest pain patients. The area under the receiver-operating characteristic curve (AUC) was used to evaluate the markers' diagnostic accuracy.

Results:

There were varieties of significant differences ($P < 0.01$- $P < 0.0001$) of Creatine Kinase MB (CK-MB) - lipid profile ratio and Troponin I-lipid profile ratio within the groups of chest pain patients. For discriminating between Non-Coronary Chest Pain (NCCP) and Stable Angina (SA) groups, the AUCs were the greatest for CK-MB- High-density Lipoprotein (HDL) ratio (0.62) and for Troponin I-HDL (0.62). Moreover, for discriminating between NCCP and Unstable Angina (UA) groups, the AUC was the greatest for CK-MB-HDL ratio (0.97). Also, for discriminating between NCCP and Acute Myocardial Infarction (AMI) groups, the AUC was the greatest for index 2 (0.99). Similarly, for discriminating between SA and UA groups, the AUC was the greatest for CK-MB-HDL ratio (0.90). For discriminating between SA and AMI groups, the AUC was the greatest for index 2 (0.97). Finally, for discriminating between UA and AMI groups, the AUC was the greatest for index 2 (0.78).

Conclusion:

Independent CK-MB-HDL ratio can be used as a good and simple index for diagnosing CHD in chest pain patients and discriminating between the different groups of these patients

Keywords: Cardiac enzymes, Lipid profile, Acute coronary syndrome, Coronary heart disease, Chest pain, Unstable Angina (UA).

Article History	Received: June 15, 2020	Revised: December 30, 2020	Accepted: January 21, 2021

1. INTRODUCTION

CHD is the leading cause of premature mortality and death worldwide, poses a severe global health burden [1]. Among CHD, Acute Coronary Syndrome (ACS) is the most common cause, a very complex complaint with pathologies encompassing tissue inflammation, remodeling, thrombosis, and necrosis [2]. ACS includes a wide spectrum of diseases because of acute myocardial ischemia secondary to a diminution in coronary blood flow owing to unstable angina [3]. Acute Myocardial Infarction (AMI) caused by atherothrombotic CHD and usually precipitated by atherosclerotic plaque disruption is designated as a type 1 AMI [4]. ACS diagnosis depends on Electrocardiogram (ECG) changes, imaging and serum level elevation of myocardial injury markers such as cardiac troponin I or T, CK-MB, myoglobin, and lactate dehydrogenase [4]. By definition, the elevation of a single or more of these markers is observed in all patients with ACS [5].

Meanwhile, cardiac troponins have been considered until

* Address correspondence to this author at the Department of Chemistry, Faculty of Science, Helwan University, Ain Helwan, 11795, Cairo, Egypt;
E-mail: drmmomran@yahoo.com

now the gold standard biomarker [6]. Troponin I is very specific for the myocardium because it is found solely in cardiac myocytes, while troponin T is found in several cells [7]. On the other hand, the ACS reasons are multi-factorial, containing some non-modifiable risk factors, like gender and age, several modifiable risk factors, as hypertension, diabetes mellitus, dyslipidemia, smoking, low physical activity, and dietary habits [8]. ACS patients are at very high risk of suffering an adverse cardiovascular incident. Such risk can be diminished by good controlling of associated modifiable risk factors [9]. Lipid abnormality, for example, high concen-tration of triglycerides or Low-Density Lipoprotein (LDL) and low level of HDL, are famous for being highly widespread in ACS patients [10].

Meanwhile, a repetitive estimation of lipid profile indexes is performed only in 50% of patients with ACS [3]. After ACS, lipid abnormality has focused primarily on raising HDL or lowering LDL to diminish recurrent CHD risk among the patients [11]. The correlation between obstructive CHD and serum levels of lipid profile is well known [12] but, the studies that assessed the critical role of lipoprotein concentration as biomarkers of ACS severity are still limited in the literature [13]. Therefore, the purpose of our study was to evaluate the diagnostic value of troponin I-lipid profile ratio and CKMB-lipid profile ratio for detecting the severity of coronary atherosclerotic disease in CHD patients.

2. MATERIALS AND METHODS

2.1. Patients

A total of 400 chest pain patients aged 30-74 years, included 336 patients with CHD [SA (n= 72), UA (n= 90), and AMI (n= 174)] and 64 patients with NCCP. The diagnosis of AMI patients is according to the study [4, 14]. The patients excluded were those who have cardiogenic shock, cardio-myopathy, or chronic kidney failure. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Blood samples were taken from all patients, and the serum was separated. The routine laboratory investigations were determined on an automated biochemistry analyzer (BT1500; Biotecnica instruments S.P.A, Italy). Troponin I was measured using a one-step sandwich enzyme-linked fluorescent immunoassay assay (bioMerieux's Vidas Troponin I Ultra, France). Myeloperoxidase and monocyte chemoattractant protein-1 were measured, according to Omran *et al*. [15].

2.2. Statistical Analysis

All data were analyzed using the Statistical Package for the Social Sciences (SPSS) (SPSS Inc., Chicago, IL, USA) software, version 15.0. The variables were presented as the mean ± standard error (SE), and P-value <0.05 was considered significant. Analysis of variance (ANOVA) and student's t-test was used to compare chest pain groups patients' markers. Receiver-Operating Characteristic (ROC) curves were proces-sed for indexes to evaluate these indexes' diagnostic performances for differentiating between the different groups of chest pain patients. Our previously developed indexes were constructed to discriminate between the different groups of the chest pain patient; the first was; Index 1 = 2.236 (numeric constant) + 0.001 × myeloperoxidase + 0.002 × CK-MB +0.074 × troponin I [16]. and the second was; Index 2 = - 0.051 (numeric constant) + 0.001* myeloperoxidase + 0.001* monocyte chemoattractant protein-1 + 0.009* CKMB + 2.5* Troponin I [15].

3. RESULTS

3.1. Comparison between Levels of Routine Investigations between Chest Pain Patient Groups

Table **1** shows the levels of lipid profile and biomarkers within groups of chest pain patients. There were extremely significant differences (P < 0.0001) in cholesterol, HDL, LDL, CK-MB, myeloperoxidase, monocyte chemoattractant pro-tein-1 and Troponin I within the groups. But, there were no significant differences (P > 0.05) of Aspartate Amino-transferase (AST) and triglycerides levels within the groups. Furthermore, there were various significant differences (P < 0.01- P < 0.0001) of CK-MB-lipid profile ratio and Troponin I-lipid profile ratio within the groups.

The value of CK-MB-lipid profile ratio and Troponin I-lipid profile ratio in the different chest pain groups, showed no significant differences between NCCP and SA groups for all indexes values. However, the CK-MB-HDL ratio has the highest significant difference between SA and UA groups and between SA and AMI groups. Both CK-MB-HDL ratio and Troponin I-HDL ratio have the highest significant differences between UA and AMI groups, between NCCP and UA, and between NCCP and AMI groups.

Table 1. Comparison between levels of routine investigations between chest pain patient groups.

Variables	NCCP (n=64)	-	CHD	-	*P*-value*
		SA (n=72)	UA (n=90)	AMI (n=174)	
AST	26.2±0.01	33.9±0.01	35.0±0.01	37.1±0.01	0.07
Cholesterol	159.6±23.6	196.3±28.6	199.7±31.2	214.1±43.2	< 0.0001
Triglycerides	128.7±40.4	139±40.7	132.8±42.1	135.1±51.5	0.7
HDL	35.6±7.1	32.9±5.0	27.1±3.9	22.1±4.9	< 0.0001
LDL	96.9±25.1	132.5±24.9	140.7±29.2	157.4±41.8	< 0.0001
CK-MB	12.5±0.06	15.9±0.07	25.1±0.09	32.2±0.14	< 0.0001
Troponin I	0.02±0.019	0.024±0.017	0.037±0.016	0.049±0.029	< 0.0001
MPO	111±70	123±88	188±144	306±163	< 0.0001
MCP-1	124±69	138±77	186±112	250±97	< 0.0001

(Table 1) contd.....

CK-MB–lipid Profile Ratio					
CK-MB–Cholesterol	0.052±0.01	0.055±0.036	0.1±0.01	0.13±0.01	< 0.0001
CK-MB– Triglycerides	0.072±0.015	0.085±0.016	0.17±0.02	0.23±0.03	< 0.0001
CK-MB– HDL	0.23±0.03	0.32±0.05	0.68±0.06	0.93±0.08	< 0.0001
CK-MB– LDL	0.10±0.026	0.082±0.012	0.15±0.01	0.18±0.02	0.01
Troponin I –lipid profile ratio					
Troponin I–Cholesterol	0.129±0.03	0.128±0.02	0.197±0.02	0.254±0.02	0.005
Troponin I–Triglycerides	0.169±0.04	0.197±0.04	0.314±0.03	0.461±0.05	0.001
Troponin I – HDL	0.533±0.12	0.733±0.15	1.28±0.13	1.82±0.16	< 0.0001
Troponin I – LDL	0.243±0.07	0.191±0.04	0.283±0.03	0.365±0.04	0.01

Variables were expressed as mean ± Standard Error (SE).

AST: Aspartate aminotransferase (U/L); CK-MB: Creatine kinase MB (IU/L); Troponin I (ng/L); Cholesterol (mg/dl); Triglycerides (mg/dl); HDL: High-density lipoprotein (mg/dl); LDL: Low-density lipoprotein (mg/dl); MPO, myeloperoxidase (ng/ml); MCP-1, monocyte chemoattractant protein-1(ng/ml).

3.2. Diagnostic Value of Routine Investigations for the Diagnosing ACS Patients (n=264) in Chest Pain Patient

The diagnostic accuracy of routine investigations at the best cutoff values for diagnosing ACS patients in chest pain patient were assessed using ROC curves as shown in Table **2**. For diagnosing ACS patients, the AUCs (P value) of cholesterol, triglycerides, HDL, and LDL were 0.67 (P = 0.002), 0.52 (P > 0.05), 0.79 (P < 0.0001), and 0.75 (P < 0.0001); respectively. However, the AUCs (P value) of CK-MB, Troponin I, myeloperoxidase, and monocyte chemo-attractant protein-1 for diagnosing ACS patients were 0.78 (P < 0.0001), 0.75 (P < 0.0001), 0.80 (P < 0.0001), and 0.77 (P < 0.0001); respectively. Also, the AUCs (P value) of CK-MB-cholesterol ratio, CK-MB-triglycerides ratio, CK-MB-HDL ratio, and CK-MB- LDL ratio for diagnosing ACS patients were 0.78 (P < 0.0001), 0.79 (P < 0.0001), 0.86 (P < 0.0001), and 0.74 (P < 0.0001); respectively. Similarly, the AUCs (P value) of Troponin I-cholesterol ratio, Troponin I-triglyceride ratio, Troponin I-HDL ratio, and Troponin I-LDL ratio for diagnosing ACS patients were 0.74 (P < 0.0001), 0.76 (P < 0.0001), 0.82 (P < 0.0001), and 0.71 (P < 0.0001), respectively.

3.3. The Diagnostic Value of the Novel Indexes; CK-MB-HDL Ratio and Troponin I-HDL in Comparison with our Previous Developed Indexes for Discriminating the Different Groups of the Chest Pain Patient

ROC curves assessing the diagnostic values of the novel indexes CK-MB-HDL ratio and Troponin I-HDL ratio compared with our previous indexes [15, 16], were constructed to discover the best index to discriminate the different groups of chest pain patients (Table **3)**.

The AUCs were the greatest of CK-MB-HDL ratio (0.62) and Troponin I-HDL (0.62) for discriminating between NCCP and SA groups. Meanwhile, the greatest CK-MB-HDL ratio (0.97) was for discriminating between NCCP and UA groups. Also, AUC was the greatest of index 2 (0.99) for discriminating between NCCP and AMI groups. Similarly, AUC was the greatest of CK-MB-HDL ratio (0.90) for discriminating between SA and UA groups. The AUC was the greatest of index 2 (0.97) for discriminating between SA and AMI groups. Finally, AUC was the greatest of index 2 (0.78) for discriminating between UA and AMI groups.

Table 2. Diagnostic accuracy of routine investigations at the best cut-off values for the diagnosing ACS patients in studied chest pain patients.

Variables	Cut-off	Sensitivity %	Specificity %	PPV %	NPV %	Efficiency %
Cholesterol (mg/dl)	200	66	70	81	52	66
Triglycerides (mg/dl)	143	52	48	66	35	51
HDL (mg/dl)	33.5	78	70	84	62	75.5
LDL (mg/dl)	130	77	70	84	62	75
CK-MB (IU/L)	25.7	84	69	84	69	79
Troponin I (ng/ml)	0.051	79	80	89	67	80
MPO (ng/ml)	121	87	71	86	74	82
MCP-1 (ng/ml)	130	81	69	84	65	77
CK-MB–Cholesterol	0.06	73	77.5	86	60	74.5
CK-MB–Triglycerides	0.09	75	70	83	60	73.5
CK-MB–HDL	0.34	80	70	84	65	77
CK-MB–LDL	0.77	76	63	80	58	72
Troponin I–Cholesterol	0.13	72	65	80	55	70
Troponin I–Triglycerides	0.14	81	65	82	64	75.5
Troponin I–HDL	0.78	81	70	84	66	77.5
Troponin I–LDL	0.89	78	70	83	62	75.5

PPV: Positive predictive value and NPV: Negative predictive value.

Table 3. The comparison of the diagnostic value of the novel indexes; CK-MB-HDL ratio and Troponin I-HDL with our previous developed scores for discriminating the different groups of the chest pain patient.

Groups	INDEX	AUC	SE	P value*	(95% CI)
NCCP vs SA	Troponin I – HDL	0.62	0.09	> 0.05	0.444-0.796
	CK-MB– HDL	0.62	0.09	> 0.05	0.445-0.798
	Index1	0.53	0.093	> 0.05	0.352-0.716
	Index2	0.60	0.092	> 0.05	0.407-768
NCCP vs UA	Troponin I – HDL	0.80	0.07	0.001	0.664-0.940
	CK-MB– HDL	0.97	0.023	< 0.0001	0.924-0.999
	Index1	0.74	0.075	0.006	0.593-0.885
	Index2	0.85	0.057	< 0.0001	0.741-0.963
NCCP vs AMI	Troponin I – HDL	0.88	0.049	< 0.0001	0.779-0.970
	CK-MB– HDL	0.87	0.043	< 0.0001	0.781-0.949
	Index1	0.95	0.029	< 0.0001	0.889-0.999
	Index2	0.99	0.002	< 0.0001	0.993-0.999
SA vs UA	Troponin I – HDL	0.74	0.078	0.006	0.588-0.894
	CK-MB– HDL	0.90	0.058	< 0.0001	0.789-0.997
	Index1	0.70	0.08	0.024	0.540-0.856
	Index2	0.81	0.065	< 0.001	0.672-0.926
SA vs AMI	Troponin I – HDL	0..81	0.06	< 0.0001	0.696-0.930
	CK-MB– HDL	0.80	0.052	< 0.0001	0.692-0.896
	Index1	0.90	0.046	< 0.0001	0.803-0.985
	Index2	0.97	0.022	< 0.0001	0.918-0.999
UA vs AMI	Troponin I – HDL	0.61	0.065	> 0.05	0.458-0.713
	CK-MB– HDL	0.62	0.064	> 0.05	0.482-0.734
	Index1	0.76	0.060	< 0.0001	0.636-0.881
	Index2	0.78	0.057	< 0.0001	0.663-0.887

• Index1 = 2.236 (numeric constant) + 0.001 × myeloperoxidase + 0.002 × CK-MB +0.074 × Troponin I.

• Index2 = - 0.051 (numeric constant) + 0.001* myeloperoxidase + 0.001* monocyte chemoattractant protein-1+0.009* CKMB + 2.5* Troponin I.

4. DISCUSSION

It is well-established that ACS patients are at extremely high risk for cardiovascular incidents [10]. Also, dyslipidemia is a well-recognized risk factor for CHD progression, and this has been confirmed in many clinical studies [17]. High serum LDL levels are directly correlated with CHD progression, and low HDL levels have been considered one of the potent independent risk factors for the atherosclerotic disease [18]. The mild elevation in triglycerides causes an increased risk of coronary events and CHD development [1]. In the present study, we observed up-regulation of levels of lipid profiles in addition to cardiac enzymes within the different groups of chest pain patients, yielding extremely significant differences in levels of cholesterol, HDL, LDL, CK-MB, and Troponin I within these groups. Our present study represents the first study that assesses the cardiac enzyme-lipid profile ratio for diagnosing CHD patients in the Egyptian population. Our data showed significant differences in CK-MB-lipid profile ratio and Troponin I-lipid profile ratio within the different chest pain patients. Our previous study has discussed the significant up-regulation of cardiac enzymes, including Troponin I and CK-MB, within the different chest pain patients [15, 16]. Zhong *et al.* demonstrated that there were significant differences ($P< 0.05$) in the serum lipid levels among various age groups for both males and female AMI patients [13]. Several early studies have demonstrated that the increase in cholesterol levels in AMI due to the occurrence of an acute phase response [8]. Several studies observed significantly higher LDL levels, VLDL, and cholesterol, and lowers HDL levels in AMI patients than in the control group [8, 19]. Dissimilar to our findings, Khan *et al*. noted that cholesterol, HDL, and LDL were significantly lower in descending order from controls, UA, AMI groups [20]. In our present study, we assessed these markers' diagnostic accuracy for diagnosing ACS patients in chest pain patients and observed that CK-MB-HDL ratio and Troponin I-HDL ratio were the perfect suitable indexes for diagnosing ACS patients with good efficiencies were 77% and 77.5%, respectively. Dyrbus *et al.* reported that the different ACS patients have significantly higher LDL levels than SA patients [21]. Gitt *et al*. reported that the mean LDL serum level was low at 108 mg/dl for premature ACS in 10661 patients aged below 18 years [18]. Islam *et al.* observed that triglycerides' level (mean ± standard deviation) was 168.2 ± 88.0 and 141.2 ± 45.3 in ACS patients and controls, respectively.

Similarly, the levels of HDL were 41.3 ± 5.1 and 34.2 ± 3.4, respectively. Also, triglycerides /HDL ratios were 4.2 ± 1.7 and 4.1 ± 1.3, respectively [1]. Our present study noted that the CK-MB-HDL and Troponin I-HDL ratios were the most efficient indexes than the other indexes for differentiating between NCCP and SA groups.In addition, CK-MB-HDL ratio was the most efficient index for differentiating between UA and (NCCP or SA) groups. Similarly, index 2 was the most efficient index than other indexes for differentiating between

AMI and (NCCP, SA, or UA) groups. Stengaard *et al*. improved a model based on Troponin I and copeptin's combination to improve the efficiency of diagnosing AMI patients at early admission [22]. Also, Yanishi *et al.* developed a score based on several laboratory investigations for diagnosing AMI patients with AUC was 0.81 [23].

Moreover, O'Donoghue *et al.* used a multimarker strategy to predict CHD or heart failure [24]. The limit of this study was the sample size, especially the number of NCCP. In the coming research paper, we will consider examining a large number of NCCP patients.

CONCLUSION

The cardiac enzymes-lipid profile ratio may be used as a good index based on the simple routine investigations for diagnosing CHD patients and discriminating between the different chest pain patients.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Ethics Committee of Damietta Faculty of Medicine, Al-Azhar University, New Damietta, Egypt (Code #. IRB0012367-1609-002).

HUMAN AND ANIMAL RIGHTS

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) in compliance with the ethical guidelines of the 1975 Helsinki Declaration as revised in 2013.

CONSENT FOR PUBLICATION

Informed written consent was signed by all patients.

AVAILABILITY OF DATA AND MATERIALS

Authors declare that all generated and analyzed data are included in the article.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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