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The utility of biomarkers in the discrimination of acute coronary syndrome patients

Mohamed M. Omran[a*], Faten M. Zahran[b], Mohamed Kadry[c], Arafa A. M. Belal [c], Hesham S. Abd Alsamie[d]

[a] Chemistry Department, Faculty of Science, Helwan University, Cairo, Egypt;
[b] Chemistry Department, Faculty of Science, Zagazig University, Zagazig, Egypt;
[c] Chemistry Department, Faculty of Science, Port Said University, Port Said, Egypt;
[d] Clinical Pathology Department, Faculty of Medicine, New Damietta, Al-Azhar University, Egypt;
[*] **Correspondence**: Mohamed Mostafa Omran, PhD, Chemistry Department, Faculty of Science, Helwan University, Ain Helwan, 11795 Cairo, Egypt, E-mail: drmmomran@yahoo.com

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ABSTRACT

Background: The assessment of acute coronary syndrome (ACS) provides useful data not only for identification but also for therapeutic decisions. **Objective:** To develop a score based on cardiac biomarker for the early diagnosis of ACS patients. **Methods:** Serum concentrations of myeloperoxidase (MPO) and monocyte chemoattractant protein-1 (MCP-1) beside cardiac troponin I (cTnI) and creatine kinase MB (CK-MB) were measured in a total 200 chest pain patients represented in two groups (estimation and validation). The diagnostics value of biomarkers for discriminating ACS patients was evaluated by area under the receiver-operating characteristic curve (AUC). Multivariate discriminant analysis (MDA) was used to create a predictive score. **Results:** A novel score depends on a combination of cTnI, CK-MB, MPO, and MCP-1 produces AUCs of 0.93 for discriminating ACS patients and 0.90 for acute myocardial infarction (AMI). This score correctly classified 95% of ACS patients and 93% of AMI patients with good efficiencies were 88.3% and 81%; respectively. This score had similar results in the validation study. **Conclusion:** Four biomarkers in combination yield a novel score to help in the early and safe prediction of ACS and AMI.

Key word: Myeloperoxidase; Monocyte chemoattractant protein-1, Acute coronary syndrome

1. INTRODUCTION

Chest pain (CP) is the second main repeated complaint of patients in the emergency departments, however, about 8 million patients with CP are presenting to emergency departments yearly (Mehmood et al., 2017). This poses a diagnostic challenge to exclude or confirm severe disease such as an ACS (Kim et al., 2018). ACS represents the major critical clinical presentation of atherosclerosis, which refers to three primary stages of severity of coronary artery disease. Affording to patients' ischemic symptoms, electrocardiograph (ECG) alters, and cardiac biomarkers elevation, ACS ranges from ST elevation myocardial infarction (STEMI) to non-ST elevation myocardial infarction (NSTEMI) or unstable angina (UA) (Makki et al., 2015). Early diagnosis of patients with ACS can assist in the prediction of AMI and is important for the best medical care, timely reperfusion treatment, and avoidance of cardiac events progression (Asaria et al., 2017). Cardiac biomarkers represent a significant role in ACS diagnosis; several biomarkers become apparent as a functional diagnostic device in ACS, such as troponin, CK-MB, lactate dehydrogenase, and myoglobin. By definition, the altitude of one or more of the latter biomarkers is observed in all ACS patients (Chacko et al., 2017). Meanwhile, because of their improved efficiency compared with other indexes, troponin has been still until now the golden standard biomarker for the diagnosis of myocardial damage (Mauro et al., 2017). The elevation of systemic and local inflammation represents a significant role in ACS pathophysiology and is involved in all stages of progression of ACS and coronary atherosclerosis (Hansson, 2005 & Zakroysky et al., 2015). This encourages new insight to improve novel inflammatory biomarkers, which may give essential information about the progression of the disease, and represent a critical principle in the ACS definition (Ma et al., 2018). MPO is a hem protein and mediator formed by the leukocytes collection at the inflammation site, mainly reflect the inflammatory process and control the inflammation progression (Kounis et al., 2015 & Huang et al., 2015). MPO is promising as a new biomarker of inflammation and has been projected as early diagnostic biomarkers of ACS patients (Govindarajan et al., 2016). MCP-1 is an effective chemoattractant for mononuclear cells, which manages and enhances the immigration of monocytes/ macrophages throughout inflammation into early damage of atherosclerosis (Siddiqui et al., 2017). Several authors were demonstrated that MCP-1 has the potential capability to be used as an inflammatory biomarker for ACS identification or risk prediction (França et al., 2017 & Korybalska et al., 2010).

The first objective of this study was to investigate the diagnostic precision of inflammatory biomarkers MPO and MCP-1 for discriminating patients with ACS. A secondary aim was to study the diagnostic validity of the score based on four biomarkers for risk stratification and investigation of patients with ACS in order to help in early diagnosis and suitable treatment to improve outcomes and reduce the cost of care.

2. MATERIALS AND METHODS

Patients

A total of 200 patients suffering from typical CP aged [mean ± standard error mean(SE)] 58.7±1.6 years admitted to the emergency department at Damietta Al- Azhar University Hospital. Overall 120 patients with clinically and laboratory-confirmed CP constituted the estimation group, whereas 80 patients with CP constituted the validation group.

Exclusion criteria

We excluded patients with cardiomyopathy, with cardiogenic shock, with hepatic failure and who have chronic renal failure.

Final diagnosis

All patient's diagnoses were assessed by the same cardiologist based on common criteria depend on the patient's history, clinical examination including ECG and laboratory investigations.

Blood samples and laboratory tests

The study protocol follows the ethical rules of the 1975 Declaration of the Helsinki. Blood samples were withdrawn from all patients after admission into the emergency department. Sera were divided from blood samples. The routine laboratory investigations of liver function tests, kidney function tests, lipid profiles**,** random blood sugar (RBS), and cardiac enzyme CK-MB were estimated using an automated biochemistry analyzer (BT1500; Biotecnica instruments S.P.A, Italy). Using a quantitative sandwich enzyme immunoassay technique to estimate the levels of serum MPO (AVISCERA BIOSCIENCE, INC, USA) and MCP-1 (Elabscience Biotechnology Co, Ltd, USA). cTn I was determined by bioMerieux's Vidas Troponin I Ultra.

Statistical Analysis

All statistical calculation was calculated via the statistical package for the social sciences (SPSS) (SPSS Inc., Chicago, IL, USA) software, version 15.0. The study investigations were described as the (mean ± SE) or percentage and using Mann–Whitney U test to compare these investigations between CP patients groups. A high significance in MDA was included in the linear regression analysis to create a score to distinguish ACS patients. AUCs were calculated for four biomarkers in single and combination mode to evaluate the best biomarkers cut-off for predicting ACS patients, in addition, the diagnostic accuracy [sensitivity, efficiency, specificity, predictive values negative (NPV) and positive (PPV)] of all indexes was computed using a 2×2 possibility table.

3. RESULTS

The baseline clinical characteristics and cardiovascular risk factors of studied CP patients groups were summarized in **Table 1**. There were no significant differences in any of the assessed variables between estimation and validation groups ($P > 0.05$). Also, Baseline levels of laboratory tests of studied CP patients groups were summarized in **Table 2**. There were no significant differences in these test levels between estimation and validation groups ($P > 0.05$). In the estimation study (n= 120), the patients with a mean ± SE of age was 58±1.5 years. According to the common criteria, patients were diagnosed as follows: 20 patients with non-coronary chest pain (NCCP) (16.7%), 20 patients with stable angina (SA) (16.7%), 25 patients with UA (20.8%) and 55 patients with AMI (45.8%). As shown in **Table 3**, there were statistically extremely significant differences ($P < 0.0001$) of levels of CK-MB, cTn I and MPO between ACS and non-ACS patients in both estimation and validation studies. Moreover, there was a very significant difference ($P < 0.001$) of the MCP-1 level between ACS and non-ACS groups.

Table (1): Baseline clinical characteristics and cardiovascular risk factors of studied chest pain patients

Variables	Chest pain patients (n=200)	Estimation group (n=120)	Validation group (n=80)	*P*- value*
Age (years)	58.7±1.6	58±1.5	58.4±1.9	P > 0.05
Female n**(%)**	76 (38%)	46 (38%)	30 (37.5%)	P > 0.05
Male n(%)	124 (62%)	74 (62%)	50 (62.5%)	P > 0.05
BMI (kg/m2)	28.14±0.9	28.18±1.1	28.06±1.0	P > 0.05
Pulse (beat/min)	83.4±3.4	83.79±2.8	81.9±2.7	P > 0.05
SBP (mmHg)	133.4±3.1	135.1±3.5	131.2±4.3	P > 0.05
DBP (mmHg)	83.6±1.6	85.2±1.6	81.9±1.9	P > 0.05
Hypertension n(%)	152 (76%)	91 (76%)	60 (75%)	P > 0.05
Diabetes Mellitus n(%)	120 (60%)	78 (65%)	44 (55%)	P > 0.05
Smoking n**(%)**	104 (52%)	54 (45%)	50 (63%)	P > 0.05
Addiction n(%)	2 (1.0%)	1 (0.8%)	1 (0.2%)	P > 0.05
Obesity n(%)	162 (81%)	102 (85%)	59 (73%)	P > 0.05
Dyslipidemia n(%)	184 (92%)	113 (94%)	71 (89%)	P > 0.05

Variables were expressed as mean ± Standard error mean (SEM)

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure.

* P > 0.05 considered not significant.

* P < 0.05 considered significant.

Table (2): Baseline levels of Laboratory tests of studied chest pain patients groups

Laboratory tests	Chest pain patients (n=200)	Estimation group (n=120)	Validation group (n=80)	*P*- value*
ALT	38.2±1.4	37.9±1.6	38.4± 1.3	P > 0.05
AST	36.8±1.6	36.7 ± 1.6	37.4±1.4	P > 0.05
Urea	32.8±0.8	32.1±0.9	33.0± 1.0	P > 0.05
Creatinine	1.2±0.02	1.2±0.02	1.19± 0.01	P > 0.05
RBS	130.3±9.6	131±9.4	128.5± 9.6	P > 0.05
Cholesterol	204.2±4.5	213.3±4.6	187.8± 3.3	P > 0.05
Triglycerides	142.8±5.7	140.1±5.6	150.5±6.0	P > 0.05
HDL	32±0.9	29.2±0.7	37.4±0.9	P > 0.05
LDL	143.7±4.0	156.1±4.3	120.3±3.5	P > 0.05

Variables were expressed as mean ± Standard error mean (SEM)

Reference values; ALT: Alanine aminotransferase up to 45 U/ml; AST: Aspartate aminotransferase up to 40 U/L; Urea up to 50 mg/dl; Creatinine up to 1.3 mg/dl; RBS: Random blood sugar up to 150 mg/dl; Cholesterol up to 200 mg/dl; Triglycerides up to 150 mg/dl; HDL: High-density lipoprotein 35 – 55 mg/dl; LDL: Low-density lipoprotein 60- 175 mg/dl;

* P > 0.05 considered not significant.

* P < 0.05 considered significant.

Table (3): Comparison of biomarkers concentrations between patients with ACS and non ACS in studied chest pain patients groups

Biomarkers	Estimation group (n=120)			Validation group (n=80)		
	ACS	**Non ACS**	**P-value***	**ACS**	**Non ACS**	**P-value***
CK-MB	26.8±2.7	11.8± 0.8	< 0.0001	34.2±2.9	18.2±1.0	< 0.0001
cTn I	0.047±0.003	0.022±0.001	< 0.0001	0.054±0.003	0.020±0.001	< 0.0001
MPO	269.4±17.6	117± 7.6	< 0.0001	310.1±24.2	157± 10.9	< 0.0001
MCP-1	230.4±10.3	131.5± 6.1	< 0.001	200.9±11.1	145.0± 9.3	< 0.001

Variables were expressed as mean ± Standard error mean (SEM).
ACS: Acute coronary syndrome; CK-MB: Creatine kinase MB (IU/L); cTnI: cardiac troponin I (ng/ml); MPO: Myeloperoxidase (ng/ml) and MCP-1: Monocyte chemoattractant protein-1 (ng/ml).
* $P < 0.001$ considered very significant.
* $P < 0.0001$ considered extremely significant.

Diagnostic performance of biomarkers

The AUCs of CK-MB, cTn I, MPO and MCP-1 for discriminating patients with ACS among CP patients were 0.81 (95% CI, 0.728-0.890; P < 0.0001), 0.78 (95% CI, 0.679-0.870; P < 0.0001), 0.82 (95% CI, 0.736-0.892; P < 0.0001) and 0.79 (95% CI, 0.693-0.869; P < 0.0001); respectively **(Figure 1A)**. Consequently, MPO was the best efficient indicator among others. Thus, it was selected as the main bookmaker to construct a model to discriminate patients with ACS. The diagnostics performance of four biomarkers for diagnosis ACS patients was summarized in **Table 4**.

The creation of a predictive model

All biomarkers in the estimation group were included in linear regression analyses to produce numerous models using MDA for the prediction of ACS patients. The best combination model was considered to have the highest AUC. However, a function selected by MDA based on absolute values of baseline levels of four biomarkers CK-MB, cTn I, MPO and MCP-1; Score = - 0.051 (numeric constant) + 0.001* MPO + 0.001* MCP-1+0.009* CKMB + 2.5* cTnI.

Table (4): Diagnostic accuracy of four biomarkers cut-off values for discriminating between ACS patients and non ACS patients in the estimation study

Performance	CK-MB (IU/L)	CTnI (ng/ml)	MPO (ng/ml)	MCP-1 (ng/ml)
AUC	0.81	0.78	0.82	0.79
Cut-off level	16.5	0.0283	102.5	123
Sensitivity %	87%	76%	89%	85%
Specificity %	71%	72%	73%	70%
PPV %	86%	85%	87%	85%
NPV %	74%	61%	76%	70%
Efficiency %	82%	75%	83%	80%

ACS: Acute coronary syndrome; CK-MB: Creatine kinase MB; cTnI: Cardiac troponin I; MPO: Myeloperoxidase; MCP-1: Monocyte chemoattractant protein-1; PPV: Positive predictive value and NPV: Negative predictive value.

Performance characteristics of our score

The diagnostic value of our score was calculated in the estimation group by AUC of 0.93 (95% CI, 0.867-0.978; P < 0.0001) for identifying ACS patients **(Figure. 1B)**. In addition, this score was applied to patients with AMI, yielding an AUC of 0.90 (95% CI, 0.847-0.954; P < 0.0001) **(Figure. 1C)**. The best cutoffs were selected from the receiver-operating characteristic curve (ROC) and the diagnostic performances were calculated as summarized in **Table 5**. Meanwhile, this score correctly classified 95% of ACS patients at a selected cutoff score = 0.41 (i.e. More than 0.41 indicated ACS patients and less than 0.41 indicated non-ACS patients), however, it classified 93% of AMI patients at cutoff score = 0.54 (i.e. More than 0.54 indicated AMI patients and less than 0.54 indicated non-AMI patients). In addition to, this score was applied to all patients within CP groups, a ROC curve analysis was also carried out comparing individual groups of CP patients, that is, NCCP versus SA, NCCP versus UA, NCCP versus AMI, SA versus UA, SA versus AMI and finally UA versus AMI are presented in **Table 6**.

Validation study

In the second part of the study, we calculated whether the diagnostic criteria identified in the estimation study were able of reproducing their diagnostic ability in a subsequent different, but a related, group of patients. In the validation study (n= 80), 12 (15%) patients have NCCP, 16 (20%) have SA, 20 (25%) have UA and 32 (40%) have AMI. We applied our score to the validation group patients and found that 92% of patients having ACS were correctly classified at the cutoff value of 0.50 with AUC of 0.91 (95% CI, 0.870-0.957; P < 0.0001) (Figure. 1D). Meanwhile, 89% of patients having AMI were correctly classified at the score cutoff value of 0.65 with AUC was 0.87 (95% CI, 0.814-0.912; P < 0.0001) (Figure. 1E). There is no significant difference between the diagnostic accuracy of our score in estimation and validation studies as summarized in **Table 5**.

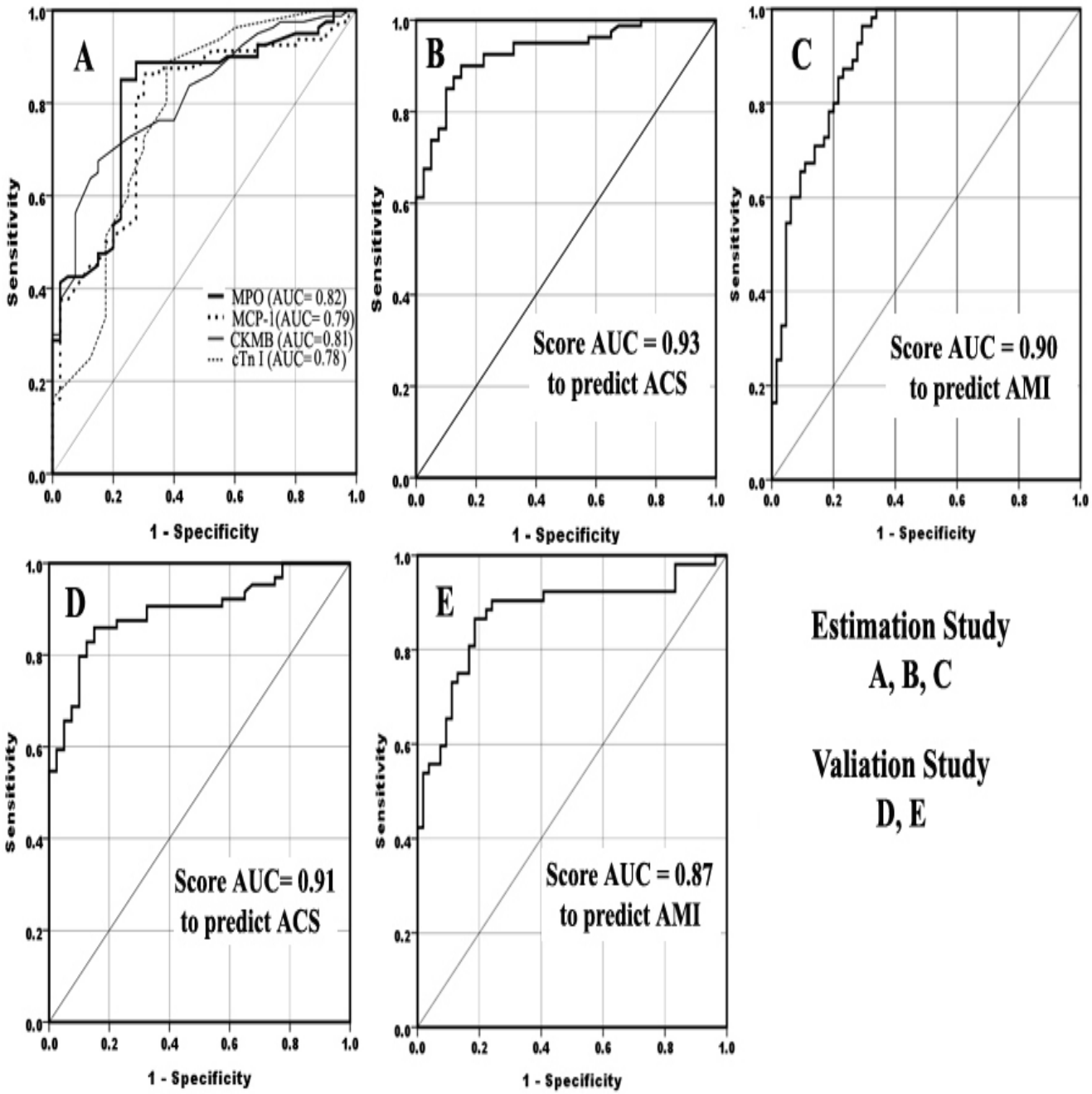

Figure 1. Areas under receiver-operating characteristics curve (AUC) in chest pain patients in the estimation study for **(A)** four biomarkers (Creatine kinase MB (CK-MB), cardiac troponin I (cTn I), myeloperoxidase (MPO) and Monocyte chemoattractant protein-1 (MCP-1)) for diagnosing ACS patients in estimation study, **(B)** The score comprising previously four biomarkers for diagnosing ACS patients in estimation study, **(C)** The score for diagnosing AMI patients in estimation study, **(D)** The score for diagnosing ACS patients in validation study, **(E)** The score for diagnosing AMI patients in validation study.

Table (5): Diagnostic performance of our score for diagnosing ACS and AMI patients in studied chest pain patients groups

Performance	Estimation group (n=120)		Validation group (n=80)	
	ACS	**AMI**	**ACS**	**AMI**
AUC	0.93	0.90	0.91	0.87
Cutoff level	0.41	0.54	0.50	0.65
Sensitivity %	95%	93%	92%	89%
Specificity %	74%	71%	73%	71%
PPV %	88%	73%	87%	86%
NPV %	87%	92%	83%	76%
Efficiency %	88.3%	81%	86.2%	82.5%

ACS: Acute coronary syndrome; AMI: Acute myocardial infarction; AUC: Area under ROC curve; PPV: Positive predictive value and NPV: Negative predictive value.

Table (6): Performance of our score in differentiating between diverse groups of chest pain patients in the estimation study

	AUC	SE	P value*	(95% CI)
NCCP vs SA	0.59	0.092	P > 0.05	0.704-768
NCCP vs UA	0.86	0.057	P < 0.0001	0.741-0.963
NCCP vs AMI	0.99	0.002	P < 0.0001	0.983-0.999
SA vs UA	0.80	0.065	P < 0.0001	0.672-0.926
SA vs AMI	0.96	0.022	P < 0.0001	0.918-0.999
UA vs AMI	0.78	0.069	P < 0.0001	0.663-0.887

AUC: Area under ROC curve; SE: Stander error mean; CI: Confidence interval; NCCP: Non coronary chest pain; SA: Stable angina; UA: Unstable angina and AMI, Acute myocardial infarction.

*P > 0.05 considered not significant.

* P < 0.0001 considered extremely significant.

4. DISCUSSION

The accurate natural history of ACS is very difficult to establish due to several reasons: the customary occurrence of silent infarction, the repeated sudden death outside the hospital, and the varying procedures and explanations used in the condition diagnosis (Grabowski et al., 2018). While ACS needs immediate hospital admission and the prediction is directly associated with the suitable beginning of revascularization, false or late diagnosis may have bad clinical implications. Early and accurate ACS diagnosis decrease complications and long-term risk of repetition, finally reducing the economic burden posed to the system of health care (Danese and Montagnana, 2016). The extent of coronary artery disease and cardiac damage besides the diseases' instability are the three main determinants of diagnosis in ACS. Where, risk classification depends on evaluation of the extent of cardiac injury and coronary artery disease through clinical findings, angiographic data, ECG, and biomarkers, counting inflammatory biomarkers may improve the prognostic accuracy due to these reflect the instability of disease (Wang et al., 2017 & Garg et al., 2017). The role of new biomarkers besides cTn has yet to be established but can help to identify those who can be safely set free from the emergency department (Corcoran et al., 2015). In our study, we observed significant up-regulation of four biomarker levels, including cTnI, CK-MB, MPO, and MCP-1 in ACS patients compared with those in non-ACS. Several studies have established the up regulation of levels of CK-MB and cTn I in ACS with high-sensitivity for cardiac events (Garg et al., 2017 & Čolak et al., 2017). Also **Calmarza et al., (2017)** who observed that the level of MPO was

significantly higher (P < 0.001) in ACS patients compared with non-ACS patients at different times after symptoms of CP, which helps to discriminate between ACS and non-ACS patients (Calmarza et al., 2017). Besides, many authors have shown that the level of MCP-1 was significantly higher in ACS patients than in non-ACS patients (Zhong et al., 2015 & Li et al., 2012). In the present study, we have assessed the diagnostic accuracy of CK-MB, cTn I, MPO and MCP-1 for discriminating ACS and MPO was the greatest efficient biomarker among others with AUC 0.82 (95% CI, 0.736-0.892; P < 0.0001), that's correctly classified 89% of ACS patients at cutoff = 0.82 ng/ml with specificity, PPV, NPP, and efficiency were 73%, 87%, 76%, and 83%; respectively. Clinical studies established the diagnostic power of cTnI and CK-MB for diagnosis ACS in addition to addressing the role of MPO as an inflammatory biomarker in ACS (Wang et al., 2017). **Mehta et al., (2016)** who observed that AUCs of MPO and high-sensitivity cardiac troponin T (hscTnT) at 0-6 hours for diagnosing patients with ACS were 0.97 (P < 0.001) and 0.80 (P < 0.001) respectively (Mehta et al., 2016). **Tsai et al., (2017)** who assessed the diagnostic accuracy of cTn I for diagnosing ACS with AUC was 0.567 (Tsai et al., 2017). **Calmarza et al., (2017)** who evaluated the diagnostic power of MPO for diagnosing ACS with AUC was 0.82 (P < 0.001) (Calmarza et al., 2017). Also, **Hamza et al., (2016)** reported that AUCs of cTnI and CK-MB for diagnosing ACS patients suspected with AMI in early admission was 0.76 (61.8%) and 0.64 (54.4%); respectively (Hamza et al., 2017). In addition, several studies suggest that MCP-1 has good diagnostics power in patients with ACS (França et al., 2017). In our study the discriminated score was designed for each CP patient on the basis of the combination of CK-MB, cTn I, MPO, and MCP-1 selected by MDA. While this score can used in early diagnosis of ACS and AMI patients with AUCs were 0.93 (95% CI, 0.867-0.978; P < 0.0001) and 0.90 (95% CI, 0.847-0.954; P < 0.0001); respectively. Several authors have used the combination of biomarkers to improve the diagnostic accuracy, **Mehta et al., (2016)** who developed a score based on a combination of hs-cTnT and MPO for the early diagnosis of ACS yielded AUC was 0.90 with specificity, sensitivity, NPV and PPV were 97, 96, 94, and 98 %; respectively (Mehta et al., 2016). **LIU et al., (2010)** who have developed a predictive score using MPO, CK-MB, amino-terminal pro-brain natriuretic peptide, high-sensitivity C-reactive protein and interleukin-6 for risk stratification of ACS with AUC was 0.98 (LIU et al., 2010). **Kavsak et al., (2017)** assessed a developmental score based on a combination of cTn I and blood sugar with another two indexes to be used to exclude a severe cardiac case or death in patients who admitted with signs suggestive of ACS (Kavsak et al., 2017). **Tsai et al., (2017)** who have used one test had multiple biomarkers counting myoglobin, cTn I, CK-MB, B-natriuretic peptide and a different one had two cardiac biomarkers cTn I and CK-MB for diagnosis elderly ACS patients with AUCs were 0.621 and 0.587; respectively (Tsai et al., 2017). In our study the discriminated score was used to distinguish between CP groups, however, it has the greatest AUC was 0.99 to differentiate patient with AMI than those with NCCP, followed by 0.96 of AMI versus SA, followed by 0.86 of UA versus NCCP, followed by 0.80 of UA versus SA, followed by 0.78 of AMI versus UA, followed by 0.59 of SA versus NCCP. The validation of our score was tested on one more group of patients to confirm its reproducibility. Actually, the latter results were reproduced in the validation study with no significant difference, yielding similar AUCs. **Wang et al., (2015)** who improved the diagnostic value of hs-cTnT for discriminating AMI patients by combining it with CK-MB to yield AUC was 0.954 (P < 0.0001) (Wang et al., 2015). **Puelacher et al., (2018)** who observed that the combination of hs-cTnI and B-type natriuretic peptide does not improve the diagnostic accuracy for diagnosis AMI patients in comparison with those in a single form (Puelacher et al., 2018). Many authors have reported that the combination of copeptin and cTn I or hs-cTnT provides a high NPV for AMI of ACS patient's early admission (Stengaard et al., 2017). **Truong et al., (2012)** who showed that the combination of natriuretic peptides with either high-sensitive or conventional troponin represented better reclassification of ACS (Truong et al., 2012).

Yanishi et al., (2016) who developed a risk stratification score based on some laboratory variables in diagnosis STEMI patients with AUCs were 0.81 and 0.74 in derivation set and validation set; respectively (Yanishi et al., 2016).

Limitation

Based on a statistic analysis and systematic review, single biomarkers including cTnI, CK-MB, MPO and MCP-1 have low to moderate diagnostic power to evaluate ACS patients in CP patients. Thus, they might not be sufficient in a single form. So the development of a predictive score derived from the combinations of four biomarkers is required. This score can use to predict patients with ACS and AMI with high efficiency were 88.3% and 81%; respectively.

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