Original Article

Cardiac Myosin-binding Protein-C as a Biomarker in the Early Diagnosis of Acute Coronary Syndrome and Differentiation of Its Types

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Abstract

Background: Coronary heart disease (CHD) is primarily caused by atherosclerotic lesions within the intima of coronary arteries and acute coronary syndrome (ACS) is the main acute clinical manifestation of CHD. The ACS is manifested in one of three subtypes and it is the leading cause of mortality worldwide. The three subtypes of ACS include: acute myocardial infarction (MI) with the electrocardiogram (ECG) presenting ST-segment elevation (STEMI), MI with no ST-segment elevation on ECG (NSTEMI), and the third subtype is unstable angina (UA). The early diagnosis of is important in decreasing morbidity and mortality in ACS patients. **Objective:** To investigate the role of serum level of cardiac myosin-binding protein-C (cMyC), compared with high-sensitivity cardiac troponin-I (hsCTn-I) in the early diagnosis of ACS and differentiation of its subtypes. **Materials and Methods:** One hundred and twenty patients (72 males and 48 females), aged ≥30 years selected from those who were admitted to emergency department (ED) of Al-Yarmouk teaching hospital and diagnosed with ACS by cardiologists. The duration between the onset of chest pain and admission to ED should not exceed 3 h in any cohort. Apparenty healthy subjects as controls group for the study were recruited from those who had no current illness, particularly CHD, no other systemic disease and each had a normal ECG. For each study subject, cMybp-C and hsCT-I serum levels on admission were measured using the enzyme-linked immunosorbent assay kits. For each ACS patient, serum level of hsCTn-I level was measured 3 h after admission. **Results:** The comparison of cMybp-C levels among study groups revealed an overall significant difference and on paired comparison of study groups, the cMybp-C mean level was significantly higher in each ACS subgroup than in controls group ($P < 0.001$), except in UA subgroup versus controls group. The cMybp-C levels showed a significant positive correlation with hsCT-I levels on admission in STEMI and NSTEMI subgroups but not in UA subgroup. The cMybp-C levels also showed a significant positive correlation with hscT-I levels 3 h after admission in STEMI and NSTEMI subgroups but not in UA subgroup. On receiver operating characteristic curve analysis, the cMybp-C level had a better diagnostic accuracy than hscTn-I on admission in differentiation of patients with "STEMI or NSTEMI" from those with UA or from controls. **Conclusion:** Serum cMybp-C mean level is significantly higher in ACS patients with STEMI and NSTEMI than in controls and the increase was more significant than hsCTn-I mean level on admission, so it could help the early diagnosis of ACS patients. The serum levels of cMybp-C also had a better diagnostic accuracy than hsCTn-I on admission in differentiation of ACS patients with STEMI or NSTEMI from those with UA or from controls.

Keywords: Acute coronary syndrome, cardiac myosin-binding protein I, high-sensitivity cardiac troponin I

Introduction

Coronary heart disease (CHD) is a condition in which there is an poor supply of blood to the myocardium that is primarily caused by a formation of atherosclerotic plaques within the intima of coronary arteries. The plaque may erode or rupture resulting in thrombosis leading to partial or total closure of a coronary artery that imped blood flow and manifested acutely as acute coronary syndrome (ACS).[1] The

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ACS could be manifested as one of three subtypes. These subtypes of ACS include myocardial infarction (MI) with the electrocardiogram (ECG) is presenting ST-segment elevationmyocardial infarction (STEMI), MI with non ST-segment elevation myocardial infarction (NSTEMI) and the third type is unstable angina (UA).[2]

Serum level of cardiac troponins I or T (cTn-I and cTn-T) has been regarded as the preferred or standard biomarker in the diagnosis of MI. The levels of troponins increase 4–10 h after the onset of MI and peak at 12–48 h and stay elevated for 4–10 days.[3] A newer generation of cardiac troponins and high-sensitivity troponin I (hsCT-I) can identify heart damage faster than traditional cardiac troponins because the method is sensitive to very low serum levels of troponins.[4]

The cardiac myosin-binding protein-C (cMybp-c) is a newly described biomarker of cardiac necrosis.[5] It is released more rapidly into the circulation than cardiac troponins T or I after MI due to its higher concentration in myocardiocytes.[6] The change in its serum level, especially in patients with an onset of chest pain of <3 h, has been shown to have a higher diagnostic accuracy for MI than that of cT-I or T and so may help in the early diagnosis of patients with MI and may help in their early management.[7]

Materials and Methods

This was a study by case–control design, patients were recruited from the emergency department (ED) and the coronary care unit of Al-Yarmouk Teaching Hospital in Baghdad, Iraq during the period from November 1, 2022 to September 1, 2023. One hundred and twenty patients (72 males and 48 females), aged ≥30 years selected from those who were admitted and assigned a diagnosis as ACS. The diagnosis was based on the presence of two out of three criteria:

- Clinical presentation
- ECG variations
- A positive cardiac troponin I test.

The ACS patients constituted three subgroups according to the subtype of ACS, namely the STEMI, NSTEMI, and UA group. The duration between the onset of chest pain and admission to ED should not exceed 3 h in any selected patient. Apparently healthy subjects as controls group for the study were recruited from those who had no current illness, particularly CHD, no other systemic disease and each had a normal ECG. For each study subject, clinical characteristics were recorded after a thorough physical examination in addition to consideration of age and sex matching with the ACS patients.

Blood analysis

Blood samples were collected from both patients and controls, left to clot, and serum was divided and separated into aliquots which were used for the measurement of serum levels of cardiac myosin binding protine -c cMybp-c, hsCT-I, conventional cT-I, and glutamate-oxaloacetate transferase (GOT) on admission. Another blood sample was collected from each ACS patient 3 h after admission and was used for the measurement of hscT-I. The assays of cMybp-C and conventional cT-I and hscTn-I were done by using the enzyme-linked immunosorbent assay kits that were supplied by MyBioSource USA company, serum GOT activity was measured by full automated devise called COBAS 111.

Statistical analysis

Utilizing the"statistical package of SPSS-24," from IBM company data were examined. Simple measurements such as the "mean, standard error, and standard deviation of the mean, frequency, and percentage" were used to determine the look of the data after confirming that it was regularly distributed. The ANOVA test was employed to examine if there was a change in means between the groups, whereas the least significant difference (LSD) test was utilized to examine the changes between the two means. Using Pearson's correlation, a correlation analysis research between cMybp-C and the other parameters was carried out. $P < 0.05$ was regarded as statistically significant. For cMybp-c and high-sensitivity cardiac troponin-I (hscTn-I)levels, receiver operating characteristic (ROC) curve analysis and an area under the curve (AUC) measurement were performed by comparing different study groups using the "Hanley and McNeil" approach.

Results

The clinical characteristics of study subjects are shown in Table 1 and shows that patients were 60% males and 40% females and the controls group subjects. The study patients who were 30–50 years in age constituted 33.3% and those who were >50–72 years constituted 66.66%. Body mass index (BMI) 20% of patients were of normal weight (with BMI = 19–24.5), 47.5% were overweight (with BMI = 25–29) and 32.5%

Table 1: Demographic and clinical characteristics of the study participants

Characteristics	Patients ($n=120$), n (%)	Controls ($n=80$), n (%)
Age (years)	30–72	30–70
≤50	40 (33.3)	27 (33.75)
>50	80 (66.66)	53 (66.2)
BMI (kg/m^2)		
Normal weight	24 (20)	16 (20)
Over weight	57 (47.5)	38 (47.5)
Obese	39 (32.5)	26 (32.5)
Sex		
Male	72 (60)	48 (60)
Female	48 (40)	32 (40)
ACS subgroups		
STEMI	40 (33.3)	80 (100)
NSTEMI	40 (33.3)	
UA	40 (33.3)	

BMI: Body mass index, STEMI: ST-elevation myocardial infarction, NSTEMI: Non-STEMI, UA: Unstable angina, ACS: Acute coronary syndrome

were within the obese category (with BMI more than 30). Smoking patients were 40% and nonsmoking were 60%. The ACS patients included those with STEMI (40 patients), NSTEMI (40 patients), or UA (40 patients) [Table 1].

The comparison of study biomarkers among the subgroups of ACS patients (STEMI, NSTEMI, and UA) and controls group is shown in Table 2. A comparison was made in regards to the levels of cMybpc using the ANOVA analysis. It is shown that cMybp-C levels had an overall significant difference among the study groups ($P < 0.001$). The comparison revealed an overall significant difference in cT-I ($P = 0.04$), hscT-I on admission ($P = 0.045$), and hscT-I 3 h after admission ($P = 0.001$) in admission to a significant difference in BMI ($P = 0.04$).

Comparison of cMybp-C level among subtypes of acute coronary syndrome and controls

Further analysis by LSD test revealed that cMybp-C level mean was significantly higher in both STEMI or NSTEMI than in controls group "STEMI versus controls, $P = 0.000$ and NSTEMI versus controls, $P = 0.000$, respectively" while it had no significant difference between UA and controls "UA versus controls, $P = 0.626$," The level was also significantly higher in STEMI than in both NSTEMI "$P = 0.001$" and UA "$P = 0.001$." Furthermore, a significantly higher mean level of cMybp-C was detected in NSTEMI than in UA subgroup ($P = 0.001$) [Table 3].

The correlation analysis of study parameters in ACS patients is shown in Table 4. The cMybp-C levels in STEMI group showed a significant positive correlation with hsCTn-I on admission ($r = 0.672$, $P = 0.048$) and also at 3 h after admission ($r = 0.545$, $P = 0.044$). In NSTEMI subgroup, the cMybp-C levels showed also significant positive correlation with hsCTn-I levels on admission ($r = 0.469$, $P = 0.029$) and at 3 h after admission ($r = 0.469$, $P = 0.029$) while in UA subgroup, the cMybp-C levels showed no significant correlation with hsCTn-I levels whether on admission ($r = 0.115$, $P = 0.088$) or 3 h after admission ($r = 0.345$, $P = 0.068$).

To test discriminative power of study biomarkers among ACS subgroups, then ROC curve analysis was conducted. The analysis between STEMI versus NSTEMI subgroups is presented in Table 5 and Figure 1. For cMybp-C, the results showed that the AUC was 0.885 and at a cut-off value of 1.145, the sensitivity was 97.2%, and the specificity was 81.3% with a diagnostic accuracy of 85.1%. For hscT-I levels at admission, the AUC was 0.791 and at a cutoff value of 76.8 ng/ml, the sensitivity of the test was 75.8% while the specificity was 78.9% with a diagnostic accuracy of 78.3%. For hscT-I levels, 3 h after admission, the AUC was 0.971

Table 2: Clinical characteristics, baseline laboratory tests, and study biomarkers in subtypes of acute coronary syndrome patients and controls

Characteristics	STEMI (n=40), mean±SE	NSTEMI (n=40), mean±SE	UA (n=40), mean±SE	Controls (n=80), mean±SE	P
Age (years), range	45–75	45–78	47–80	34–77	0.065, NS
Mean	59±2	60±3	61±3	57±2	
cMybp-C (ng/mL)	3.11±0.21	1.36±0.11	0.6±0.05	0.53±0.04	<0.001, significant
hscT-I on admission	195.2±10.63	66.21±4.12	50.21±2.16	49.23±2.34	0.045, significant
hscT-I 3 h after admission	307.11±12.63	103.72±6.18	57.31±3.51	49.23±2.34	<0.001, significant
cT-I	104.19±5.41	32.52±3.07	22.71±2.34	15.01±0.78	<0.041, significant
BMI (kg/m^2)	28.53±0.57	28.17±0.53	27.53±0.57	23.37±0.46	0.032, significant
GOT (IU/L)	146.1±14.86	58.69±3.17	15.74±1.2	14.42±0.56	<0.001, significant

cMybp-C: Cardiac myosin-binding protein-C, cT-I: Cardiac troponin-I, hscT-I: High-sensitive cT-I, GOT: Glutamate oxaloacetate transaminase, BMI: Body mass index, STEMI: ST-elevation myocardial infarction, NSTEMI: Non-STEMI, UA: Unstable angina, SE: Standard error, NS: Not significant

Table 3: Comparison of cardiac myosin binding protein-C levels between paired study groups (least significant difference-test)

		LSD				
(I) groups	(J) groups	Mean difference cMybp-C (ng/mL) (I−J)	SE	P	95% CI	
					Lower bound	Upper bound
STEMI	NSTEMI	1.74750*	0.15985	0.000	1.4321	2.0629
	UA	2.50925*	0.15985	0.000	2.1938	2.8247
	Controls	2.57969*	0.14408	0.000	2.2954	2.8640
NSTEMI	UA	0.76175*	0.15985	0.000	0.4463	1.0772
	Controls	0.83219*	0.14408	0.000	0.5479	1.1165
UA	Controls	0.07044	0.14408	0.626	0.2139	0.3547

*Significant difference between groups ($P \leq 0.05$). STEMI: ST-elevation myocardial infarction, NSTEMI: Non-STEMI, UA: Unstable angina, SE: Standard error, cMybp-C: Cardiac myosin-binding protein-C, CI: Confidence interval, LSD: Least significant difference

Table 4: Correlations of cardiac myosin-binding protein-C levels with high-sensitive cardiac troponin-I levels in subgroups of acute coronary syndrome patients

Group	Parameter (cMybp-C)	hscT-I on admission	hscT-I 3 h after admission
STEMI	*r*	0.672	0.672
	P	0.048*	0.048*
NSTEMI	*r*	0.469	0.469
	P	0.029*	0.029*
UA	*r*	0.115	0.345
	P	0.088	0.068

*A significant correlation between subgroups of ACS ($P<0.05$). ACS: Acute coronary syndrome, cMybp-C: Cardiac myosin-binding protein-C, hscT-I: High-sensitive cardiac troponin-I, STEMI: ST-elevation myocardial infarction, NSTEMI: Non-STEMI, UA: Unstable angina

and at a cutoff value of 132.58 ng/ml, the sensitivity of the test was 97.5% and the specificity was 83% with a diagnostic accuracy of 89.2%.

The ROC curve analysis between STEMI versus UA subgroups of ACS patients is presented in Table 6 and Figure 2. For cMybp-C levels, the results showed that the AUC was 0.997 and at a cutoff value of 1.420, the sensitivity of the test was 95% and the sensitivity was 97.5% with a diagnostic accuracy of 96.2%. For hscT-I levels on admission, the AUC was 0.678 and with a cutoff value of 87.7 ng/ml, the sensitivity of the test was 76.5% and the specificity was 70.8% with a diagnostic accuracy of 78.3%. For hscT-I levels at 3 h after admission, the AUC was 0.981 and with a cutoff value of 123.44 ng/ml, the sensitivity of the test was 97.5%, and the specificity was 74.2% with a diagnostic accuracy of 82.6%.

The ROC curve analysis between NSTEMI versus UA subgroups of ACS patients is presented in Table 7 and Figure 3. For cMybp-C levels, the results showed that the AUC was 0.918 and at a cutoff value of 0.595 ng/ml, the sensitivity of the test was 95%, and the specificity was 92.5% with a diagnostic accuracy of 88.3%. For hscT-I levels at admission, the AUC was 0.760 and with a cutoff value of 43.1 ng/ml, the sensitivity of the test was 71.5%, and the specificity was 68.7% with a diagnostic accuracy of 77.1%. For hscT-I levels at 3 h after admission, the AUC was 0.885 and with a cutoff value of 56.25 ng/ml, the sensitivity of the test was 85% and the specificity was 81% with a diagnostic accuracy of 86.2%.

Discussion

Laboratory investigation of certain biomarker, principally the cardiac troponins, is complementary to the clinical evaluation and ECG in the diagnosis, triage, and management of patients with suspected ACS. The interval of "1–2" h which permits for ruling out of acute MI or its early diagnosis is currently the most significant clinical hurdle to overcome. The release of cardiac troponin I (cTn-I) is relatively delayed after the onset of MI. The use of troponins and ECG to rule out AMI is slow because serial blood sampling is required to determine

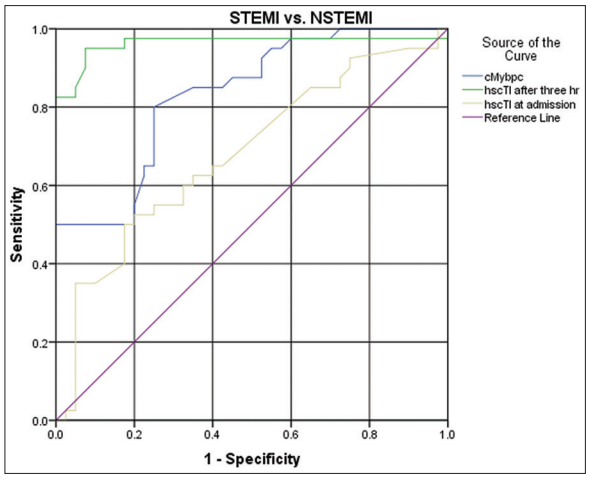

Figure 1: Receiver operating characteristic curves of study biomarkers in STEMI versus NSTEMI subgroups of acute coronary syndrome. STEMI: ST segment elevation myocardial infarction, NSTEMI: non ST segment elevation myocardial infarction

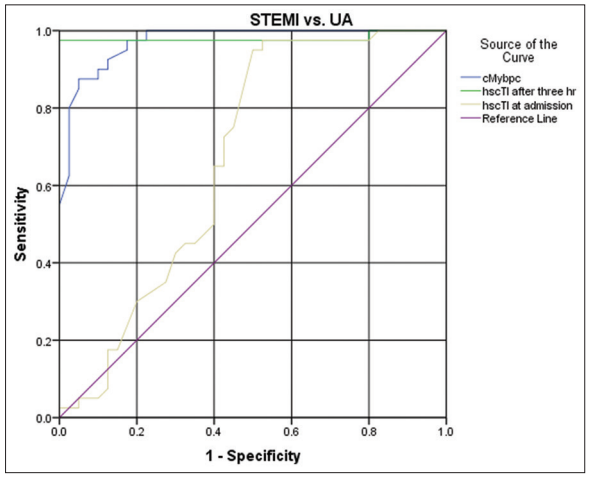

Figure 2: Receiver operating characteristic curves of study biomarkers in STEMI versus unstable angina subgroups of acute coronary syndrome patients. UA: Unstable angina, STEMI: ST segment elevation myocardial infarction

variations in troponin con., primarily in patients with "non-ST elevation ACS." It is important to conduct successive assessments during the extended patient monitoring period in emergency medical and/or cardiology centers to drive the development of new rule-in and rule-out tactics for the timely identification of AMI.[8]

Accordingly, an early diagnosis and clinical subtyping of the heterogeneous patients who present with suspected ACS may be improved by the finding of other biomarkers that their levels may change faster and so could be used for the earlier diagnosis of patient with chest pain. In such a search for newer biomarker that may aid in early diagnosis of ACS and may possibly have importance in understanding of its progression was this study which has evaluated certain novel biomarker that its level is changed in the first few hour after onset of chest pain which is cMybp-C[8] and its level was compared with that of hsCT-I.

Table 5: Discriminative cutoff values of study biomarkers that best predicted patients in ST-elevation myocardial infarction versus non-ST-elevation myocardial infarction subgroups of acute coronary syndrome

Parameters	AUC	Cutoff value	Sensitivity	Specificity	Diagnostic accuracy (%)
cMybp-C (ng/mL)	0.885	1.145	97.2	81.3	85.1
hscT-I (pg/mL) on admission	0.791	76.8	75.8	78.9	78.3
hscT-I (pg/mL) 3 h after admission	0.971	132.58	97.5	83.0	89.2

AUC: Area under curve, hscT-I: High-sensitive cardiac troponin-I, cMybp-C: Cardiac myosin-binding protein-C

Table 6: Discriminative cutoff values of study biomarkers that best predicted patients in ST-elevation myocardial infarction versus unstable angina subgroups of acute coronary syndrome

Parameter	AUC	Cut-off value	Sensitivity	Specificity	Diagnostic accuracy (%)
cMybp-C (ng/mL)	0.997	1.420	95.0	97.5	96.2
hscT-I (pg/mL) on admission	0.678	87.7	76.5	70.8	78.9
hscT-I (pg/mL) 3 h after admission	0.981	123.445	97.5	74.2	82.6

AUC: Area under the curve, hscT-I: High-sensitive cardiac troponin-I, cMybp-C: Cardiac myosin-binding protein-C

Table 7: Discriminative cutoff values of study biomarkers that best predicted patients in non-ST-elevation myocardial infarction versus unstable angina subgroups of acute coronary syndrome

Parameters	AUC	Cutoff value	Sensitivity	Specificity	Diagnostic accuracy (%)
cMybp-C (ng/mL)	0.918	0.595	95.0	92.5	88.3
hscT-I (pg/mL)/0 h	0.760	43.1	71.5	68.7	77.1
hscT-I (pg/mL)/3 h	0.885	56.25	85.0	81.0	86.2

AUC: Area under the curve, hscT-I: High-sensitive cardiac troponin-I, cMybp-C: Cardiac myosin-binding protein-C

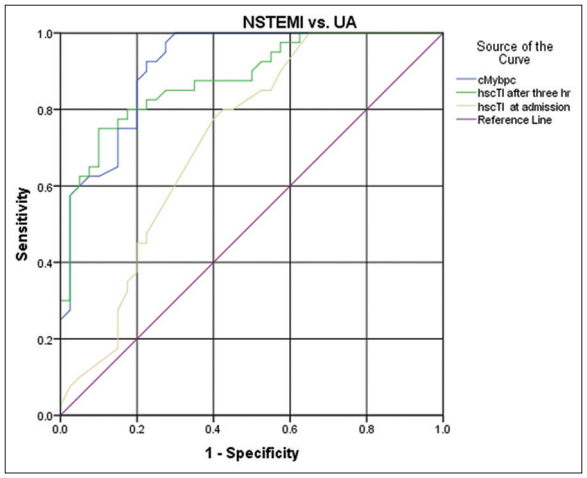

Figure 3: Receiver operating characteristic curves of the study biomarkers in NSTEMI versus unstable angina subgroups of acute coronary syndrome patients. UA: Unstable angina, NSTEMI: non ST segment elevation myocardial infarction

The present study showed a significant difference in the levels of cMybp-C when the subgroups of ACS and the controls group are compared using the ANOVA test. On further analysis by LSD test, the cMybp-C mean levels were significantly higher in both STEMI and NSTEMI subgroups of ACS patients than in UA subgroup or controls group. This agree with the study by Kaier *et al*.[9] because this marker is more abundant than cTn, then it is released into the bloodstream faster during MI and it is useful to evaluate the accuracy of C-Mybp-C as useful biomarker in the early diagnosis of MI patients, the finding of no significant difference in cMybp-C between UA and controls is something that is expected due to no presence of myocardial necrosis in UA patients. This finding is consistent with many previous studies such as that by Nappi *et al*.[7]

The study finding that STEMI subgroup of ACS patients had the highest level of cMybp-C, compared with other subgroups NSTEMI and UA and reflects its role as a biomarker of cardiac necrosis.[9] Such role is again reflected by the finding of positive significant correlations with hsCT-I on admission and at 3 h after admission in STEMI and NSTEMI subgroups while no significant correlations in UA subgroup. This agree with a study by Nappi *et al*.[7] because a more dynamic increase in cMybp-C in the early stages of MI than hsCTn-I. The finding may be due to cMybp-C in higher concentrations in myocardial cells or to presence of a different mechanism for protein release from damaged myocardial cells. The study finding that serum level of cMybp-C increases and then decreases faster than serum level of hsCTn-I as revealed in patients with MI on admission and at 3 h after admission, is also consistent with the finding of studies that described a faster release of cMybp-C into the circulation than hsCT-I following MI and attribute it to its higher concentration in myocardiocytes.[7]

The finding that cMybp-C level has a good AUC and high sensitivity and specificity and diagnostic accuracy is to differentiate between the types of ACS (STEMI, NSTEMI, and UA). This result is associated with the early elevation of cMybp-C in patients with MI, occurring <3 h after the

onset of chest pain. This is consistent with other research, such as that conducted by[10] who reported the use of a unique formula known as the 0/1 h-algorithm, which offered excellent safety in identifying a higher percentage of patients eligible for direct rule-out or rule-in based on a single measurement than the same formula utilizing hsCTnT-I.[10] Compared to troponin, cMybp-C does not require serial collection, which makes it a potentially reliable anchor point for diagnosing MI in patients who are admitted to the ED. There is now a claim that a cMybp-C level-based diagnosis of MI may allow for the more accurate confirmation or exclusion of ACS with increased sensitivity and specificity, which could further lower the death rate and lower the financial burden of treating MI.[10]

Conclusion

Serum cMybp-C mean level is significantly higher in ACS patients with STEMI and NSTEMI than in controls and the increase was more significant than hsCTn-I mean level on admission, so it could help the early diagnosis of ACS patients. The serum levels of cMybp-C also had a better diagnostic accuracy than hsCTn-I on admission in differentiation of ACS patients with STEMI or NSTEMI from those with UA or from controls.

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Conflicts of interest

There are no conflicts of interest.

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