Original Article
Soluble fibrin monomer complex assay enhances early and accurate diagnosis of acute myocardial infarction

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Abstract: Background: Soluble fibrin monomer complex (SFMC) was shown to be raised in patients with acute myocardial infarction (AMI). It provides information regarding fibrin formation prior to thrombus formation and the development of myocardial cell damage in thrombosis-mediated type 1 MI. The introduction of high sensitivity cardiac troponin assays has increased the diagnostic sensitivity (SE) for diagnosis of MI, but the diagnostic specificity (SP) was compromised. Such a defect was partially conformed by recommending serial measurements, which comes at the expense of a timely definitive diagnosis. We suppose that SFMC can act as an advantageous marker to promote the diagnostic performance of sensitive cardiac troponin I (s-cTnI) to diagnose AMI using the on-admission sample of acute chest pain patients. Methods and findings: s-cTnI and SFMC were assayed in 75 acute chest pain patients presenting within 3 hours of symptoms onset and 20 healthy control subjects. Thirty-five patients were diagnosed as having AMI, and 40 patients had non-AMI chest pain. Either marker was significantly higher in AMI. The receiver operating characteristic-area under the curve, SP and positive predictive value (PPV) of the combined use of both markers were 0.985, 97.5% and 97%, respectively, which were higher than the values for s-cTnI (0.903, 85%, 84.2%, respectively) or SFMC (0.946, 90%, 89.5%, respectively). No improvement of SE or negative predictive value was noted on simultaneous use of both markers. Conclusion: adding SFMC to s-cTnI during early stages of acute chest pain has promoted the diagnostic accuracy of s-cTnI in terms of SP and PPV.

Keywords: Soluble fibrin monomer complex, sensitive troponin, myocardial infarction, chest pain

Introduction

Cardiac troponins (cTn) have been playing a central role in the diagnosis of acute myocardial infarction (AMI) because of their specificity for cardiac muscle and sensitivity to its injury. In reference to the third universal definition of MI, AMI is diagnosed by a rising and/or falling pattern of cTn concentrations with, at least, one value above the 99th percentile limit of the reference value along with clinical features of myocardial ischemia as indicated by one of the following: symptoms of ischemia, electrocardiographic (ECG) changes indicative of new ischemia, development of pathological Q-waves, imaging evidence of the new loss of viable myocardium or new regional wall motion abnormalities, or intracoronary thrombus by angiography or autopsy [1].

The diagnosis of non ST segment-elevation myocardial infarction (NSTEMI) is required to be early and accurate to avoid missing MI patients and improve rule out. These criteria are supposed to be met by the introduction of the new generations of cTn assays, sensitive and high sensitivity cardiac troponin (s-cTn and hs-cTn, respectively). These assays are able to detect very low concentrations, approximately 10- to 100-fold lower than conventional cTn assays. Good hs-cTn assays should have imprecision (CV) at the 99th percentile of reference population of $\leq 10\%$ and able to measure cTn concentrations above the limit of detection in $\geq 50\%$ of healthy subjects [2, 3].

However, the introduction of hs-Tn has revealed the problem of the attending lower diagnostic specificity (SP), as it tests positive in a wide range of non-ischemic clinical conditions, including acute and chronic conditions, of cardiac or non-cardiac origin. This reduced specificity may lead to an increased number of inappropriate hospitalizations [4]. The second

sample for cTn was recommended at time intervals of 6 h to confirm or exclude AMI [5]. The current European Society of Cardiology guidelines on management of NSTEMI recommend reducing the time between two consecutive blood samples for hs-cTn testing from 6 h to 3 h with a comparable efficacy [6, 7]. Recently, a one hour algorithm for rule-out and rule-in using hs-cTn was validated [8, 9]. Although persistent steady elevations of hs-cTn can be found in patients with stable conditions, the rise or fall patterns could also be found in acute conditions other than ischemic heart disease like acute pericarditis and myocarditis, cardiac arrhythmias and acute pulmonary embolism [4, 10]. The need for differentiation of true "thrombotic" MI from other causes of myocardial damage is an ongoing challenge for proper disease management.

According to the recent classification of MI, type 1 MI occurs due to thrombus-mediated obstruction of the coronary artery [1]. So, it was of interest to study the relations between MI, coronary artery disease (CAD) and hypercoagulable state and/or thrombosis process. In this context, several prothrombotic markers were found to be linked to prediction, occurrence, or prognosis of AMI: prothrombin time and activated partial thromboplastin time were found to be significantly increased in AMI patients [11]; tissue plasminogen activator and plasminogen activator inhibitor-1 were raised in AMI patients and were correlated to prognosis [12]; pre- and post-operative concentrations of fibrin monomer and D-dimer were increased in patients with peri-operative myocardial ischemia showing strong positive correlations with post-operative cTn [13]; thrombus precursor protein had been shown to be linked to prognosis in patients with acute coronary syndrome (ACS) [14]; soluble fibrin was increased in AMI patients having the strongest predictor value of MI at a young age [15]. In addition, a soluble fibrin bedside test has been found to be useful for the early identification of patients with unstable angina with a non-diagnostic electrocardiogram [16].

During the extremely early stage of blood coagulation, soluble fibrin monomer appears in the blood stream and generally forms a complex with fibrinogen, termed soluble fibrin monomer complex (SFMC). SFMC is an established marker reflecting thrombin activity and the activity of the coagulation system. It seems to be a potential risk factor for intra-operative hemorrhagic diathesis [17] and a good indicator of thrombogenic conditions [18]. SFMC was significantly raised in patients with MI than patients with coronary insufficiency or healthy subjects and its dynamics had been linked to prognosis [19, 20]. Furthermore, cTnT in patients with unstable angina was reported to be correlated with the plasma levels of SFMC [21].

SFMC provides information regarding fibrin formation immediately prior to the formation of thrombus and, accordingly, prior to even the development of myocardial cell damage. Its role in the early diagnosis of AMI was found superior to D-dimer and CK-MB, and their levels were reported not to be affected by therapy with heparin or thrombolytic agents [22]. Because of its rapidity of release and simplicity of assay, the test for these complexes may be of diagnostic value in MI. We suppose that SFMC may act as an advantageous marker that can hypothetically promote the diagnostic performance of s-cTnI in the setting of combined testing of both markers using the on-admission sample of acute chest pain patients.

Subjects and methods

The present study was conducted over a period of three months and included 75 patients who presented with non-traumatic chest pain or other symptoms suggestive of AMI that started within the last 3 hours before admittance to emergency department of Ain Shams University hospital, Cairo, Egypt. Written consent was obtained from each participating subject after the approval of the local ethics committee. They were grouped as: 35 patients diagnosed as having AMI (group I) and 40 patients with non AMI chest pain (group II). Group I patients were further sub-classified into STEMI (n=11) and NSTEMI (n=24). The patient exclusion criteria included age <18 years, recent surgery, active infection, significant hepatic or renal dysfunction and malignancy. Twenty healthy subjects were included as a healthy control group (group III). AMI was diagnosed according to the current guidelines [1]. Unstable angina was diagnosed when a patient had normal troponin levels and typical angina at rest representing a deterioration of previously stable angina. Further diagnostic categories included cardiac non-coronary causes (e.g., pericarditis, myocar-

Table 1. Baseline demographics and clinical characteristics

Characteristic	AMI (n=35)	Non-AMI chest pain (n=40)	P value
Age [Years, Mean ± SD]	62.4±11.4	56.2±10.9	0.18
Male [n. (%)]	22 (62.9)	27 (67.5)	0.17
BMI [Kg/m² , Mean ± SD]	28.6±6.4	30.5±5.3	0.16
Systolic BP [mmHg, Mean ± SD]	136±18	145±16	0.008
Diastolic BP [mmHg, Mean ± SD]	85.6±17	88.2±14	0.41
Current smoking [n. (%)]	16 (45.7)	21 (52.5)	0.56
History of DM [n. (%)]	24 (68.6)	23 (57.5)	0.32
History of hypertension [n. (%)]	29 (82.9)	24 (60)	0.03
History of hyperlipidemia [n. (%)]	26 (74.3)	24 (60)	0.19
History of angina [n. (%)]	14 (40)	17 (42.5)	0.83
History of MI [n. (%)]	19 (54.3)	12 (30)	0.03
ECG changes			0.0017
ST-segment elevation [n. (%)]	11 (31.4)	2 (5)	
ST-segment depression [n. (%)]	8 (22.9)	4 (10)	
T-wave inversion [n. (%)]	6 (17.1)	7 (17.5)	
Non-significant ECG findings [n. (%)]	10 (28.6)	27 (67.5)	

AMI: acute myocardial infarction; BMI: body mass index; BP: blood pressure; DM: diabetes mellitus.

at 540 nm. The increase in absorbance is related to the SFMC level present in the test sample which is plotted against a calibration curve developed using 5 levels calibration (STA-Liatest FM Calibrator) and buffer (STA-Owren-Koller buffer) as zero point. To ensure accuracy and reproducibility of the results, two different levels of control were included with the run using the STA-Liatest FM Control kit. The observed limit of detection was 2.0 μg/mL and the assay was linear up to 150 μg/mL. The reported reproducibility ranges from 3.1% to 8.0%. The reference range is reported to be less than 6.0 μg/mL.

ditis or tachyarrhythmias), non-cardiac causes, and symptoms of unknown origin. Blood samples were collected from patients on admission, and from control subjects, for SFMC and s-cTnI assays. Second samples were collected from patients after 3 hours of admission for s-cTnI assay. Nine volumes of blood were collected in 1 volume 3.2% trisodium citrate for the SFMC assay. Samples were centrifuged for 10 minutes at 2500 g. As for s-cTnI, EDTA blood was collected and centrifuged. The recovered plasmas were immediately stored at -80°C till analysis for a maximum of 1 month. Frozen plasmas were thawed directly at 37°C for 15 minutes before testing.

a) Soluble fibrin monomer complexes (SFMC) was estimated using the immunoturbidimetric assay STA-Liatest FM and STAGO COMPACT CT ST4 analyzer (Diagnostica Stago, France). The assay is based on the change in turbidity of a microparticle suspension that is measured by photometry. The latex microparticles, coated with monoclonal antibodies specific for fibrin monomers, are mixed with the test plasma. The resultant antigen-antibody reaction leads to agglutination of the microparticles causing increase in turbidity of the reaction medium that is reflected by an increase in absorbance and measured photometrically by the analyzer

b) The cTnI assays were done using PATHFAST cTnI sensitive assay (Mitsubishi Kagaku Iatron Inc., Tokyo, Japan). The assay is based on chemiluminescence enzyme immunoassay (CLEIA). Alkaline phosphatase (ALP)-labeled anti-cTnI monoclonal antibody and anti-cTnI monoclonal antibody-coated magnetic particles are mixed with the sample where cTnI is sandwiched between magnetic latex antibody and the ALP-labeled antibody. Bound/Free (B/F) separation is then performed using Magtration technology. Chemiluminescent substrate is then added and catalyzed by ALP in retained sandwiches resulting in emission of light (461 nm) whose photons are counted by photomultiplier tube detection system. Concentrations are calculated through a standard calibration curve. Quality control assay was run daily. The limit of detection is reported to be 1 ng/L. The upper reference limit (99th percentile) for cTnI concentration is 20 ng/L. The lowest concentration witha CV% less than or equal to 10% is 3.1 ng/L.

Statistical methods

Statistical analyses were done using Medcalc Version 14.12.0-64 bit (Medcalc Software bvba). Mann-Whitney test and student t-test were used for comparisons of independent samples. ROC was used for diagnostic performance evaluations. Wilcoxon test and paired

Table 2. Levels of SFMC and s-cTnI in the 3 study groups

Assay	AMI (n= 35)	Non-AMI chest pain (n=40)	Control subjects (n=20)	P value
On admission-SFMC (µg/mL)	14.2 (11.4-24.9)	6.1 (5.0-7.6)	3.0 (2.5-4.0)	<0.001
	STEMI: 15.8 (11.7-27.3) *NSTEMI: 13.2 (10-21.7)* (P=0.19)			
On admission-s-cTnI (ng/L)	70 (41.25-136.25)	11 (6.8-14.0)	3.7 (3.2-4.1)	<0.001
	STEMI: 72.5 (21.9-154.9) *NSTEMI: 87.5 (51.5-133.5)* (P=0.53)			
Second sample-s-cTnI (ng/L)	441.5 (251.5-721.25)	12.0 (7.7-15.9)	-	<0.001
2nd sample-1st sample s-cTnI difference %	281 (102.6-400)	9.7 (6.0-10)	-	<0.001

SFMC: soluble fibrin monomer complex; s-cTnI: sensitive cardiac troponin I; AMI: acute myocardial infarction; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction.
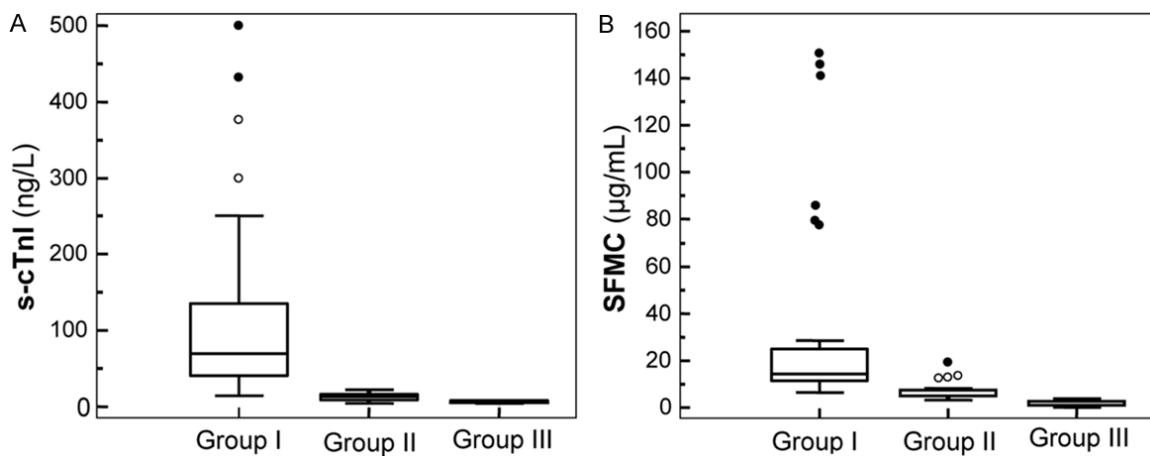
Figure 1. Levels of s-cTnI and SFMC on admission in the 3 study groups; Box plot presentation: (A) sensitive cardiac troponin I (s-cTnI), (B) soluble fibrin monomer complex (SFMC). Both markers show significantly higher levels in acute myocardial infarction patients (Group I) than in non-AMI chest pain patients (Group II), and both groups (I and II) are higher than healthy control subjects (Group III).

t-test were used for paired samples. Chi-squared test was used for testing association or distribution. Ranked Spearman correlation test was used for correlation studies. Probability of error (P value) at 0.05 was considered statistically significant.

Results

Characteristics of patients

Baseline characteristics of the 75 patients with suspected AMI are shown in **Table 1**, of whom the diagnosis of AMI was concluded for 35 patients (46.7%). The results have shown no significant difference in the age or gender ratio among the two groups. Of the baseline clinical data, the systolic blood pressure recorded at presentation was significantly higher in group II patients, whereas significantly higher

number of patients reported history of hypertension and previous attacks of AMI in group I than in group II (**Table 1**). Only 7 patients from group I and 9 patients from group II were subjected to blood collection within less than 2 hours after symptom onset. The remainders were drawn between 2 to 3 hours after symptom onset. The mean time of collection was 2.15 hours.

s-cTnI and SFMC levels among the three study groups

Significantly higher levels of s-cTnI and SFMC were found in group I than group II, as well as when either group was compared with group III (P<0.001). Within the AMI patients, no significant differences were found between the STEMI and NSTEMI patients (**Table 2**; **Figure 1**). Interestingly, on admission levels of s-cTnI and

Table 3. Diagnostic performance of s-cTnI and SFMC assays at presentation

Assay	AUC	Best Cutoff	Sensitivity	Specificity	PPV	NPV
	(95% confidence interval)		(95% confidence interval)			
s-cTnI	0.903 (0.812-0.959)	18.0 ng/L	91.4% (76.9-98.2)	85.0% (70.2-94.3)	84.2% (68.8-94.0)	91.9% (78.1-98.3)
SFMC	0.946 (0.868-0.985)	8.2 µg/ml	97.1% (85.1-99.9)	90.0% (76.3-97.2)	89.5% (75.2-97.1)	97.3% (85.8-99.9)
Combined	0.985 (0.925-0.999)		91.4% (76.9-98.2)	97.5% (86.8-99.9)	97.0% (84.2-99.9)	92.9% (80.5-98.5)

s-cTnI: sensitive cardiac troponin I; SFMC: soluble fibrin monomer complex; AUC: area under the curve; PPV: positive predictive value; NPV: negative predictive value.
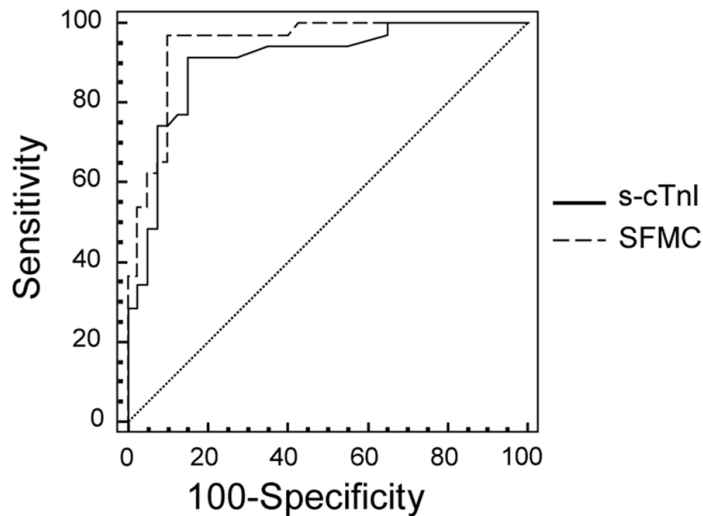
Figure 2. Diagnostic performance of s-cTnI and SFMC assays on admission of chest pain patients as presented by receiver operator characteristic (ROC) curves. Area under the curve (ROC-AUC) for SFMC is 0.95 and for s-cTnI is 0.9; the best cutoff for SFMC is 8.2 mg/mL and for s-cTnI is 18.0 ng/L.

SFMC were not significantly correlated in any of the patient groups (group I: r=0.28, P=0.1; group II: r=0.09, P=0.7).

Diagnostic performance of s-cTnI and SFMC assays at presentation

The diagnostic performance of s-cTnI and SFMC for early AMI diagnosis was evaluated by the ROC analysis. For s-cTnI, a cutoff value of 18 ng/L was found to be efficient in discriminating patients with AMI from those with non-AMI chest pain (AUC: 0.903, sensitivity: 91.4%, specificity: 85%, PPV: 84.2%, NPV: 91.9). The SFMC cut off value that could define AMI cases was 8.2 µg/mL (AUC: 0.946, sensitivity: 97.1%, specificity: 90%, PPV: 89.5%, NPV: 97.3%). The diagnostic significance of combined testing of both assays was evaluated using the two cutoff levels and the following diagnostic criteria were obtained: sensitivity 91.4%, specificity 97.5%, PPV 97%, NPV 92.9%. The AUC has increased to 0.985 for AMI diagnosis on simultaneous implementation of the two diagnostic cut offs, which was significantly higher than s-cTnI AUC (P=0.013), whereas no significant difference was detected when compared to SFMC AUC (P=0.098) (**Table 3**; **Figure 2**).

*Assay values of s-cTnI three hours after admission*

The relative change of s-cTnI levels between the on admission sample and the 3 hour-sample was calculated for each patient. The 3 hour-s-cTnI levels of group I patients were significantly higher than those of group II patients (P<0.001). The same result was obtained when the median values of percent difference were compared between patients of both groups (**Table 2**; **Figure 3**).

Discussion

Adequate interpretation of sensitive troponin assay values is crucial because of the criticality of ACS conditions. Despite the high sensitivity of these assays for cardiac myocyte necrosis, their specificity for AMI has been always debated. The rising/falling values are required, as an additional tool, to make the diagnosis of AMI by quantifying the relative or absolute change in cTn concentration, or using the different cutoff age approach [23]. Several studies have addressed the inherent deficiencies in sensitive or high sensitivity cTn assays and had largely advocated the use of other markers to increase cTn diagnostic performance either for rapid triage or rule out [24-27]. In this context, SFMC was investigated as an early marker for diagnosis of MI owing to its ability to provide information about thrombus formation immediately before its being fully developed.
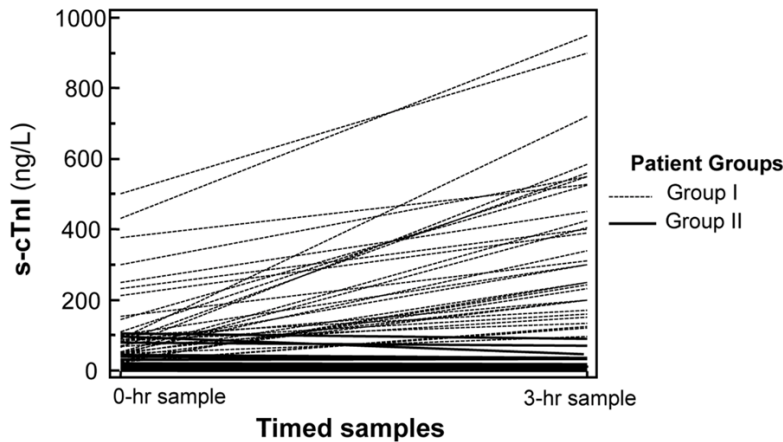
Figure 3. s-cTnI 3 h relative changes in AMI patients (group I) and non-AMI chest pain patients (group II), showing that all cases that were finally diagnosed as AMI have exhibited a pronounced increase in s-cTnI levels (281%; IQR: 103%-400%), in contrast to non-AMI chest pain patients who showed relative increase of 9.7% median value (IQR: 6%-10%).

In this study, we're investigating the potentiality of SFMC to infer an increased specificity to s-cTnI assay when both markers are tested on admission. The study was designed to verify the combined use of the two principally different markers to indicate a thrombotic cardiac muscle necrosis, which make most cases of AMI, as well as testing their competence to function as a substitute to serial measurement of the s-cTnI.

Patients who presented early, i.e. within 3 hours of start of chest pain, were selectively included in the study. Either marker was expressed at significantly higher levels in patients who were diagnosed as AMI than those who had non-AMI chest pain, complying with the results revealed in a previous study [22].

We tested the diagnostic performance of either marker separately, as well as the combined diagnostic performance, to diagnose AMI at a very early point of the disease course. The ROC-derived optimal cutoff values for s-cTnI and SFMC were 18 ng/L and 8.2 μg/mL, respectively, with AUC values of 0.903 (95% CI= 0.812-0.959), 0.946 (95% CI=0.868-0.985), respectively. SFMC showed a higher specificity (90%) than s-cTnI (85%), indicating a higher false positive rate for s-cTnI that may be referred to non-thrombotic, non-MI cardiac conditions as per diagnostic criteria for MI. To evaluate the rationality of combined use of both mark-

ers, we contrasted cases that showed increase in both markers to those with no or isolated increase of either marker. The ROC AUC for the combined markers (0.985, 95% CI=0.925-0.999) was significantly higher than that for s-cTnI indicating an appreciable improvement of the diagnostic performance of s-cTnI when combined with SFMC assay. Specificity on using both markers was significantly improved (97.5%). Although the two markers showed a comparable PPV (84.2% for s-cTnI and 89.5% for SFMC), The PPV of the combined use of both assays was boosted to 97% (compared to 84.2 for S-cTn and 89.5% for SFMC).

The results indicate that the addition of SFMC to s-cTnI has indeed improved the diagnostic specificity and PPV, with a consequent increase in the credibility of simultaneous use of both tests to detect cases of AMI at an early stage.

However, the on-admission sample combined sensitivity and NPV were almost comparable to those acquired by s-cTnI. In view of the values of s-cTnI on serial testing (i.e. using a second sample obtained after 3 h of admission), the falsely low values of s-cTnI detected in the on-admission samples of 3 patients showed significantly increased levels in the second sample results (showing increments of 347%, 470%, 545.5%), and consequently complying with the diagnostic criteria for AMI implemented in this study. This implies that these 3 patients were early presenters of chest pain and the on-admission s-cTnI values failed to reach the diagnostic levels.

The individuality of each assay was noticeable in the non-AMI chest pain patients, in which 4 patients were found to exceed the 8.2 μg/mL cutoff value of SFMC (19.3, 12.3, 13.5, 15.3 μg/mL), 3 of whom were diagnosed as having unstable angina and showed s-cTnI levels <18 ng/L, and only 1 patient had increased levels of both markers (SFMC: 13.5 μg/mL; s-cTnI: 40.6

ng/L). On the other hand, s-cTnI was independently higher than the cutoff level in 6 non AMI chest pain patients (30.5, 20.4, 78, 104.1, 97.7, 43.8 ng/L). Evidently, the two markers identified different patients in the non-AMI patients. Based on the process by which they would appear in blood, the SFMC might exceed the threshold level in case of occurrence of thrombosis causing ischemia that was not high enough to cause infarction, and hence, s-cTnI will not be elevated. On the other hand, s-cTnI might exist at detectable levels in cases where there is minute cardiac damage in cases other than thrombotic conditions. This suggests the power of the combined use of both markers for a more accurate diagnosis of AMI, where either marker expressed in low values, would merely nullify the effect of the non-specific increase of the other marker.

No correlation was found between SFMC and s-cTnI levels at presentation in any of the study groups. Ieko et al. [22] have come to the same result in AMI patients in the first 24 hrs of chest pain. However, Mega et al. [14] reported significant positive correlations and Bottiger et al. 2005 [13] had revealed variable correlations in specimens with different timing. This recurrently reinforces the difference in origin of rise and dynamics of both markers.

Conclusion, limitation, and recommendation

In conclusion, adding SFMC to s-cTnI during early stages of acute chest pain has considerably promoted the diagnostic accuracy of s-cTnI in terms of specificity and PPV. Failure to improve diagnostic sensitivity and NPV by cmbining both assays at presentation signifies the incidental need of a subsequent second sample to detect increment in s-cTnI values as required to make the diagnosis of AMI, especially in patients showing low s-cTnI values in the on-admission sample and, thus, may escape the diagnosis of AMI. Reasonable use of combined assays for early and accurate diagnosis of AMI requires judicious interpretation of the results in view of other diagnostic criteria of AMI. The present results are limited by the small number of samples used for testing, calling for more comprehensive studies that would permit more appropriate categorization of acute chest pain conditions. Another limiting factor is the lack of sequential testing of both markers to investigate the expected gradual decrease of SFMC levels in late sampling, and hence to establish the time limits for the efficient use of combined testing of both markers.

Disclosure of conflict of interest

None.

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