

Copeptin, Troponin-I, Pro-BNP and hs-CRP levels in Diagnosing Acute Coronary Syndromes

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Abstract

Background: Chest pain is a frequent symptom patients present with to the emergency room. Copeptin, the C-terminal fragment of arginine-vasopressin, is a marker of stressful situations. Recent studies showed that normal levels of copeptin combined with a normal troponin accurately excluded the diagnosis of acute coronary syndrome (ACS). In this prospective, single center study we evaluated if negative levels of copeptin, pro-BNP and hs-CRP combined with negative troponin (cTn-I) can accurately rule out the diagnosis of ACS and also other life-threatening causes of chest pain.

Results: Of 120 enrolled patients (69.2% males, median age 60 yrs), 31.7% were diagnosed with ST elevation myocardial infarction (STEMI), 17.5% with non ST-elevation myocardial infarction (NSTEMI), 17.5% with unstable angina (USAP), 12.5% stable angina pectoris (SAP) and 20.8% normal coronary arteries (NCA). Copeptin levels were significantly higher in ACS patients with STEMI and NSTEMI than in those with other diagnoses (0.855 ± 0.279 vs. 0.516 ± 0.127 , $p < 0.001$). In the correlation analyses, copeptin and cTn-I, and copeptin and pro-BNP were positively correlated (r values 0.397; $p < 0.001$). Diagnostic accuracy of copeptin over 0.583, had 91% sensitivity and 79% specificity the myocardial infarction (95% CI 0.86 to 0.91).

Conclusions: The combined use of copeptin, pro-BNP, hs-CRP and cTn-I significantly improved the diagnostic accuracy of troponin alone both in myocardial infarctions and in other life-threatening diseases. Measurement of these markers might be therefore considered not only as a rule-out strategy but also as a warning sign of life-threatening disease.

Keywords: Copeptin; Pro-BNP; hs-CRP; cTn-I acute coronary syndrome

Introduction

Chest pain is one of the most frequent symptoms leading to patient presentation at the emergency room (ER) and is associated with a wide spectrum of diseases, some more benign (i.e. musculo-skeletal or gastroesophageal) and others potentially lethal such as acute coronary syndrome (ACS), aortic dissection and pulmonary embolism [1].

In ACS, despite the clinical development and the introduction of new indicators in clinical practice, a significant proportion of patients are still misdiagnosed and 2–4% of those with ACS are discharged from the ER [2] without a correct diagnosis. On the other hand, many patients suffering from non-life-threatening diseases do unnecessarily undergo repeated blood tests, X-rays and clinical monitoring leading to an extended stay in overcrowded ERs. The most specific marker of myocardial necrosis, troponin (Tn), has a blind period during the first few hours after the onset of symptoms owing to its delayed release into the blood after myocardial injury [3].

Copeptin, the c-terminal fragment of the pro-hormone arginine-vasopressin, is very stable and sensitive as a stress marker, while full-length arginine-vasopressin is unstable and rapidly cleared from plasma [4]. The endogenous stress caused by an acute myocardial infarction (AMI) leads to the release of copeptin, resulting in high

plasma values in the first three to four hours after the onset of myocardial injury. Reichlin et al. showed that on arrival of the patient to the ER a normal plasma level of copeptin combined with a normal troponin does accurately rule out the diagnosis of ACS, with a negative predictive value as high as 99.7% [5]. This finding was confirmed by others [6,7]. A correlation was also shown between the values of copeptin as a stress marker and potentially acute lethal diseases such as stroke, heart failure and severe sepsis [8,9].

B-type natriuretic peptide (BNP) and amino-terminal pro B-type natriuretic peptide (NT-proBNP) are also useful for risk assessment in suspected MI patients. BNP represents the active hormone and when it is released from myocytes and acts to reduce hemodynamic stressors such as wall stretch through natriuresis, vasodilation, inhibition of the renin-angiotensin-aldosterone axis and sympathetic nervous system [10]. NT-proBNP, on the other hand, is an inactive co-metabolite of the common intracellular precursor [11]. BNP and NT-proBNP are predominantly released from the cardiac ventricles in response to hemodynamic stresses such as wall stretch or tension. Analytically, the measurement of NT-proBNP is advantageous compared to BNP as it is more stable after collection and upon long-term freezing; NT-proBNP also has a longer biological half-life [11]. Although BNP and NT-proBNP are most commonly associated with a clinical role in the diagnosis or rule-out of congestive heart failure, they have been evaluated for use in MI for prognostication, risk stratification, and rule-out of ACS in low-risk patients [12].

Inflammation is always present throughout the period of ACS, and its degree of activity is closely related to plaque instability. Serum high-sensitivity C-reactive protein (hs-CRP) is a sensitive indicator of inflammation, which is closely related with plaque progression. Hs-CRP levels are significantly higher in ACS patients with unstable plaque (thin fibrous cap) [13], and such patients usually show a poor prognosis [14]. Therefore, hs-CRP levels can reflect the prognosis of ACS patients; however, hs-CRP is a non-specific inflammatory factor, and therefore has poor specificity.

In this study, we aimed to discuss the importance of copeptin in the diagnosis of ACS, also aimed to determine the correlations among copeptin, pro-BNP, hs-CRP and cTn-I levels in ACS patients.

Materials and Methods

From May 2012 to June 2013, consecutive patients presenting to the ER with symptoms suggestive for AMI with onset or peak within the last 8 hours were included. The inclusion criteria were the following: patients older than 25 years and younger than 80 years with chest pain suggestive of ACS of <8 h duration since its onset. Written informed consent was obtained from all participating patients. Pregnant patients, and those with terminal renal dysfunction, congestive heart failure, malignant disease, hepatic failure, pulmonary thromboembolic event, severe mitral-aortic or tricuspid valve diseases, dissecting aortic aneurysm, trauma or muscle injury anamnesis in last seven days, and prior myocardial infarction in last one month or percutaneous coronary intervention or coronary artery bypass graft surgery in last one month were excluded from the study.

All patients underwent on arrival a complete clinical evaluation including a standard 12-lead electrocardiogram (ECG) and blood tests (including cTn-I), while further tests (chest X-ray, echocardiography) and a cardiologist evaluation were performed according to the physician's judgment and hospital protocols. All patients underwent coronary angiography, interventional procedures immediately.

Values of copeptin were determined in the blood sample obtained at admission within 8 h from the onset of symptoms, according to the kinetics of the biomarker. Blood samples for the measurement of copeptin (Phoenix Europe GmbH, Karlsruhe, Germany) were collected in tubes with potassium ethylenediamine tetra-acetic acid, centrifuged, plasma was frozen at -80°C and then analyzed as described previously. A cutoff value of 0.12 ng/ml was considered the lower normal limit for copeptin, as indicated by the manufacturer.

NT-proBNP determination was performed on a Cobas h 232[®] system from Roche Diagnostics (Rotkreuz, Switzerland), which uses an immunochromatographic reagent strip to obtain quantitative NT-proBNP results in whole blood (150 μL) at point of care. Plasma NT-proBNP values are expressed in pg/mL (analytical range, 60-3000 pg/mL). A cutoff value of 125 pg/mL was considered the lower normal limit for copeptin, as indicated by the manufacturer.

Cardiac troponin I (cTn-I) measurement was performed with the use of the Cobas e 601 system (Roche Diagnostics, Rotkreuz, Switzerland) with a limit of detection of 0.1 $\mu\text{g/L}$, a 99th percentile cutoff point of less than 0.1 $\mu\text{g/L}$, and a coefficient of variation of less than 10% at 0.35 $\mu\text{g/L}$.

Hs-CRP was tested with CardioPhase[™] hs-CRP kit with the use of BN[™] II System (Siemens Healthcare Diagnostics, Marburg, Germany). The reference value to assess the risk of vascular disease was <1.0

mg/L. The detection limit of the method was 0.15 mg/L, and the coefficient of variation was 7.6% at a concentration of 0.4 mg/L.

Statistical analysis

Statistical analysis was performed using the software SPSS 15.0 (Statistical Package for Social Sciences) software package. Kolmogorov-Smirnov test was used to test normal distribution. Variables were expressed as mean \pm standard deviation (avg. \pm SD) or median (min-max). Additionally, a paired t-test and Wilcoxon signed rank nonparametric test for paired data were used to compare the differences between the before and after treatment. The relationships between variables were analyzed with the Pearson correlation analysis. To determine the diagnostic value of copeptin, receiver operating characteristic (ROC) analysis was performed. $P < 0.05$ was considered statistically significant.

Results

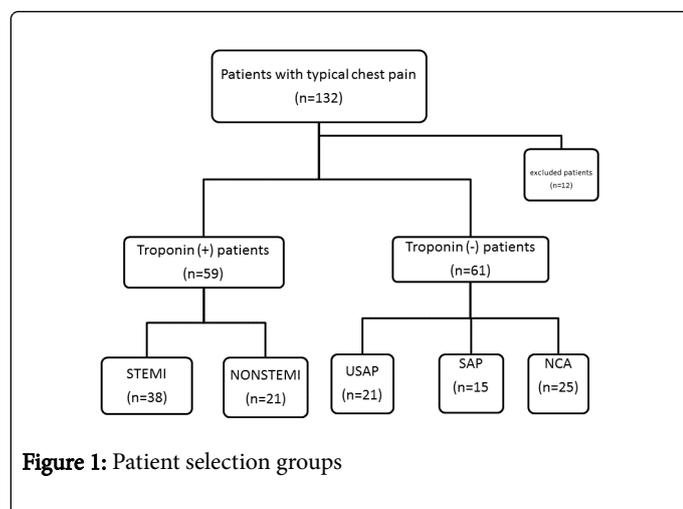
132 patients were enrolled in the study; however 12 of them were excluded for different reasons (four of them were older than 80 years, 5 for them had decompensated heart failure, and 3 of them had terminal renal failure). Patients were divided into two groups based on cardiac troponin; troponin positive (Group 1) and negative (Group 2) groups. 59 (49.2%) of them in Group 1, and 61 (50.8%) of them were in Group 2. 38 of 59 patients (64.4%) were diagnosed with STEMI, 21 (35.6%) of them were diagnosed with NONSTEMI in group 1. 21 of 61 (34.4%) were diagnosed with USAP, 15 (24.6%) were diagnosed with SAP, and 25 (41%) were diagnosed with normal coronaries in group 2 (Figure 1). 83 patients (69.1%) were male, while 37 (30.9%) were female. 43 male and 16 female patients were included in Group 1, while 40 male and 21 female patients were included in Group 2. The age difference between the groups was statistically significant ($p < 0.05$) however gender difference was not different between the groups (Table 1). There were no differences between groups in aspect of diabetes, hypertension and hyperlipidemia. In group 1, 21 (17.5%) patients were active smokers, however 10 (8.3%) patients were active smokers in group 2 ($p < 0.05$).

	Group 1 n=59	Group 2 n=61	P
Age (years)	62 (32-82)	60 (38-79)	0.045
Male/Female	43/16	40/21	0.39
BMI (kg/m ²)	28.3 \pm 5.1	29.2 \pm 2.5	0.63
Heart rate (beat/min)	77 \pm 10	75 \pm 10	0.457
Systolic blood pressure (mmHg)	141.3 \pm 10.6	139.7 \pm 11.9	0.295
Diastolic blood pressure (mmHg)	74.2 \pm 10.1	75.7 \pm 10.1	0.164
Hemoglobin (g/dl)	13.9 \pm 1.9	14.2 \pm 1.5	0.435
Hematocrit (%)	41.3 \pm 6.2	42.8 \pm 5.9	0.431
WBC (10 ³ μL)	9.7 \pm 3.0	7.5 \pm 1.6	0.001
Platelet (10 ³ μL)	257.5 \pm 74.6	253.3 \pm 68.7	0.72
Creatinine (mg/dl)	0.7 \pm 0.2	0.7 \pm 0.1	0.193
Glucose (mg/dl)	127 \pm 13	122 \pm 18	0.366

Total cholesterol (mg/dl)	193.2 ± 42.6	203.1 ± 39.7	0.288
LDL cholesterol (mg/dl)	114.7 ± 31.2	121.0 ± 28.2	0.339
HDL cholesterol (mg/dl)	43.7 ± 8.2	45.0 ± 8.3	0.343
Triglyceride (mg/dl)	165.9 ± 71.4	185.8 ± 77.6	0.341
CK (μ/L)	969.9 ± 156.3	99.5 ± 11.2	<0.001
CK-MB (μ/L)	100.4 ± 16.7	12.9 ± 1.7	<0.001
Troponin-I (ng/L)	11.31	0.005	<0.001
	(0.13-51.2)	(0-0.06)	
hs-CRP (mg/L)	17.8 ± 4.3	6.7 ± 4.9	0.007
Copeptin (ng/ml)	0.855 ± 0.279	0.516 ± 0.127	<0.001
Pro-BNP (pg/ml)	307	124	<0.001
	(19-9465)	(18-1570)	
Critical coronary lesion	34 patients = 1	15 patients = 1	0.001
	25 patients ≥2	6 patients ≥2	
LVEF (%)	52.2 ± 7.8	57.7 ± 7.4	0.001
Systolic PAB (mmHg)	32.9 ± 11.9	32.1 ± 10.7	0.267
LVSD (cm)	4.6 ± 0.6	4.3 ± 0.7	0.312
LVDD (cm)	3.1 ± 0.5	2.9 ± 0.4	0.201

Table 1: Patient demographics, laboratory analyses, angiographic and echocardiographic properties of the groups.

WBC: White blood cell; LDL: Low density lipoprotein; HDL: High density lipoprotein; CK: Creatinine kinase; hs-CRP: High sensitive C-reactive protein; BNP: Brain natriuretic peptide; LVEF: Left ventricular ejection fraction; PAB: Pulmonary artery pressure; LVSD: Left ventricular systolic diameter; LVDD: Left ventricular diastolic diameter



There were no significant differences between groups in terms of glucose, hemoglobin, hematocrit, creatinine, and lipid profile. In contrast, white blood cell and hs-CRP levels were significantly higher in group 1 (Table 1). In group 1, 34 patients had one critical

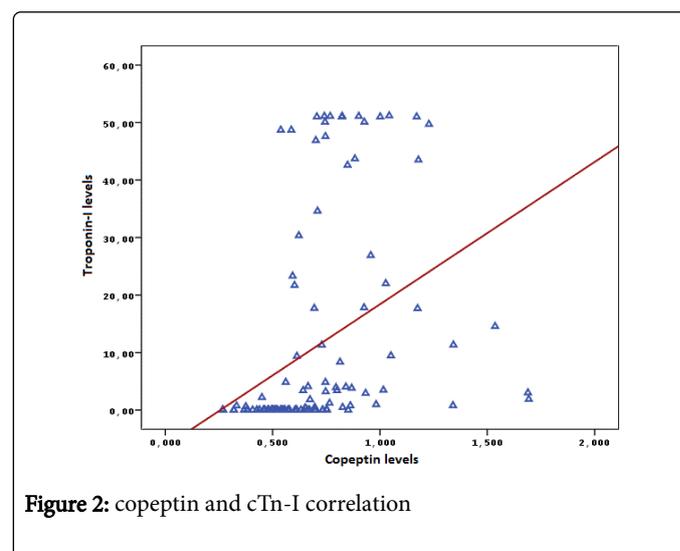
lesion and 25 patients had more than one lesions after coronary angiogram; however 15 patients had single critical lesions, and 6 patients had multiple lesions in group 2 (Table 1). There were no significant difference between groups in terms of hemodynamic parameters (heart rate, systolic and diastolic blood pressure) (Table 1).

When analyzing transthoracic echocardiography parameters, left ventricle systolic and diastolic diameters, and the systolic pulmonary artery pressures were not significantly different between the groups while left ventricular ejection fraction was lower in group 1 (Table 1).

Cardiac necrosis markers (CK, CK-MB and cTn-I levels) were higher in group 1 (Table 1). Copeptin and pro-BNP levels were also statistically higher in group 1 ($p < 0.001$). In subgroup analyses; copeptin levels were 0.910 ± 0.300 ng/ml in STEMI patients and, 0.747 ± 0.198 ng/ml in NONSTEMI patients and this difference was statistically significant ($p < 0.016$). And this difference was more pronounced when comparing group 2 and STEMI subgroup ($p < 0.001$). There were no significant difference among the unstable angina pectoris, stable angina pectoris, and normal coronary arteries subgroup in terms of copeptin levels ($p > 0.05$). However, there was a significant difference when comparing separately the group 2 and NONSTEMI subgroup ($p < 0.05$).

There was not any significant difference for the pro-BNP between STEMI and NONSTEMI ($p = 0.07$). Pro-BNP have 0.987 power (two-sided test, $\alpha = 0.05$). On the other hand, a meaningful difference was found between STEMI and Group 2 ($p < 0.001$), while no difference was found between NONSTEMI and Group 2 ($p > 0.05$). Also, no evident difference was found in the subgroups of Group 2.

In the correlation analyses, copeptin and cTn-I was positively correlated ($r = 0.397$; $p < 0.001$) (Figure 2). There were significant relations between copeptin levels and critical lesions in coronary angiogram ($r = 0.439$; $p < 0.001$). This positive correlation was linearly increased up until a critical lesion number greater than two (Figure 3). There was a negative correlation between Pro-BNP and EF ($r = 0.353$; $p < 0.001$) (Figure 4). ROC curves were constructed to assess the diagnostic accuracy of the primary outcome for copeptin over the 0.583 level, yielding a sensitivity of 91%, a specificity of 79% for myocardial infarction (AUC: 0.903 95% CI 0.86 to 0.91) (Figure 5).



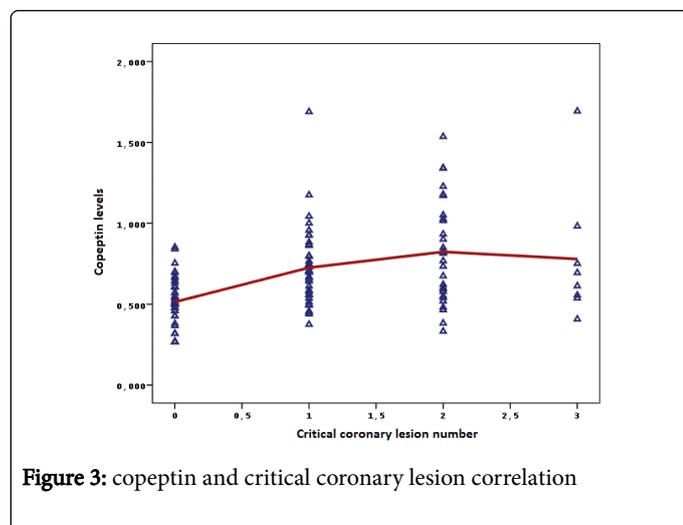


Figure 3: copeptin and critical coronary lesion correlation

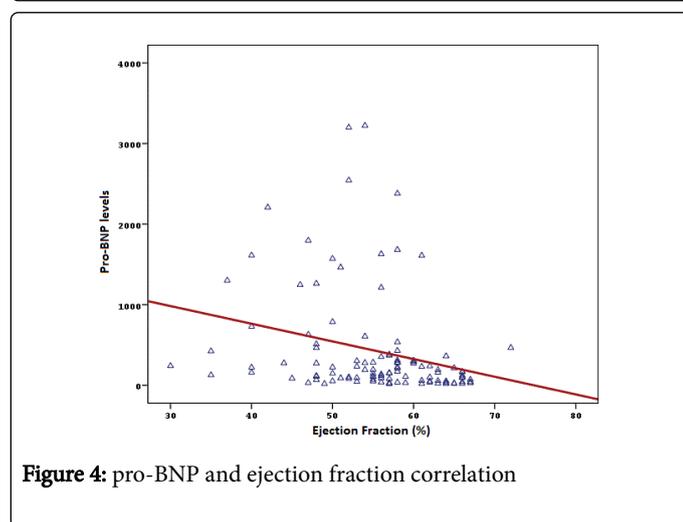


Figure 4: pro-BNP and ejection fraction correlation

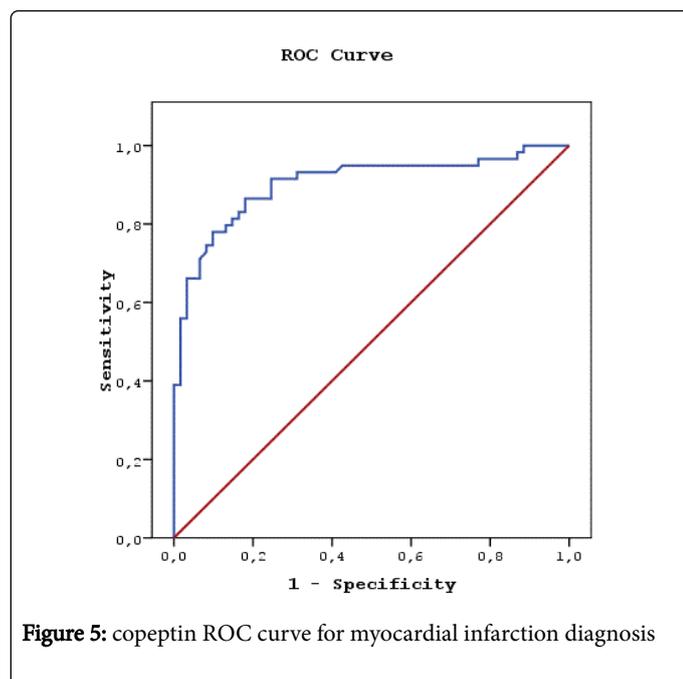


Figure 5: copeptin ROC curve for myocardial infarction diagnosis

Discussion

It has been shown that two-thirds of patients with chest pain are hospitalized, and only 15% of them were diagnosed with an acute MI [15,16]. On the other hand, 2-10% of the 40% of the patients that were not admitted to the hospital, and were discharged from the ER, were later diagnosed with an acute MI [17]. Statistical data have been shown that patients with non-specific chest pain that were discharged from the ER have lower mortality rates, although they were also often admitted to the ER and had multiple diagnostic tests [18].

Various biomarkers have been used for the diagnosis of acute MI and as a guide to subsequent prognosis [19,20]. The role of new biomarkers in ER settings is still extensively discussed. Copeptin is related to the stress response and therefore the use of this biomarker was proposed in acute, life-threatening diseases. The combination of additional specific cardiac markers, such as troponins with copeptin, acts a crucial role in the exclusion of an AMI diagnosis [5,21]. In this study, the combined use of the three biomarkers was evaluated in patients with chest pain, a frequent and often challenging cause of ER admission. The addition of copeptin to troponin confirmed the improvement of the diagnostic accuracy in patients with AMI [6,7].

Similar to the literature, in our study copeptin levels were found to be higher in group 1 than group 2. In subgroup analysis, copeptin levels were higher in STEMI patients than those NONSTEMI. This result showed us that transmural tissue damage that depends on high stress stimulates higher copeptin levels. Similarly, more copeptin levels were secreted in acute MI groups than USAP; SAP and NCA groups. However, no difference was found among USAP, SAP, NCA subgroups. When compared with the number of critical lesions in coronary angiogram and copeptin levels, a positive correlation was found between them. This correlation linearly increased until the critical lesion number reached more than two. It can be postulated that ischemia is increasing in severity when the critical lesion number increases, thereby copeptin levels increase.

It has been known that ANP and BNP are released from cardiac muscle during acute MI. The magnitude of the response in ANP and/or BNP has been shown by some authors [22,23] to be predictive of subsequent ventricular dysfunction, morbidity or mortality. Although BNP and NT-proBNP are most commonly associated with a clinical role in the diagnosis or rule-out of congestive heart failure, they have been evaluated for use in MI for prognostication, risk stratification, and exclusion of low-risk patients in acute coronary syndromes [12,24]. Gene expression of this molecule is up-regulated in the presence of myocardial ischemia and thus a reasonable mechanism exists for its elevation in this situation, even in the absence of hemodynamic pressure increases [25]. Gill et al. demonstrated that NT-proBNP exhibits a greater absolute and proportional rise after acute MI than ANP or BNP [26]. NT-proBNP's use in combination with cTn has been shown in studies to improve the diagnostic ability of clinicians to differentiate between MI, unstable angina, and non-cardiac causes of chest pain [27]. cTn is the most heart-specific marker of myocardial injury, but NT-proBNP has been shown to have slightly superior prognostic sensitivity [28,29]. The combination of this marker into a system to diagnose ACS reportedly adds to the sensitivity of a single cTn collection and allows for a better negative predictive value [30]. In low risk patients, combining cTn and NT-pro-BNP in a "rule-out" biomarker based model may provide the opportunity to safely discharge these patients without the current standard of care, stress test [29]. In our study there was no differences between STEMI and NONSTEMI for the pro-BNP levels, however a significant difference

was found among STEMI, USAP, SAP, and NCA subgroups. Delta EF changes and pro-BNP levels were inversely correlated, decreases in EF percentage triggered an increase in pro-BNP levels. At the same time pro-BNP and copeptin levels were positively correlated.

Hs-CRP is a chemotactic factor inside fibrinogen, and fibrinogen may make macrophages attach to the endothelial surface, which would then transfer them into the intima, thus promoting plaque rupture and vasoconstriction. Therefore, the elevation of hs-CRP levels in ACS, as an instability indicator of atherosclerotic lesions, can disrupt stable coronary plaque. Moreover, hs-CRP could promote monocytes to release tissue factors, which would initiate the extrinsic coagulation system and stimulate thrombosis [31]. In a study, the hs-CRP level was higher in the ACS group compared to the stable angina pectoris and healthy people groups, and was particularly high in the AMI group, whereas there was no statistically significant difference between the stable angina pectoris and healthy people groups [32]. In another study, CRP levels in the unstable angina group were found to be significantly low compared with both the NSTEMI and STEMI groups [33]. Similarly, in our study, hs-CRP levels were found to be higher in STEMI and NSTEMI groups than those USAP, SAP and NCA subgroups.

In an ER setting, physicians might consider the use of copeptin, pro-BNP, hs-CRP as biomarkers in patients whom the cardiac origin of chest pain can be safely excluded according to anamnesis and family history, clinical characteristics and ECG. In subjects with chest pain of unknown origin, we may recommend to use copeptin, in order to evaluate the body stress situation of a patient. Therefore, measurement of this biomarker might be considered not only as an exclusion strategy, but also as a possible caution sign of a life-threatening disease.

This is the first study comparing copeptin, pro-BNP, and hs-CRP in conjunction with coronary angiogram and echocardiography in patients with chest pain admitted to the emergency room. As a conclusion, copeptin, hs-CRP, and pro-BNP levels were all together elevated in ACS, especially in STEMI, in conjunction with other cardiac damage markers. A single combined testing of troponin, hs-CRP, pro-BNP and copeptin to rule-out AMI, for early discharge of low or intermediate risk patients with suspected ACS seems to be safe and has the potential to reduce length of stay in the ED.

Limitations

This study was conducted only in a single center and coronary artery disease group patients. Patients in this study were a special group that has infarction or evokes highly clinical suspicion. Therefore, a multicenter comprehensive study should be designed to adapt our results into general practice.

Conclusion

The combination of cTn-I, pro-BNP, hs-CRP and copeptin analyzed at admission had a higher sensitivity to diagnose ACS than cTn-I alone and the use of the combination at admission was found to be equivalent to, or better than, a renewed cTn-I after eight hours. We conclude that biomarkers alone are not adequate to rule out ACS, but we suggest that the combination of cTn-I, pro-BNP, hs-CRP and copeptin have the potential to help the clinician in the ER to make prompt and safe decisions on further investigations and on level of care.

Conflict of Interest

None declared.

Disclosure

All authors state that they have no relevant financial or nonfinancial relationships to disclose.

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