Could serum copeptin level be an indicator of coronary artery disease severity in patients with unstable angina?

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Abstract

Objective: The aim of this study is to identify serum copeptin levels in patients diagnosed with unstable angina (UA) and to evaluate the relationship between copeptin levels and angiographic severity of the patients. Materials and Methods: Two hundred patients who had been diagnosed with UA and undergone coronary angiography were included in the study. Each patient underwent a clinical evaluation, including a 12-lead electrocardiogram, echocardiographic evaluation, laboratory tests (high sensitive troponin-T and copeptin level tests) and The Global Registry of Acute Coronary Events (GRACE) 1.0 risk score calculation at the time of admission. Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX-1) score was calculated after coronary angiography. Results: We isolated and defined two subgroups within our study population: group 1 included patients with non-significant coronary artery disease (CAD) (<50% diameter stenosis, n:105); group 2 included patients with significant CAD ([?]50% diameter stenosis, n:95). The number of cases with a GRACE score higher than 140 was significantly higher in group 2 than in group 1 (p<0.001). SYNTAX scores and copeptin levels were significantly higher in group 2 than in group 1 (p<0.001 for both). A positive correlation was detected between copeptin levels and SYNTAX scores (r = 0.683; P < 0.001), and the cutoff level of copeptin level was 18.3 pmol/l (sensitivity of 74.7 %, specificity of 83.8% and area under curve of 0.795). Conclusion: Our study suggests that it may be beneficial to use both conventional scoring systems and serum copeptin levels when attempting to identify high-risk UA patients.

INTRODUCTION

The term acute coronary syndrome (ACS) refers to any clinical symptoms that may result in a diagnosis of acute myocardial ischemia. These symptoms include unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI), and ST segment elevation myocardial infarction (STEMI) [1] . An important type of ACS, UA is often diagnosed in emergency services situations, although diagnoses of UA often decrease with the emergence of biomarkers susceptible to myocardial damage, resulting in the patient's condition being reclassified as NSTEMI [2]. Despite this emerging clinical finding, when diagnosing and treating UA patients, there are still practitioners who follow guidelines that were created as a result of studies carried out in the era of cardiac troponins instead of high sensitive cardiac troponins (hsTn), which are no longer commonly used. Current guidelines do not differ so much in terms of the management of biomarker-positive or negative non-ST segment elevation acute coronary syndromes (UA and NSTEMI)[3,4]. Although some existing studies and the resultant guidelines have demonstrated the positive effects of early invasive interventions on cardiac endpoints in hsTn positive NSTEMI patients, these positive effects may be delayed in patients with UA due to hsTn negativity [5] . Although assessing hsTn levels is the gold standard in identifying myocardial damage, it may not be sufficient for early risk evaluation. There have been many subsequent studies examining the value of hsTns in diagnosing ACS, and these studies have emphasized that complementary biomarkers are important [6]. One of these biomarkers is copeptin, which is the C-terminal part of the prohormone for vasopressin (pro-vasopressin); copeptin becomes prominent in conditions of acute endogenous stress due

to its rapid release pattern [7]. Many studies have investigated the accuracy and sensitivity of copeptin in diagnosing ACS disorders [8-10]. There are many studies on the joint use of hsTn and copeptin levels for diagnosing ACS; however, there are insufficient studies assessing copeptin levels among non-ST segment elevation acute coronary syndrome patients with negative hsTn levels during admission to the emergency room and during follow-ups. The aim of our study is to identify serum copeptin levels in patients with UA and to evaluate the relationship between copeptin levels and the clinical and angiographic severity of these patients.

METHODS

This study was cross-sectional and observational. At the time of admission, each patient underwent a clinical evaluation, which included a routine physical examination, a 12-lead electrocardiogram (ECG), echocardiographic evaluation and standard laboratory tests (blood count, sodium, potassium, creatinine, glomerular filtration rate, HbA1c, hsTn, creatine kinase myocardial bound [CK-MB], and copeptin levels) and a GRACE 1.0 risk score calculation [11]. High sensitive Tn and CK-MB levels were reevaluated after six hours.

The study was carried out in a university hospital with a tertiary cardiology center. Among patients who were admitted to the emergency services clinic with complaints of chest pain or equivalent between September 2018 and October 2019, 200 in total were diagnosed with UA and underwent coronary angiography (CAG). These patients were included in the study (see Figure 1). Patients with hsTn elevation (either at admission or at the six-hour follow-up), STEMI, end stage renal failure (GFR<15 ml/min/1.73 m2 or renal replacement treatment), profound anemia (hemoglobin level <10 gr/dl for men, hemoglobin level <8 gr/dl for women), sepsis, injury or major surgery in past four weeks, active malignancy, pregnancy, or those who were unwilling or unable to give informed consent were excluded.

Biochemical Assays

High sensitive Tn-T measurements were conducted with Elecsys Troponin T hs STAT kits (Roche Diagnostics GmbH, Mannheim, Germany). High sensitive troponin-T is regarded as positive when [?]14 ng/l, according to the manufacturer's indications and guidelines [3]. Copeptin levels were measured using the serum samples taken during the hospital admission process and preserved under the manufacturer's recommended conditions. Copeptin measurements were performed using the BRAHMS Copeptin KRYPTOR assay on a BRAHMS KRYPTOR compact plus analyzer (BRAHMS GmbH, Hennigsdorf, Germany). Copeptin is regarded as positive when >17.4 pmol/l, as per the manufacturer's guidelines.

Coronary Angiography

The severity of CAD was assessed by two experienced cardiologists using the SYNTAX score[12] . They were blinded to the patients' clinical characteristics. The SYNTAX-1 score was calculated using dedicated software (version 2.11) that integrates the number of lesions with their specific weighting factors, based on the amount of myocardium distal and the morphologic features of each lesion.

We isolated and defined two subgroups within our study population: group 1 included patients with non-significant CAD (<50% diameter stenosis); group 2 included patients with significant CAD ([?]50% diameter stenosis) (see Figure 1).

Ethics

The study received approval from the Ethical Committee of the Cukurova University Faculty of Medicine and was conducted according to Declaration of Helsinki policies. All patients who met the inclusion criteria gave informed consent before taking part in the study.

Statistical Analysis

Statistical analysis of the data was done using the IBM SPSS Statistics Version 20.0 (SPSS Inc., Chicago, IL, USA) software package. Descriptive data are shown as n and percentages in the categorical data fields and

as median interquartile range values in the continuous data fields. A chi-square test was used to compare categorical data. Measured data were tested using Kolmogorov-Smirnov tests to confirm an assumption of normal distribution. Mann-Whitney U tests and Kruskal-Wallis tests were used when appropriate to compare measurement data that did not show normal distribution. A Spearman correlation analysis was used to assess the correlation between the two sets of measured data. The threshold value for predictability of the prevalence of CAD (the SYNTAX score) of serum copeptin levels was determined using a receiver operating characteristic curve (ROC) analysis. P<0.05 was accepted for statistical significance in all analyses.

RESULTS

Table 1 includes the demographic and clinical characteristics of groups 1 and 2. The number of cases with a GRACE score higher than 140 was statistically higher in group 2 than in group 1. When comparing echocardiography and laboratory parameters for each group, it was evident that SYNTAX scores and copeptin levels were significantly higher in group 2 (copeptin: 9.4 vs 28.8 pmol/l, p<0.001; SYNTAX score: 8 vs 24, p <0.001). Other examined parameters were similar across both groups (see Table 2).

Serum copeptin levels were significantly higher in patients with ST segment depression than in those with normal ECG results (13.7 vs 26.9 pmol/l, p<0.001). Serum copeptin levels were higher in the group with SYNTAX scores above 32 and lower in the group with scores below 23; all paired comparisons were found to be statistically significant for the 3 SYNTAX score category. (SYNTAX score<23 vs SYNTAX score 23-32; 11.6 pmol/l vs 30.5 pmol/l, P<0.001; SYNTAX score<23 vs SYNTAX score >32; 11.6 pmol/l vs 40.9 pmol/l, p<0.001, SYNTAX score 23-32 vs SYNTAX score >32; 30.5 pmol/l vs 40.9 pmol/l, p<0.001; see Figure 2). Similarly, serum copeptin levels were significantly higher among those with GRACE scores above 140 than among those with lower GRACE scores (GRACE score<109 vs GRACE score>140; 12.6 pmol/l vs 27pmol/l, p<0.001; and GRACE score 109-140 vs GRACE score>140; 15.8pmol/l vs 27pmol/l, p:0.002; see Figure 2). The paired comparison of the group with GRACE scores below 109 and the group with GRACE scores between 109 and 140 was statistically similar (12.6 pmol/l vs 15.8pmol/l, p:0.114; see Figure 2).

When examining the correlation between serum copeptin levels and CAD severity, there was a high level of positive correlation between copeptin levels and SYNTAX scores (r:0.683, p value <0.001). When the serum copeptin level was used as a predictor of high SYNTAX scores with a threshold of 18.3 pmol/l, diagnostic sensitivity was found to be 74.7%, specificity was 83.8%, the positive predictive value was 80.7%, the negative predictive value was 78.6%, and the area under the curve was 0.795 (see Figure 3).

DISCUSSION

Unstable angina is a clinical condition that is responsible for around 16.6% of all ACS. On the ACS spectrum, its frequency falls below NSTEMI and STEMI [13]. Despite the fact that UA is an ACS type with pronounced myocardial ischemia, there are no detectable circulating cardiac biomarkers for its' diagnosis (CK-MB, hsTn, Myoglobin)[14] . The use of a new biomarker that can be used for the early diagnosis and treatment of UA immediately after the onset of ACS may be a valuable contribution to clinical practice. There are two hypotheses for the increase in serum arginine vasopressin (AVP)/copeptin levels in cases of ACS. The first is that it is an endocrine response to acute stress, while the second suggests that inadequate filling of the left ventricle caused by ACS stimulates cardiac baroreceptors or causes direct damage to baroreceptors, subsequently leading to AVP and copeptin secretion from the posterior pituitary gland [15,16] .

We found a statistically significant positive correlation between patients' serum copeptin levels and GRACE and SYNTAX scores the former being as a prospectively studied scoring system for risk stratification in patients with diagnosed UA/NSTEMI to estimate their in-hospital and 6-month to 3-year mortality and the latter which is the angiographic indicator of CAD severity. There are many studies that have investigated serum copeptin levels alone or in conjunction with hsTn levels in relation to ACS diagnosis. Some studies demonstrated that patients who had been admitted to the emergency services with chest pain, the use of both serum troponin and copeptin levels increase the sensitivity and negative predictive values in acute myocardial infarction diagnosis[10,17,18] . Although Reichlin et al [10] demonstrated that acute MI patients had significantly higher levels of copeptin compared to UA patients, our study revealed the correlation

between copeptin levels and CAD severity in UA patients with negative hsTn values. This finding may be important for the possible prognostic value of copeptin in UA patients. Keller et al [17]impressed the negative predictive value of copeptin levels for acute MI, but they found that even in diabetic UA patients, copeptin levels were high. This finding is compatible with ours, thus copeptin levels may have diagnostic and even prognostic value in all spectrum of ACSs. Also, Keller et al [17] demonstrated earlier increase in copeptin levels than that of hsTn, which makes copeptin an important biomarker for early diagnosis of acute MI. The diagnostic and prognostic performances of copeptin were found to be additive to hsTn in NSTEMI, independent of the effect of gender [18-20] .

In a large-scale study conducted by O'Malley et al [21], which consisted of 4,432 patients, the use of multiple biomarkers, including copeptin, was shown to be a strong prognostic factor of outcomes such as cardiovascular death or heart failure in patients with non-STE acute coronary syndromes.

In patients with STEMI, Reinstadler et al [22] found an association between higher serum copeptin levels and acute and chronic infarct size, reduced left ventricular ejection fraction, and adverse remodeling during follow-ups. Although our study used a different patient population, its findings support those of Reinstadler et al. Our study found increased copeptin levels were associated with more severe CAD, this may also explain why increased copeptin levels resulted in worse left ventricular systolic performance and adverse remodeling.

In our study, we did not use a control group with individuals undergoing elective coronary angiography due to stable coronary artery disease. This was firstly because we were seeking to determine any correlation between different copeptin levels and clinical and angiographic disease levels among patients with similar clinical symptoms who had been diagnosed with UA after being admitted to an emergency room. Secondly, it has already been reported that stable coronary artery disease patients have shown increased copeptin levels [23] .

When evaluating the study data in detail, the mean serum copeptin levels in patients with non-critical CAD or normal coronary arteries were found to be 9.4 pmol/l. In our study, the low mean values for copeptin levels and SYNTAX scores in group 1 are consistent with the existing literature. Zellweger et al [24] found 9 pmol/l as a prognostic cut-off value, above which 2-year mortality was significantly higher in diabetic acute MI patients. They concluded that copeptin levels predicted mortality more accurately when used in conjunction with hsTn. In many studies, when the threshold serum copeptin level was <14 pmol/l, the negative predictive value for ACS has been found to reach 97%, while the p value has been shown to be statistically significant [10,25,26] .

In our study, the threshold value of 18.3 pmol/l, which was selected to predict a high SYNTAX score, is consistent with the literature. In a study that sought to detect non-ST segment elevation acute coronary syndrome patients in emergency room situations, Morawiec et al[27] found that 17.4 pmol/l to be the threshold copeptin value. Reinstadler et al [22], who studied STEMI patients, found that the threshold copeptin level which was a predictor of poor left ventricular ejection fraction and adverse remodeling was 16.7 pmol/l.

LIMITATIONS

Our study was a single-center, cross-sectional study, and we did not follow patients to document their various cardiac endpoints. The sample size was relatively low and further large scale studies may illuminate the use of copeptin levels in UA patients as a prognostic marker. Even though we tried to include only UA cases in the study, based on available clinical and laboratory data (the hsTn values at hour 0 and at hour 6), it should be noted that some of the participants may also be NSTEMI patients and despite every diagnostic attempt we could be unable to detect these patients. Another limitation is that there is currently no consensus regarding the correct sampling time for copeptin levels.

CONCLUSION

Our study suggests that it may be beneficial to use both conventional scoring systems and serum copeptin levels when attempting to identify high-risk UA patients.

Conflicts of Interest

There are no conflicts of interest.

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Figure and Table Legends

Table 1 : Comparison of demographic and clinical parameters in Group-1 and Group-2.

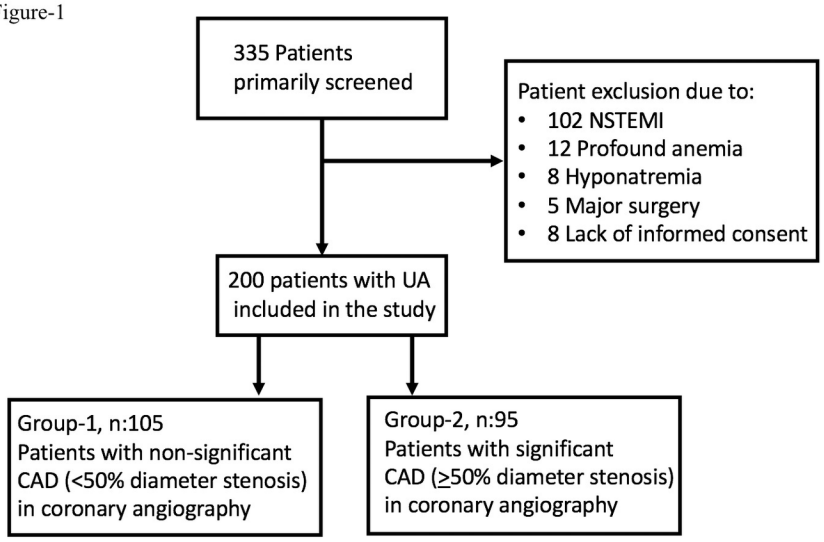
Table 2 : The comparison of echocardiographic parameters, lipid parameters, SYNTAX scores and copeptin levels in Group-1 and Group-2.

Figure 1: Flow chart of patient exclusion and inclusion.

Figure 2 : The correlation between copeptin levels and GRACE scores and SYNTAX scores.

Figure 3 : Representation of the diagnostic performance of serum copeptin (pmol/l) level as the predictor of the SYNTAX score with ROC analysis.

Figure-1



UA: Unstable Angina, NSTEMI: Non-St elevation myocardial infarction, CAD: Coronary artery disease,

Figure-2

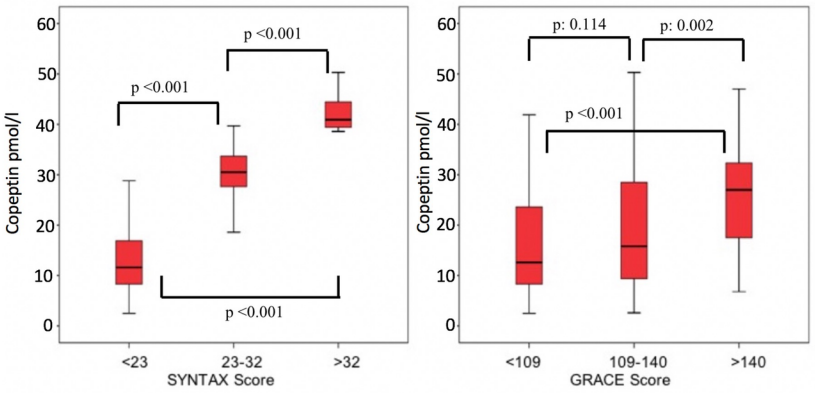
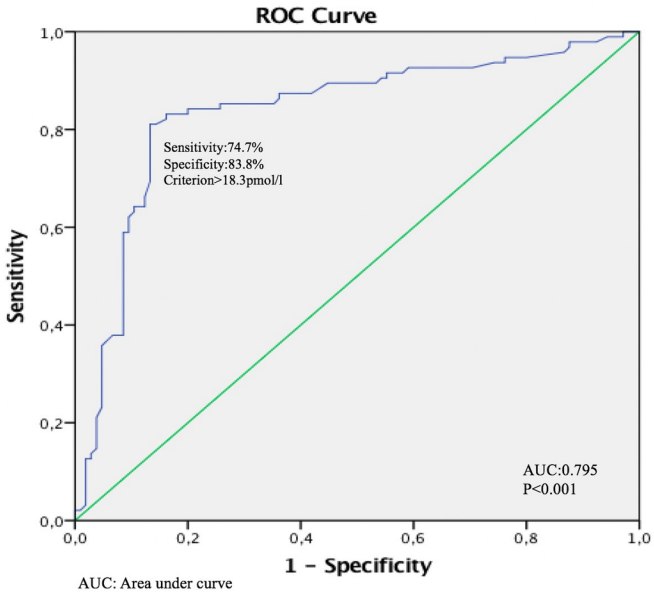


Figure-3



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