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ORIGINAL ARTICLE

Diagnostic Value of Delta Copeptin Levels in Patients with Acute Coronary Syndrome Presenting to the Emergency Department

ABSTRACT

Objective: A significant proportion of patients presenting to the emergency department present with symptoms of acute coronary syndrome (ACS). These symptoms range from simple medical conditions to life-threatening emergencies, making it difficult to diagnose ACS. In this context, studies on various biomarkers for a more effective diagnosis are ongoing. Patients presenting with ACS symptoms come from all age groups and the wide range of symptoms makes it difficult to recognize and manage patients. In this study, we aimed to compare copeptin with high sensitive troponin (hs-tn) level, which is currently used as a diagnostic tool.

Methods: In this prospective study, 130 patients over the age of 18 who presented to the Emergency Medicine Clinic of Ankara Etlik City Hospital with chest pain between December 10, 2023 and December 20, 2023 and met the inclusion criteria were included. Patients were evaluated in the light of current guidelines (AHA 2021 Chest Pain Guideline, ESC 2020 Non-ST Eleve Myocardial Infarction (NSTEMI) Guideline, ESC 2023 Acute Coronary Syndromes Guideline) and divided into 2 groups as ACS (n=65) and non-ACS (n=65). Delta copeptin and hs-tn levels, HEART scores and vital parameters were evaluated. Statistical analyses were performed using SPSS 23.0 and $p<0.05$ was considered significant.

Results: There was no significant difference in age and gender between ACS and non- ACS groups ($p>0.05$). HEART score was significantly higher in the ACS group ($p<0.001$). Normal sinus rhythm was observed more frequently in the non-ACS group ($p=0.024$). All ACS patients were hospitalized in the coronary intensive care unit (CICU), whereas the non-ACS group was usually discharged ($p<0.001$). Troponin levels were significantly higher in the ACS group ($p<0.001$), while copeptin levels were higher in the non-ACS group ($p<0.05$). There was no difference between the groups in terms of delta copeptin ($p=0.119$).

Conclusion: Our study confirmed the gold standard role of hs-tn in the diagnosis of ACS and showed that the contribution of copeptin in this field is limited. Studies with larger samples are needed to confirm the results. hs-tn should be used as the primary biomarker in the diagnosis of ACS, whereas copeptin should be considered only as a supportive parameter.

Keywords: Acute coronary syndrome, chest pain, copeptin, high-sensitive troponin

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Every year in the United States, more than ten million people present with chest pain, and approximately 15% of them are diagnosed with acute coronary syndrome (ACS), which is a serious health problem. It is estimated that more than four hundred thousand people die each year due to myocardial ischemia (1).

Early diagnosis of myocardial infarction (MI) in patients presenting to the emergency department with chest pain is critical both to improve the patient's prognosis and to ensure prompt initiation of treatment. Acute myocardial infarction (AMI) is diagnosed by combining several factors such as clinical symptoms, electrocardiographic (ECG) findings and biomarker levels (2). In this process, high sensitive troponin (hs-tn) is considered the gold standard for AMI detection and its use is strongly recommended in modern guidelines (3).

Symptoms of ACS typically include acute chest discomfort, usually manifested as pain, pressure, burning or tightness. Angina equivalents such as dyspnea, epigastric pain and pain radiating to the upper extremities may also be present (4). Patients may also exhibit non-specific symptoms such as hypertension, diaphoresis or syncope (4,5). These clinical presentations are common in the high-demand environment of emergency departments, but

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often pose diagnostic challenges. As a result, the need for fast and reliable diagnostic tools has become increasingly critical in this setting.

However, in early or suspected cases where troponin levels are not diagnostically adequate, evaluation of additional biomarkers may improve diagnostic performance. Copeptin, the C- terminal part of the prohormone vasopressin, has attracted attention as an indicator of endogenous stress levels (6). The elevation of endogenous stress levels in many patients at the onset of MI suggests that copeptin may make an important contribution to early diagnosis. Copeptin may offer a potential synergy in diagnostic value when used in combination with cardiac troponin (7,8).

The aim of this study was to examine the contribution of the copeptin biomarker in the early diagnosis of patients with suspected AMI and whether it provides additional value to the information provided by hs-tn. We also aim to determine whether the combination of copeptin and hs-tn is superior to the evaluation with hs-tn alone and to prospectively test the comparison of the 0-1 h h hs-tn protocol with the 0-1 h copeptin protocol

MATERIALS AND METHODS

Our single-center prospective study was conducted in the Emergency Medicine Clinic of Ankara Etlik City Hospital between December 10, 2023 and December 20, 2023. The study was initiated according to the principles of the Declaration of Helsinki, after obtaining Ethics Committee approval (AEŞH-EK1-2023-737) and written informed consent was obtained from all patients participating in the study. A total of 130 patients with suspected ACS who presented with chest pain or angina equivalents and met the inclusion criteria were included in the study. Patients were evaluated according to the American Heart Association (AHA) 2021 Chest Pain Guidelines, the European Society of Cardiology (ESC) 2020 NSTEMI Guidelines, and the ESC 2023 ACS Guidelines (9-11).

Inclusion criteria were defined as patients presenting with chest pain or angina equivalents, aged 18 years or older, who gave written informed consent. On the other hand, patients were excluded in cases of pregnancy, malignancy, chronic renal failure, history of chronic heart failure, severe infections, ST elevation on ECG at presentation, patients with a known history of CAD who could not be classified as low risk, intermediate risk patients with no known CAD and no recent coronary imaging, and missing data.

The diagnostic and therapeutic processes of the patients were evaluated in accordance with standard clinical and laboratory protocols from the time of admission, with no intervention in patient management. Demographic data, medical history, vital signs, electrocardiographic examinations, laboratory parameters, HEART score and invasive coronary angiography results were recorded and analyzed in detail (12).

Patients who met the inclusion criteria were directed to the appropriate observation area after initial examination and anamnesis. Blood samples were collected for hs-tn measurement at the 0th hour and 1st hour (±10 minutes) from patients who were followed up under cardiac monitoring in these areas. Blood samples were collected in 5 mL BD Vacutainer SST II Advance Plus Blood Collection Tubes with gel separator containing clot activator. The tubes with gel separator were left for 30 minutes and then centrifuged at 1250 g for 15 minutes. Troponin measurements were performed on a Roche C8000 analyzer (Roche Diagnostics, Mannheim, Germany) using the Roche Diagnostics high-sensitivity troponin kit (Elecsys® Troponin T-high sensitive).

For the analysis of copeptin levels, 2 mL of serum samples obtained for troponin measurement were aliquoted and stored at -80°C until the day of the study with patient information noted. Serum samples were thawed gradually on the day of the experiment and all measurements were performed on the same day. Repeated freezing and thawing were avoided. Copeptin level was measured using Cloude Clone (USCN) commercial ELISA kit (23603 W. Fernhurst Dr., Unit 2201, Katy, TX 77494, USA) according to the manufacturer's instructions. The calibration curve was constructed with 1000 pg/mL, 333.33 pg/mL, 111.11 pg/mL, 37.04 pg/mL and 12.35 pg/mL standards. The intra-assay coefficient of variation of the samples was <10%, inter-assay coefficient of variation was <12% and the limit of detection was determined as 5.31 pg/mL. Copeptin levels are reported in pg/mL. These procedures were performed in accordance with international standards to ensure the accuracy and reliability of biochemical analysis of the samples.

The non-ACS group included 18 patients who were in the intermediate or high risk group according to the HEART score, but received an alternative diagnosis (e.g. pulmonary embolism, pneumonia, pneumothorax, etc.) to explain chest pain during emergency department follow-up, and 47 patients classified in the low risk group according to the AHA chest pain guideline and HEART score. A total of 65 patients were evaluated in this group.

Statistical Analysis

Data were analyzed using SPSS 23.0 software. For continuous variables, normally distributed data were presented as mean ± standard deviation and non-normally distributed data were presented as median (minimum-maximum). Categorical variables were expressed as percentage and frequency. For the analysis of differences between groups, t-test was used for normally distributed data or Mann-Whitney U test for non-normally distributed data. Chi-square test was used to compare categorical data. Significance level was accepted as $p<0.05$.

Work Plan

Based on clinical evaluation, laboratory results and electrocardiographic findings, patients were divided into two groups: ACS (n=65) and non-ACS (n=65). The ACS-diagnosed group consisted of patients who were classified as intermediate or high risk according to the HEART score and included in further investigation and treatment processes accordingly. In this group, 27 patients underwent percutaneous coronary intervention (PCI) after invasive coronary angiography revealed a responsible lesion. In addition, 10 patients underwent coronary artery bypass grafting (CABG) after invasive coronary angiography and were recommended this procedure by the council. In addition, there were 28 patients in whom no interventional procedure was performed despite detection of the responsible lesion by invasive coronary angiography, but whose diagnosis of ACS was accepted based on symptoms, troponin elevation, electrocardiographic changes and echocardiographic findings, and in whom optimal medical therapy was initiated in accordance with guidelines. In total, 65 patients were included in the group classified as ACS. The study plan is presented in Figure 1.

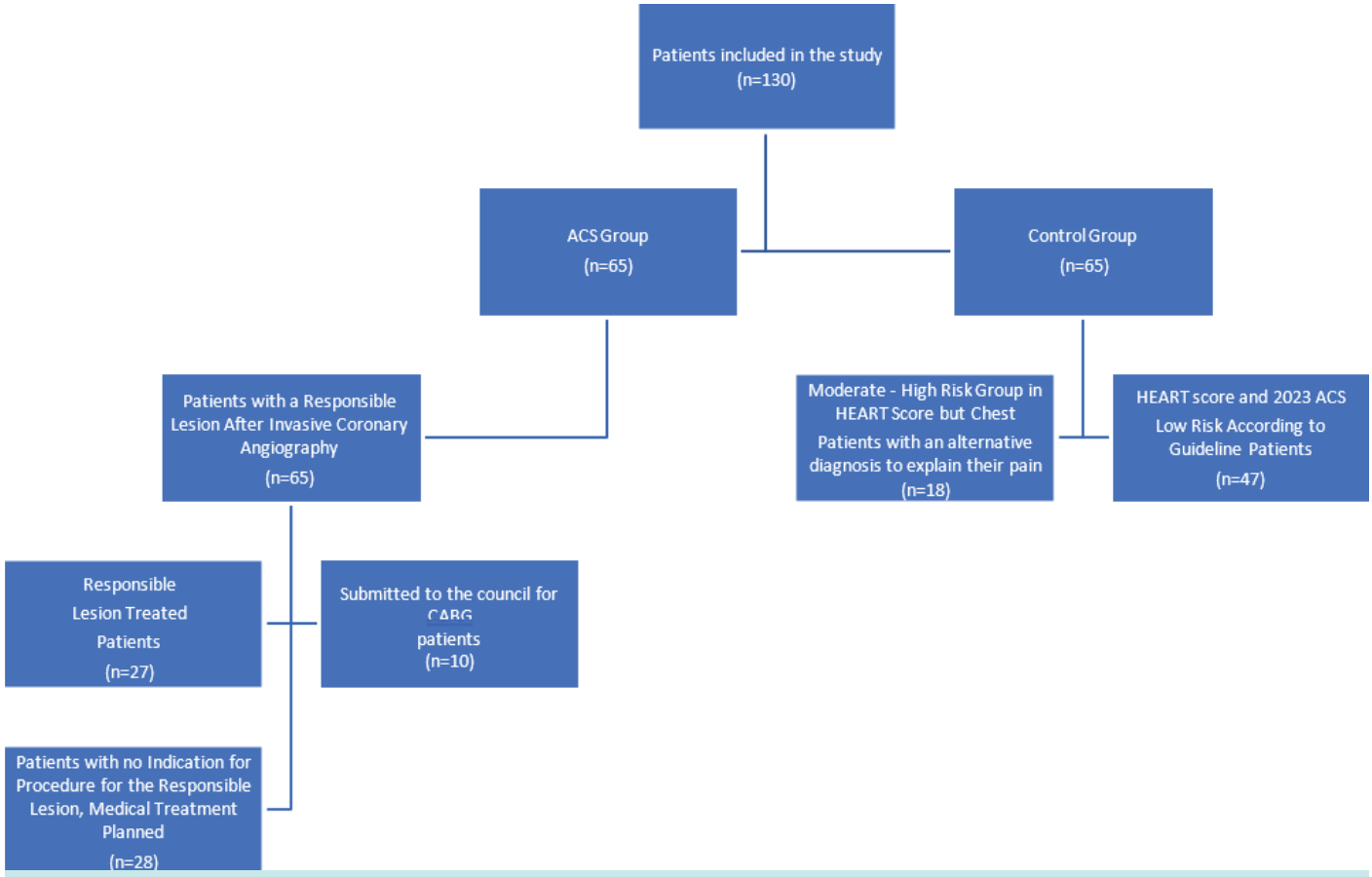

Figure 1. Study plan.

A total of 130 patients were included in the study. Demographic and clinical characteristics of the patients are presented in Table 1. The mean age of the patients was 58.45±13.3 years and 70% were male. The difference between the groups in terms of age and male patient ratio was not statistically significant (p>0.05). No significant difference was observed between the two groups in terms of vital parameters. However, HEART score was significantly higher in the ACS group (p<0.001). When electrocardiographic findings were analyzed, the rate of normal sinus rhythm was higher in the non-ACS group and this difference was statistically significant (p=0.024). In terms of hospitalization, all patients in the NSTEMI-ACS group were hospitalized in the coronary intensive care unit, whereas the non-ACS group was mostly discharged. The difference in terms of hospitalization location was statistically significant (p<0.001).

Troponin and copeptin levels at hour 0 and hour 1 and the change values (delta) of these parameters in the ACS and non-ACS groups are compared in Table 2. Troponin levels were significantly higher in the ACS group. Copeptin levels at 0 and 1 hour were significantly higher in the non-ACS group (p<0.05). However, no significant difference was found between the groups in terms of delta copeptin values (p=0.119).

DISCUSSION

In our study, we evaluated the diagnostic performance of delta copeptin level and high- sensitivity troponin (hs-tn) in the diagnosis of ACS. Our findings showed that delta copeptin levels did not significantly contribute to the diagnosis of ACS either alone or when combined with hs-tn.

Compared to previous studies, there are findings that delta copeptin levels increase in the early period and may increase diagnostic accuracy with hs-tn (13,14). Kankra et al. (13) reported that copeptin levels were higher in ACS patients compared to the control group and increased diagnostic accuracy (13). However, our study shows that this early elevation of copeptin does not provide a significant advantage in clinical practice and that the use of hs-tn alone is more appropriate (15-17).

Another result we obtained is that the combined use of these two markers does not provide additional benefit compared to the use of hs-tn alone. In the 2020 ESC Guidelines for the Management of ACS, the use of the copeptin biomarker with conventional troponin is more sensitive than the use of conventional troponin alone (18).

Kankra et al. (13) reported that the combined evaluation of hs-tn and copeptin was more meaningful in excluding ACS patients compared to the use of hs-tn alone (13). However, the 2023 ESC Guidelines for the Management of ACS do not recommend the use of any other biomarker other than cardiac troponin (19). We also found that the use of copeptin with hs-tn did not show any additional benefit as it is also included in the guideline.

In the study by Mu et al. (14), it was shown that the combined use of hs-tn and copeptin was more sensitive than hs-tn alone in making the diagnosis of NSTEMI. However, at the point of exclud-

Table 1. Comparison of demographic, vital, ECG and clinical characteristics of ACS and non-ACS groups

Parameter	ACS (n=65)	Non-ACS Group (n=65)	p value
Demographic Characteristics			
Age	60.6±12.3	56.4±14.2	0.078
Male	48, (%73.8)	43, (%66.2)	0.34
Vital Parameters			
SBP	125.2±22.2 SS	125.5±23.9 SD	0.952
DBP	73 (34,112)	75 (34,112)	0.872
Pulse	72 (40,184 (min,max))	76 (49,100 (min,max))	0.305
HEART score	5 (1.9)	3 (1.5)	**0.000**
Noncardiac chest pain	3 (4.6)	4 (6.2)	>0.005
ECG features			
NSR	45 (69.2)	51 (78.5)	
Branch Block	5 (7.7)	11 (16.9)	
T negativity	6 (9.2)	3 (4.6)	
ST depression	1 (1.5)	0	
Wellens	1 (1.5)	0	**0.024**
AV block	1 (1.5)	0	
VF,VT	2 (3.1)	0	
ST elevation at follow-up	4 (6.2)	0	
Place of Hospitalization			
Discharged	0	58 (89.2)	
Cardiology service	0	3 (4.6)	
			<0.001
KYBU	65 (100)	3 (4.6)	
Exitus	0	1 (1.5)	

ACS: Acute coronary syndrome, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, NSR: Normal sinus rhythm, AV Block: Atrioventricular block, VF: Ventricular fibrillation, VT: Ventricular tachycardia, PICU: Coronary intensive care unit, min: minimum, max: maximum

Table 2. Comparison of troponin and copeptin values in ACS and non-ACS Group

Parameter	ACS (n=65)	Non-ACS Group (n=65)	p value
Troponin 0h	25.6 (4, 918)	9.98 (3, 351)	**0.000**
Troponin 1h	37.3 (3, 9665)	10.3 (3, 366)	**0.000**
Delta Troponin	7.6 (0,9560)	0.64 (0,15)	**0.000**
Copeptin 0h	74.9 (2.5, 475.2)	120.3 (5.1, 503.2)	**0.002**
Copeptin 1h	63.6 (1.5, 470.5)	133.2 (21, 532.7)	**0.001**
Delta Copeptin	21.9 (0.8, 132.1)	27.5 (0.5, 245.9)	0.119

ing the diagnosis of NSTEMI, it was stated that the combined use of copeptin and hs-tn was not superior to the use of troponin alone. In our study, copeptin value was higher in patients in the control group. The use of copeptin in combination with troponin or alone was not significant in making the diagnosis of ACS or ruling out the diagnosis of ACS. This result differs from the literature. We think that the reason for this difference is that the diagnosis of the patients in the control group increased the copeptin value more as a result of the follow-up and this situation changed the statistical data in a way that is incompatible with the literature. It should be noted that taking this into account in future studies between hs-tn and copeptin will improve the quality of these studies.

The fact that delta copeptin is also elevated in non-ACS conditions such as sepsis and pulmonary embolism is an important factor limiting the specificity of this biomarker (20). In our study, delta copeptin was found to be significantly elevated especially in the non-ACS group, supporting this finding. This result suggests that copeptin is sensitive not only to myocardial ischemia but also to

stress response in general.

There are not enough studies in the literature on the absolute change of copeptin value in ACS patients in the first hour. In our study, delta copeptin value was lower in ACS patients compared to the control group. This was statistically insignificant.

LIMITATION

The primary limitation of our study is the relatively small sample size. Conducting the study in a larger patient population may yield different results. In addition, the presence of other pathologies in the patients in the control group may have affected the results of our study. Finally, copeptin is a marker that increases in stress-related conditions. The copeptin biomarker value may have been affected by other stress-inducing conditions.

RESULTS

Consistent with the existing literature, our study confirms the position of hs-tn as the gold standard in the diagnosis of ACS and shows that the role of copeptin in this field is minimal. Our study shows that hs-tn optimizes the rapid diagnostic process in ACS due to its high specificity and sensitivity, whereas copeptin offers only limited prognostic value. Studies with larger sample sizes are needed to confirm this.

Ethics Committee Approval: This study was approved by the Ethics Committee of Etlik City Hospital (No: AEŞH-EK1-2023-737, Date: 06/12/2023).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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