

# 흉통과 경한 트로포닌 I 상승을 보이는 환자에서, 비-ST분절 상승 급성 심근 경색증을 진단하기 위한 코펩틴의 유용성 평가

## Evaluation of Copeptin for Diagnosing Non-ST Segment Elevation Acute Myocardial Infarction in Patients with Chest pain and Mild Troponin I Elevation

김지훈 · 김지명 · 임진숙 · 김선영 · 권계철 · 구선희

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**Background:** Although troponin assays improve the detection of acute myocardial infarction (AMI), troponin elevation is observed in various non-ischemic conditions. Studies have proposed that, when used in combination with a cardiac troponin I (TnI) assay, serum copeptin would increase the diagnostic accuracy for AMI. Therefore, we assessed the utility of copeptin in the diagnosis of non-ST-segment elevation myocardial infarction (NSTEMI).

**Methods:** A total of 180 patients (age,  $68.2 \pm 13.3$  years; M:F, 113:67) were enrolled for the study, who are presented with chest pain and mild TnI elevation ( $0.04\text{--}1.0$  ng/mL) in the emergency department, excluding those with ST elevation on the electrocardiogram. Copeptin was measured using an automated immunofluorescent assay, Copeptin proAVP KRYPTOR (Thermo Fisher Scientific, Germany).

**Results:** The subjects included 49 patients (27.2%) who had NSTEMI, 64 (35.6%) patients who had angina, and 67 (37.2%) patients who had other diseases. The median (interquartile range) copeptin level in the NSTEMI group ( $69.57$  [ $35.56\text{--}172.50$ ] pmol/L) was significantly higher than those in the angina group ( $7.64$  [ $3.36\text{--}17.19$ ] pmol/L) and the other diseases group ( $6.75$  [ $4.33\text{--}13.02$ ] pmol/L) ( $P < 0.0001$ ). At the  $14.4$  pmol/L cutoff for copeptin, TnI plus copeptin had a higher area under the curve than TnI plus CK-MB ( $0.898$  vs.  $0.711$ ,  $P = 0.0001$ ) for diagnosing NSTEMI.

**Conclusions:** Non-ischemic mild TnI elevation is common. Copeptin levels provide additional information for differentiating NSTEMI from non-NSTEMI patients with mild TnI elevation. The combination of copeptin and TnI could improve NSTEMI diagnosis by excluding non-ischemic mild TnI elevation.

**Key Words:** Copeptin, Troponin, Creatine kinase-MB, Non-ST elevation myocardial infarction

## INTRODUCTION

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Received: March 29, 2021

Revision received: June 20, 2021

Accepted: June 30, 2021

This article is available from <https://www.labmedonline.org>

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In patients with suspected acute myocardial infarction (AMI), electrocardiograms (ECGs) reliably detect ST-elevation myocardial infarction. However, as ECGs yield ambiguous results in a significant proportion of the patients with AMI, it is difficult to diagnose non-ST elevation myocardial infarction (NSTEMI) using this test [1]. Moreover, a significant proportion of the patients admitted to the emergency department with chest pain do not have an AMI, and the number of such patients is increasing [2].

Cardiac troponin (cTn) assays performed within 1–3 hours of admission are recommended to rule out AMI. The cTn assay can

detect circulating cTn at extremely low concentrations and thus offers high diagnostic performance [3, 4]. Although the availability of cTn assays allows earlier AMI detection, increased cTn concentration can be observed in the absence of acute coronary syndrome. Therefore, the increasing number of patients with elevated cTn values renders the differential diagnosis in the emergency department challenging for clinicians [5]. Particularly, it is difficult to exclude AMI when the degree of cTn elevation is mild, thereby necessitating serial measurement of cTn.

Copeptin, the C-terminal part of the pro-arginine vasopressin precursor peptide, has been considered an alternative biomarker for the detection of evolving AMI [6]. Copeptin is released quickly after the onset of symptom and can compensate for troponin limitation, that is, its late release from the damaged myocardium [7]. Moreover, previous studies revealed that the copeptin plus hs-cTn combination aids in reliably ruling out AMI [8, 9]. A cTn level below the 99th percentile and copeptin level below 10 pmol/L exhibit high negative predictive values (NPVs) when used in combination with ECG [10]. Moreover, copeptin levels can help in predicting infarct size and alterations in myocardial function in patients with STsegment elevation myocardial infarction (STEMI) [11]. However, few studies have been performed on the additional value of copeptin in patients with mild cTn elevation.

In this study, we evaluated the diagnostic value of copeptin levels for NSTEMI in patients who are presented with chest pain and mild cTn elevation in the emergency department. We also investigated whether the risk scoring using simultaneous assessment of cardiac biomarkers would aid in reducing false-positive cTn results in NSTEMI diagnosis.

## MATERIALS AND METHODS

### 1. Study population

The study population included all the patients who were admitted to the emergency department between August 2017 and March 2018 for non-traumatic chest pain. On admission, an ECG was performed, and blood samples were collected. The cardiac troponin I (TnI) level (reference range, 0.01–0.04 ng/mL) was measured for each patient. The patients with mild TnI elevation ( $>0.04$  and  $<1.0$  ng/mL) were enrolled. The range of mild TnI elevation was defined based on the change in the diagnostic cutoff between 1995 and 2007 [12].

The exclusion criteria included STEMI, stroke, renal disease, infection, and late presentation for more than 6 hours after chest pain. The diagnosis was made by a physician using all available data, such as ECG, cardiac markers, and percutaneous coronary intervention results. Patient records were reviewed for AMI occurrence within 12 months of discharge in patients without NSTEMI. All study participants provided informed consent, and the study design complied with all the relevant national regulations and institutional policies and is in accordance with the tenets of the Helsinki Declaration. This study was approved by the institutional review board of our institution.

### 2. Biomarker analysis

Copeptin, TnI, and creatine kinase-MB (CK-MB) levels were measured using blood samples obtained from patients upon arrival. TnI and CK-MB were tested using the Access immunoassay performed with a UniCel DxI analyzer (Beckman Coulter, Brea, CA, USA). Copeptin was measured using the automated immunofluorescent assay Copeptin proAVP KRYPTOR (Thermo Fisher Scientific BRAHMS GmbH, Neuendorfstr, Hennigsdorf, Germany). The upper reference limits of CK-MB and copeptin were 6.3 ng/mL and 10.0 pmol/L. All assays were performed according to the manufacturer's instructions.

### 3. Statistical analysis

Continuous variables were presented as mean  $\pm$  standard deviation (SD) or median (interquartile range) and were compared using analysis of variance (ANOVA) or the Kruskal–Wallis test (if not normally distributed). Categorical variables were expressed in terms of rates or proportions and were compared using the chi-square test or Fisher's exact test. The diagnostic performance of all cardiac markers were assessed using receiver operating characteristic (ROC) curve analysis. Analyses were performed using MedCalc version 19.6 (MedCalc Software, Mariakerke, Belgium).

## RESULTS

### 1. Baseline characteristics of study population

A total of 180 patients (age,  $68.2 \pm 13.3$  years; M:F, 113:67), who presented with non-traumatic chest pain and admitted to the emergency department, met the inclusion criteria and were included as study population. Among those patients, 49 patients (27.2%)

were diagnosed with NSTEMI, and 131 (72.8%) were diagnosed with non-NSTEMI. The non-NSTEMI group comprised 64 patients (35.6%) with angina and 67 patients (37.2%) with other diseases. In two-thirds of cases with mild cTnI elevation, non-ischemic causes were observed.

The clinical characteristics are summarized in Table 1. The age of the patients did not significantly differ among the groups; however, the number of men in the angina group was lower than that in the NSTEMI group. During the follow-up period, AMI events did not occur in any of the cases in the non-NSTEMI group.

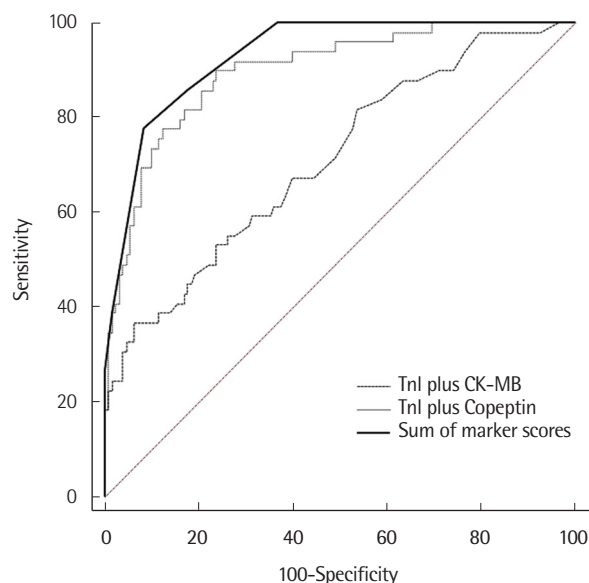
## 2. Cardiac markers according to the diagnostic groups

The median TnI concentration in the NSTEMI group (0.103 ng/mL) was significantly higher than that in the angina group (0.060 ng/mL,  $P=0.003$ ) and other disease groups (0.070 ng/mL,  $P=0.024$ ). Moreover, median CK-MB and copeptin concentrations in the patients with NSTEMI (4.0 ng/mL, 69.57 pmol/L) were higher than those in the patients with angina (2.2 ng/mL,  $P=0.0001$ ; 7.64 pmol/L,  $P<0.0001$ ) and other diseases (2.3 ng/mL,  $P=0.0002$ ; 6.75 pmol/L,  $P<0.0001$ ). The frequency of CK-MB and copeptin levels exceeding the upper reference limit was significantly higher in the NSTEMI group (36.7% and 87.7%, respectively) than in the non-NSTEMI group (6.9% and 33.6%, respectively;  $P<0.0001$ ) (Table 1).

## 3. Diagnostic performance of combined cardiac markers

Considering the high prevalence of non-ischemic mild TnI elevation, we assessed the diagnostic value of combined markers (TnI plus CK-MB or TnI plus copeptin) in discriminating NSTEMI cases from non-NSTEMI cases. The best cutoff level of CK-MB in cases with mild TnI elevation was 6.5 ng/mL. The area under the curve (AUC) of the ROC curve was 0.711 (95% confidence interval

[CI], 0.639–0.776). At this cutoff level, the sensitivity and specificity of TnI plus CK-MB analysis were 36.7% and 93.9%, respectively. In the ROC curve analysis of TnI plus copeptin, the AUC increased to 0.898 (95% CI, 0.845–0.938) and was significantly higher than that of TnI plus CK-MB ( $P=0.0001$ ). The best cutoff level of copeptin was 14.4 pmol/L, and its diagnostic sensitivity and specificity were 89.8% and 76.3%, respectively. The positive predictive value (PPV) of TnI plus CK-MB for NSTEMI detection was 66.7%, which was higher than the PPV of 49.4% for TnI plus copeptin. In contrast, the NPV of “TnI plus copeptin” was 93.5%, which was higher than the NPV of 79.7% for “TnI plus CK-MB” (Fig. 1).



**Fig. 1.** ROC curve analysis results showing the diagnostic performance of CK-MB, copeptin, and the sum of marker scores in NSTEMI group versus non-NSTEMI group in patients presented with chest pain and mild TnI (>0.4 and <1.0 ng/mL) elevation.

Abbreviation: ROC, receiver operating characteristics; NSTEMI, non-ST elevation myocardial infarction.

**Table 1.** Characteristics of study population and their levels of cardiac markers

|                   | NSTEMI (N=49)        | Angina (N=64)       | Other diseases (N=67) | P value |
|-------------------|----------------------|---------------------|-----------------------|---------|
| Age (yr)          | 68.9 ± 13.2          | 68.4 ± 10.0         | 67.6 ± 16.0           | 0.860   |
| Male              | 37 (75.5%)           | 32 (50.0%)          | 44 (65.7%)            | 0.017   |
| TnI (ng/mL)       | 0.103 (0.050–0.475)  | 0.060 (0.050–0.113) | 0.070 (0.050–0.161)   | 0.008   |
| CK-MB (ng/mL)     | 4.0 (2.2–9.1)        | 2.2 (1.3–3.8)       | 2.3 (1.5–3.7)         | 0.0001  |
| Copeptin (pmol/L) | 69.57 (35.56–172.50) | 7.64 (3.36–17.19)   | 6.75 (4.33–13.02)     | 0.0001  |
| CK-MB > 6.3       | 18 (37.5%)           | 7 (10.9%)           | 2 (3.0%)              | 0.0001  |
| Copeptin > 10     | 43 (87.7%)           | 23 (35.9%)          | 21 (31.3%)            | 0.0001  |

Values are presented as mean ± SD or median (interquartile range).

Abbreviations: TnI, troponin I; CK-MB, creatine kinase-MB; NSTEMI, non-ST-elevation myocardial infarction.

**Table 2.** Scores based on the levels of cardiac biomarkers

| TnI (ng/mL) | Score | CK-MB (ng/mL) | Score | Copeptin (pmol/L) | Score |
|-------------|-------|---------------|-------|-------------------|-------|
| 0.041–0.200 | 0     | ≤ 6.5         | 0     | ≤ 14.4            | -1    |
| 0.201–0.400 | 1     | > 6.5         | 1     | 14.5–35.0         | 0     |
| ≥ 0.401     | 2     |               |       | 35.1–70.0         | 1     |
|             |       |               |       | > 70.0            | 2     |

Abbreviations: TnI, troponin I; CK-MB, creatine kinase-MB.

#### 4. Diagnostic accuracy for the sum of cardiac marker scores (SMS)

Considering the higher levels of cardiac markers in the NSTEMI group, highest PPV of TnI plus CK-MB, and highest NPV of TnI plus copeptin, we scored the value of each cardiac marker. We devised a cardiac marker score based on the diagnostic cutoff of cardiac markers, multiples of TnI cutoff, and distribution of copeptin in NSTEMI cases.

For TnI, the score was assigned from 0 to 2 using the diagnostic cutoff (0.04 ng/mL) and its five-fold/10-fold values (0.2 ng/mL, and 0.4 ng/mL). As TnI plus CK-MB exhibited the highest PPV for NSTEMI detection, the CK-MB score was set to 0 or 1 using the cutoff (6.5 ng/mL). TnI plus copeptin exhibited the highest NPV for NSTEMI detection. Therefore, the score of copeptin was set from -1 to 2 using cutoff (14.4 pmol/L), the 25th percentile/50th percentile of NSTEMI group (35.0 pmol/L, 70.0 pmol/L) (Table 2).

In 115 (63.9%) of the 180 patients, SMS was ≤ 0. Sixteen (8.9%) patients had an SMS of 1, and 49 (27.2%) patients had an SMS of ≥ 2. In the NSTEMI group, the median (interquartile range) of the SMS was 2 (2–4) and was significantly higher than -1 (-1 to 0) in the non-NSTEMI group ( $P < 0.0001$ ) (Table 3). In the ROC curve analysis of the SMS, the best cutoff was 1, and its diagnostic sensitivity and specificity were 77.6% and 91.6%, respectively. The AUC of the SMS was 0.931 (95% CI, 0.883–0.963) and was not significantly higher than that of TnI plus copeptin (0.898;  $P = 0.106$ ; Fig. 1).

## DISCUSSION

Estimating the probability of NSTEMI in patients with chest pain with mild TnI elevation (≤ 1.0 ng/mL) is difficult. Therefore, in this study, we assessed the diagnostic performance of copeptin in such patients. We observed that a significant proportion (72.8%) of patients with mild TnI elevation exhibited non-NSTEMI-related troponin elevation. Thus, our results confirmed that mild TnI ele-

**Table 3.** Distribution of sum of cardiac marker scores (SMS) in disease groups

|           | All (N = 180)        | NSTEMI (N = 49)     | Angina (N = 64)       | Other diseases (N = 67) | P value |
|-----------|----------------------|---------------------|-----------------------|-------------------------|---------|
| SMS       | 0.0<br>(-1.0 to 2.0) | 2.0<br>(2.0 to 4.0) | -0.5<br>(-1.0 to 1.0) | -1.0<br>(-1.0 to 0.0)   | <0.0001 |
| -1        | 83                   | 0                   | 38                    | 45                      |         |
| 0         | 32                   | 7                   | 17                    | 8                       |         |
| 1         | 16                   | 4                   | 3                     | 9                       |         |
| 2         | 28                   | 19                  | 5                     | 4                       |         |
| 3         | 8                    | 6                   | 1                     | 1                       |         |
| 4         | 8                    | 8                   | 0                     | 0                       |         |
| 5         | 5                    | 5                   | 0                     | 0                       |         |
| SMS ≥ 2.0 | 49 (27.2%)           | 38 (77.6%)          | 6 (10.7%)             | 5 (7.5%)                | <0.0001 |

Values are presented as median (interquartile range).

vation is observed in various non-ischemic conditions. Mild TnI elevation was accompanied by concomitant elevation of CK-MB and copeptin in 15.0% and 48.3% of patients, respectively. The higher frequencies of CK-MB and copeptin elevation in the NSTEMI group support the notion that the concomitant elevation of CK-MB and copeptin reflects the occurrence of NSTEMI. TnI, CK-MB, and copeptin levels were higher in the NSTEMI group than in the non-NSTEMI group. NSTEMI was associated with a concomitant increase in the elevation of cardiac markers. Therefore, a combination of CK-MB, copeptin, and TnI testing may aid in early and accurate detection of NSTEMI when the TnI level is mildly elevated.

Both CK-MB and copeptin levels were significantly higher in the NSTEMI group than in the non-NSTEMI group; however, their NPVs and PPVs for detecting NSTEMI differed. As a diagnostic marker, elevated CK-MB levels were specific for myocardial cellular injury and were observed almost simultaneously with TnI elevation. Copeptin is a marker of acute stress independent of cardiac cell necrosis; however, its initial rise is observed early, that is, within 1 hour after the onset of MI symptoms, as compared to 2–3 hours for TnI [13]. In our cases with mild TnI elevation, the NPV of copeptin was excellent (93.5%); however, the PPV was not good. Due to the higher NPV, the copeptin assay was superior to the CK-MB assay, excluding NSTEMI in patients with chest pain accompanied by mild troponin elevation. The elevation of CK-MB levels was strongly associated with NSTEMI because of the higher PPV.

Previous studies have reported that the use of dual markers (copeptin and cardiac troponin) increases the NPV for myocardial

infarction in patients with chest pain [14–16]. A meta-analysis revealed that the copeptin plus cTn combination had significantly greater sensitivity and NPV for NSTEMI than cTn alone [17]. In our patients with mild troponin elevation, the NPV of copeptin was excellent, and copeptin plus TnI exhibited higher diagnostic accuracy than CK-MB plus TnI for NSTEMI, as revealed by the AUC values (0.898 vs. 0.711). We suggest that the use of complementary markers would increase the accuracy of TnI analysis; the addition of copeptin would be useful in differentiating non-NSTEMI from NSTEMI in patients with chest pain and mild troponin elevation.

To further increase the sensitivity of troponin for diagnostic and prognostic evaluation, clinical scores and cardiac biomarker scores were evaluated [18, 19]. A cardiac biomarker score based on the number of elevated biomarkers at presentation has revealed prognostic value in predicting the risk of major cardiac events in patients with acute coronary syndrome and stable cardiac patients [19, 20]. In this study, we devised a score to assign weight based on the values of three measured cardiac biomarkers: TnI, copeptin, and CK-MB.

The more TnI exceeded the cutoff (0.04 ng/mL), the more likely that NSTEMI would be confirmed. The scores of TnI levels were divided into three sections from 0 to 2. As elevated levels of CK-MB suggested the possibility of NSTEMI, the scores of CK-MB levels were assigned 0 and 1. TnI plus copeptin increased NPV, and therefore, the score of copeptin levels was divided into four sections from -1 to 2. The median SMS was significantly higher in the NSTEMI group than in the non-NSTEMI group. A high SMS of 2 or more supports the diagnosis of NSTEMI, whereas a low SMS of -1 may exclude NSTEMI. However, the diagnostic performance of SMS was similar to that of the combination of TnI and copeptin, and a scoring system was not proven to be necessary.

In addition to AMI, copeptin is linked to various other diseases, including exposure to endogenous stress [21]. In non-NSTEMI patients with a high SMS ( $\geq 2$ ), the reason for high SMS was moderate to high increase ( $>35.0$  pmol/L) of copeptin, and the degree of copeptin increase in the NSTEMI group was not associated with the future development of cardiac events. An increase in copeptin levels is not specific to AMI; therefore, copeptin should be used as an adjuvant biomarker and not as a single marker for analysis.

In conclusion, the copeptin assay provides additional informa-

tion for differentiating NSTEMI from non-NSTEMI patients with mild TnI elevation. The use of risk scores using TnI, CK-MB, and copeptin levels could help in improving the diagnosis of NSTEMI in patients with mild TnI elevation.

## 요 약

**배경:** 트로포닌 분석은 급성심근경색의 검출을 개선한다. 그러나 트로포닌 상승은 다양한 비 허혈 조건에서도 관찰된다. 혈청 코펩틴을 심장 트로포닌 I 분석과 함께 사용하면 급성 심근 경색에 대한 진단 정확도를 높일 수 있다는 연구들이 발표된 바 있다. 본 연구에서는 비-ST분절상승 심근경색증을 진단하기 위한 코펩틴의 유용성을 평가하였다.

**방법:** 심전도에서 ST 상승이 있는 환자를 제외하고, 응급실에서 흉통과 경한 트로포닌 I 상승( $0.04\text{--}1.0$  ng/mL)을 보인 180명의 환자(나이,  $68.2 \pm 13.3$ 세; 남:여 비, 113:67)를 등록하였다. 코펩틴은 자동화된 면역형광분석 Copeptin proAVP KRYPTOR (Thermo Fisher Scientific, Germany)을 사용하여 측정되었다.

**결과:** 대상자는 비-ST분절 상승 심근경색증 환자 49명(27.2%), 협심증 환자 64명(35.6%), 기타 질환 환자 67명(37.2%)이었다. 비-ST 상승 심근경색증 그룹( $69.57$  [ $35.56\text{--}172.50$ ] pmol/L)에서의 코펩틴 중앙값(사분위수 범위)은 협심증군( $7.64$  [ $3.36\text{--}17.19$ ] pmol/L) 및 다른 질환 군( $6.75$  [ $4.33\text{--}13.02$ ] pmol/L)들의 중앙값보다 유의하게 더 높았다( $P < 0.0001$ ). 코펩틴의 판정기준치를  $14.4$  pmol/L로 할 때, TnI와 코펩틴 조합은 TnI와 CK-MB 조합보다 비-ST분절 상승 심근경색증을 진단하는데 있어 높은 곡선하면적( $0.898$  대.  $0.711$ ,  $P = 0.0001$ )을 보였다.

**결론:** 비허혈성 질환에 의한 경한 트로포닌 I 상승은 흔하다. 코펩틴 수치는 경한 트로포닌 I 상승이 있는 환자에서 비-ST상승심근경색을 비-ST분절 상승 심근경색증 이외의 질환과 구별하는 데 도움이 되는 추가 정보를 제공한다. 트로포닌 I와 코펩틴 조합은 비허혈성 질환에 의한 경한 트로포닌 I 상승을 배제함으로써 비-ST분절 상승 심근경색증의 진단을 개선하는데 도움이 수 있다.

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