Diagnostic accuracy of adding copeptin to cardiac troponin for non-ST-elevation myocardial infarction: A systematic review and meta-analysis

Hyungoo Shin¹*, Bo-Hyoung Jang²*, Tae Ho Lim¹,³*, Juncheol Lee¹, Wonhee Kim⁴,⁵, Youngsuk Cho⁴,⁵, Chiwon Ahn⁶,⁷, Kyu-Sun Choi⁷

¹ Department of Emergency Medicine, College of Medicine, Hanyang University, Seoul, Korea, ² Department of Preventive Medicine, College of Korean Medicine, Kyung Hee University, Seoul, Korea, ³ Convergence Technology Center for Disaster Preparedness, Hanyang University, Seoul, Korea, ⁴ Department of Emergency Medicine, College of Medicine, Hallym University, Seoul, Korea, ⁵ Department of Biomedical Engineering, Graduate School of Medicine, Hanyang University, Seoul, Korea, ⁶ Department of Emergency Medicine, Armed Forces Yangju Hospital, Yangju, Korea, ⁷ Department of Neurosurgery, College of Medicine, Hanyang University, Seoul, Korea

* These authors contributed equally to this work.

Abstract

Introduction
This study aimed to determine the diagnostic accuracy of adding copeptin to cardiac troponin (cTn) on admission to the emergency department (ED) for non-ST elevation myocardial infarction (NSTEMI) compared to cTn alone.

Materials and methods
A literature search of MEDLINE, EMBASE, and the Cochrane Library was performed (search date: April 13, 2018). Primary studies were included if they accurately reported on patients with symptoms suggestive of acute myocardial infarction and measured both cTn alone and cTn with copeptin upon admission to the ED. The patients with evidence of ST elevation myocardial infarction were excluded. To assess the risk of bias for the included studies, the QUADAS-2 tool was used.

Results
The study participants included a total of 7,998 patients from 14 observational studies. The addition of copeptin to cTn significantly improved the sensitivity (0.81 [0.74 to 0.87] vs. 0.92 [0.89 to 0.95], respectively, p < 0.001) and negative predictive value (0.96 [0.95 to 0.98] vs. 0.98 [0.96 to 0.99], respectively, p < 0.001) at the expense of lower specificity (0.88 [0.80 to 0.97] vs. 0.57 [0.49 to 0.65], respectively, p < 0.001) compared to cTn alone. Furthermore, adding copeptin to cTn showed significantly lower diagnostic accuracy for NSTEMI compared to cTn alone (0.91 [0.90 to 0.92] vs. 0.85 [0.83 to 0.86], respectively, p < 0.001).
Conclusions
Adding copeptin to cTn improved the sensitivity and negative predictive value for the diagnosis of NSTEMI compared to cTn alone. Thus, adding copeptin to cTn might help to screen NSTEMI early upon admission to the ED.

Introduction
Acute myocardial infarction (AMI) is the leading cause of death and disability worldwide [1]. A 12-lead electrocardiography (ECG) recording, biomarker analysis, and clinical assessment are commonly performed for the initial evaluation of AMI [2]. While ST elevation myocardial infarction (STEMI) can be readily identified through a clinical assessment and ECG, the diagnosis of non-ST elevation myocardial infarction (NSTEMI) is made based on the serum biomarkers of myocardial necrosis [3].

Cardiac troponin (cTn) has been regarded as a standard marker for myocardial injury, and its elevation is a component of the universal definition of AMI [1]. However, cTn is not sufficiently sensitive within the first hours of myocardial injury, a phenomenon called the “troponin-blind” period [4]. Although high-sensitivity cTn assays are increasingly being used to allow for a more rapid assessment, alternative biomarkers that may be more sensitive to early myocardial injury have gained increasing interest.

Recently, copeptin, an acute endogenous stress neuropeptide [5], has gained attention in the clinical field, with results available within 60 min [6,7]. The combination of copeptin and cTn has been proposed to be used for the assessment of patients with suspected AMI [8,9]. Although copeptin is nonspecific to myocardial injury, it responds to an immediate neural trigger with concentrations rising early and decreasing gradually over several hours [10]. This rapid release may help to cover the “troponin-blind” period.

Hence, a diagnostic systematic review and meta-analysis were performed to determine the diagnostic accuracy of examining both copeptin and cTn in identifying NSTEMI when compared to cTn alone on admission to the emergency department (ED).

Materials and methods
1. Study design
This study was conducted in accordance with the principles outlined by the Systematic Reviews of Diagnostic Test Accuracy [11] and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) groups [12].

2. Eligibility criteria
2.1. Type of studies. Relevant studies were included in our meta-analysis if they: (1) reported results from patients with symptoms suggestive of AMI without evidence of ST-segment elevation, (2) measured both cTn alone and combination of cTn and copeptin on admission to the ED, or (3) assessed the diagnostic performance. Studies that (1) included patients with STEMI, (2) had insufficient data in spite of contacting the authors, or (3) did not meet the criteria for enrollment in our study were excluded.

2.2. Participants. Our selected studies included adult patients who presented to the ED with suspected AMI using both cTn alone and combination of cTn and copeptin.
2.3. **Index tests.** This study included only studies examining the diagnostic accuracy of both baseline cTn alone and adding copeptin to cTn measured in blood samples obtained upon admission to the ED. The cTn index tests included conventional and high-sensitivity assays. Copeptin index tests included manual immunoluminometric assays and automated immunofluorescent assays.

2.4. **Reference tests.** The reference standard was comprised of all available medical records including cTn assay results. NSTEMI is defined by electrocardiographic ST-segment depression or prominent T-wave inversion and positive biomarkers in the absence of ST-segment elevation and in a clinical assessment [1,13].

3. **Search strategy**
Two experienced reviewers (H. Shin and C. Ahn) performed the literature search on April 13, 2018. The search encompassed the MEDLINE (1974 to April 11, 2018) and EMBASE (1974 to April 11, 2018) databases via the Ovid interface and the Cochrane Library (all years). The following keywords were searched: copeptin, myocardial infarction, acute coronary syndrome, coronary artery disease, and angina. No language restrictions and no methodology filters were used. S1 Table presents the details of the search strategies. Articles that reported any prospective or retrospective observational studies were included.

4. **Study selection**
The reference management software Endnote 7.4 was used for all identified studies. The title, abstract, and type of each of the identified articles were examined by two reviewers. Those articles that fell under the exclusion criteria (reviews, case reports, editorials, letters, comments, conference abstracts, or meta-analyses; animal studies; duplicate studies; irrelevant population; irrelevant index test; and irrelevant outcomes (Fig 1)) were not considered. In case of disagreement between the two reviewers, a third reviewer (BH Jang) intervened, and differences were discussed until a consensus was reached. The full texts of the chosen articles were acquired, which were then rescreened and evaluated more thoroughly for eligibility using the same exclusion criteria.

5. **Data extraction**
The two reviewers obtained the characteristics and results of selected studies. Studies with lacking data despite contacting the authors were excluded from the meta-analysis. Data regarding true-positive, false-positive, false-negative, and true-negative results for individual studies were obtained. Variables such as the use of different cut-points for copeptin and both conventional and high-sensitivity cTn were considered. The following variables were also extracted from studies: first author, year of publication, country, study population, inclusion period, assay method for cTn and copeptin detection, and patients’ baseline characteristics. The corresponding author (TH Lim) had full access to all the data in the study and took responsibility for its integrity and the data analysis.

6. **Assessment of methodological quality**
Two reviewers assessed the methodological quality of the primary studies at the study level. Patient selection, index test, reference standard, flow, and timing were assessed using a checklist adapted from the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool [14]. The key methodological issue of including studies would be the potential for
incorporation bias. Elevation of cTn, which is a part of NSTEMI, was included as one of the index tests in this study.

7. Statistical analysis

For each primary study, sensitivity and specificity point estimates and corresponding 95% confidence intervals (CI) were calculated from extracted data for cTn alone and cTn with copeptin. We used SAS software, version 9.4 (SAS Institute, Cary, NC, USA), to perform a bivariate
random effects model, R version 3.2.3 (r-project.org) with “mada” package, and Review Manager (RevMan) 5 version 5.1.7. The statistical significance for hypothesis testing was set at 0.05 for 2-tailed heterogeneity testing and at 0.10 for 2-tailed tests. Dichotomous variables are reported as proportions (%), whereas continuous variables are reported as mean (standard deviation [SD]) or median (interquartile range [IQR]).

7.1. Summary diagnostic accuracy estimates. The summary estimates of sensitivity, specificity, and positive and negative likelihood ratios were derived from bivariate mixed-effect regression model parameter estimates. The area under the summary receiver operating characteristic curve (AUC) was plotted using logistic estimates of sensitivity and specificity and the respective variance and covariance. True-positive, true-negative, false-positive, and false-negative rates were used to compute the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

7.2. Sensitivity analyses. A sensitivity analysis was performed for all studies except for one study where the enrolled patients were aged ≥70 years [15]. Subgroup analysis was also performed for the studies comparing the addition of copeptin to cardiac troponin I (cTnI) and high-sensitivity cardiac troponin T (hs-cTnT) assays.

Results

1. Characteristics of study subjects

1.1. Literature search. A total of 1,496 records were identified through database searching (Fig 1). After removing 369 duplicates, the titles and abstracts for 1,127 records were screened for eligibility. Of these, 48 records were identified as being potentially relevant, and full-text articles were retrieved for a more thorough review. After excluding 34 manuscripts after assessment of the full-text articles, 14 studies, which enrolled 7,998 patients, were included in the meta-analysis.

1.2. Characteristics of included studies. The 14 studies included a total of 7,998 patients, and the prevalence of NSTEMI was 14.2% (range 6.0–35.6%) [10,15–27]. Only the CHOPIN study was a multinational study conducted in the USA and Europe, whereas all the other studies were conducted in Europe. The diagnostic threshold for copeptin was 14 pmol/L (range 7.4–14 pmol/L) in seven studies, and the cTn index tests consisted of cTnI assays in six studies (range 40–100 ng/L) and hs-cTnT assays in eight studies with a diagnostic threshold of 14 ng/L (Table 1). S2 Table presents the patients’ baseline characteristics. The number of true-positive, false-positive, false-negative, and true-negative values with the corresponding sensitivities, specificities, PPV, and NPV for NSTEMI is provided based on the cut-points for cTn (S3 Table) and the addition of copeptin to cTn (S4 Table).

1.3. Assessment of study quality. All included studies were assessed to determine if they were low risk in patient selection and applicability (S1 Fig). Eight studies were considered low risk. One study was assessed as high risk for flow and timing bias. In addition, the risk of bias for the index test and reference test were unclear in four and five studies, respectively.

2. Main results

2.1. Comparison of overall diagnostic accuracy for cardiac troponin alone and the addition of copeptin. The combined assessment of cTn and copeptin ranged from 0.84 to 1.00 for sensitivity and from 0.23 to 0.74 for specificity (Fig 2). On the other hand, cTn alone showed a sensitivity ranging from 0.56 to 1.00 with specificity ranging from 0.39 to 0.99. Overall, the addition of copeptin to cTn significantly improved the sensitivity (0.81 vs. 0.92, p < 0.001) and NPV (0.96 vs. 0.98, p < 0.001) and decreased the specificity (0.88 vs. 0.57,
p < 0.001) compared to cTn alone (Table 2). In addition, adding copeptin to cTn has a lower diagnostic accuracy (0.91 vs. 0.85, p < 0.001) than the cTn alone (Fig 3).

2.2. Subgroup analysis for adding copeptin between cardiac troponin I and high-sensitivity cardiac troponin T. The addition of copeptin to either cTnI or hs-cTnT significantly improved the sensitivity and decreased the specificity compared to cTnI or hs-cTnT alone (Table 3). More specifically, adding copeptin increased the sensitivity for cTnI (0.71 vs. 0.89, p < 0.001) and hs-cTnT (0.86 vs. 0.93, p < 0.001) and reduced the specificity for cTnI (0.96 vs.
Table 2. Paired comparison of diagnostic accuracy for adding copeptin to cardiac troponin for NSTEMI.

| Study        | TP (cTn) | FP (cTn) | FN (cTn) | TN (cTn) | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|--------------|----------|----------|----------|----------|----------------------|----------------------|----------------------|----------------------|
| Alquezar 2017| 57       | 70       | 6        | 164      | 0.90 (0.80, 0.96)    | 0.70 (0.64, 0.76)    |                      |                      |
| Bahmann 2013 | 37       | 163      | 1        | 105      | 0.97 (0.86, 1.00)    | 0.39 (0.33, 0.45)    |                      |                      |
| Charpentier 2012 | 53   | 7        | 42       | 539      | 0.56 (0.45, 0.66)    | 0.99 (0.97, 0.99)    |                      |                      |
| Collinson 2013 | 49     | 28       | 14       | 712      | 0.78 (0.66, 0.87)    | 0.96 (0.95, 0.97)    |                      |                      |
| Dupuy 2012    | 13       | 3        | 2        | 103      | 0.87 (0.60, 0.98)    | 0.97 (0.92, 0.99)    |                      |                      |
| Eggers 2012   | 101      | 59       | 27       | 173      | 0.79 (0.71, 0.86)    | 0.75 (0.68, 0.80)    |                      |                      |
| Jacobs 2015   | 66       | 20       | 29       | 469      | 0.69 (0.59, 0.79)    | 0.96 (0.94, 0.97)    |                      |                      |
| Maisel 2013   | 97       | 184      | 19       | 1627     | 0.84 (0.76, 0.90)    | 0.90 (0.88, 0.91)    |                      |                      |
| Meune 2011    | 13       | 11       | 0        | 34       | 1.00 (0.75, 1.00)    | 0.76 (0.60, 0.87)    |                      |                      |
| Ricci 2016    | 23       | 2        | 6        | 165      | 0.79 (0.60, 0.92)    | 0.99 (0.96, 1.00)    |                      |                      |
| Sebbane 2013  | 19       | 21       | 6        | 121      | 0.76 (0.55, 0.91)    | 0.85 (0.78, 0.91)    |                      |                      |
| Thelin 2013   | 61       | 124      | 9        | 284      | 0.87 (0.77, 0.94)    | 0.70 (0.65, 0.74)    |                      |                      |
| Vafaie 2015   | 24       | 34       | 4        | 69       | 0.86 (0.67, 0.96)    | 0.67 (0.57, 0.76)    |                      |                      |
| Wildi 2015    | 268      | 132      | 90       | 1439     | 0.75 (0.70, 0.79)    | 0.92 (0.90, 0.93)    |                      |                      |

The prevalence of target condition was 14.2% for the cohort of patients with suspicion of NSTEMI.

Abbreviations: 95% CI = 95% confident interval; cTn = cardiac troponin; PPV = positive predictive value; NPV = negative predictive value; AUC = area under the summary receiver operating characteristic curve; NA = not available.
0.67, p < 0.001) and hs-cTnT (0.76 vs. 0.50, p < 0.001). Adding copeptin increased the NPV for cTnI (0.96 vs. 0.97, p = 0.011), but adding copeptin decreased the NPV for hs-cTnT (0.97 vs. 0.94, p = 0.001). Adding copeptin had a lower diagnostic accuracy compared to both cTnI and hs-cTnT.

2.3. Sensitivity analysis. The sensitivity analysis was performed in 13 studies, with the exception of one study [15]. Adding copeptin to cTn significantly improved the NPV for cTnI (0.96 vs. 0.97, p = 0.011), but adding copeptin decreased the NPV for hs-cTnT (0.97 vs. 0.94, p = 0.001). Adding copeptin had a lower diagnostic accuracy compared to both cTnI and hs-cTnT.

Table 3. Subgroup analysis for assessing the diagnostic accuracy of adding copeptin to cardiac troponin.

| Type of cTn | cTnI | hs-cTnT |
|------------|------|---------|
| No. of studies | 6 | 8 |
| No. of patients | 5398 | 2600 |
| Diagnostic tests (95% CI) | | |
| Sensitivity | 0.71 (0.60, 0.82) | 0.86 (0.79, 0.93) |
| Specificity | 0.96 (0.92, 1.00) | 0.76 (0.60, 0.91) |
| PPV | 0.73 (0.58, 0.89) | 0.44 (0.33, 0.56) |
| NPV | 0.96 (0.94, 0.98) | 0.97 (0.95, 0.99) |
| AUC | 0.93 (0.92, 0.95) | 0.90 (0.88, 0.92) |

*The prevalence of target condition was 13.1% for the cohort evaluating cTnI and 16.5% for the cohort evaluating hs-cTnT assay.

Abbreviations: cTn = cardiac troponin; cTnI = cardiac troponin I; hs-cTnT = high sensitivity cardiac troponin T; No = number; 95% CI = 95% confident interval; PPV = positive predictive value; NPV = negative predictive value; AUC = area under the summary receiver operating characteristic curve; NA = not available.

https://doi.org/10.1371/journal.pone.0200379.t003
copeptin to cTn showed lower diagnostic accuracy (0.91 vs. 0.83, \( p < 0.001 \)) compared to cTn alone.

**Discussion**

As demonstrated by this meta-analysis, the addition of copeptin significantly increased the sensitivity and NPV of cTn in NSTEMI patients compared to cTn alone. However, adding copeptin to cTn did not improve the diagnostic accuracy of NSTEMI as assessed by the pooled AUC, when compared to cTn alone. Sensitivity analysis was performed on all studies except for one study [15]; adding copeptin to cTn increased NPV but showed lower diagnostic accuracy to cTn alone.

In two recent meta-analyses, adding copeptin to cTn showed a higher sensitivity and lower specificity in the early rule-out of suspected AMI patients [4,28]. The patients with STEMI should be assessed for immediate reperfusion therapy [3]; suspected STEMI patients should not have to wait for laboratory results [1]. Meanwhile, cTn is essential in the diagnosis and management of patients with suspected NSTEMI [2]. It is of diagnostic value when ECG reveals no ST segment elevation in the presence of a high suspicion of myocardial necrosis. Thus, diagnostic characteristics of cardiac biomarkers for NSTEMI patients were assessed in this study.

Myocardial injury triggers neuroendocrine changes that result in the rapid release of copeptin into the circulation [29]. The measurement of copeptin <6 hours from the presentation of chest pain would make best use of its early release kinetics [10,30,31]. In AMI patients, copeptin levels are elevated 0–4 hours after the symptoms occur [32–34]. This rapid-release kinetic can cover the cTn delayed release period known as the "troponin-blind" period.

Physicians are frequently faced with the clinical decision-making scenario to either retain the patient for further observation or discharge low-risk patients whose initial cTn values were negative [35]. The sensitivity and specificity of a test have limited clinical usefulness as they cannot be used to estimate the probability of disease in an individual patient [36]. However, NPV, which tells us the probability of not having a disease, given as a negative test may be more useful to rule out AMI. Clinical assessment and the more reliable high NPV would help to rule out patients highly likely to not have AMI in the ED. Reichlin et al. tried to determine whether a combined testing strategy using copeptin and cTn could result in improved NPV for the rapid ruling-out of suspected AMI patients [37].

In this study, we observed how the NPV varies when adding copeptin to cTn compared to cTn alone; the addition of copeptin to cTn significantly improved NPV compared to cTn alone. The discharge of patients negatively presenting with cTn would result in 4% of patients being inappropriately discharged with NSTEMI. However, adding copeptin to cTn would lead to a 50% reduction of inappropriate discharges. Nevertheless, this suggests that 2% of patients with both initially negative copeptin and negative cTn will still have an AMI. Although the NPV had significantly improved, the slight increase in the NPV raises questions about how effective it is in clinical situations.

The early diagnosis of AMI has significantly improved with the recent development of high-sensitivity assays, which reliably measure cTn concentrations that were not detected by previous generations of tests [38–40]. High-sensitivity cTn assays allow a more frequent and earlier detection of AMI in patients with chest pain than conventional assays [2]. Therefore, we analyzed the diagnostic characteristics of adding copeptin to cTn by distinguishing between cTnI and hs-cTnT.

As demonstrated by this meta-analysis, adding copeptin to either cTnI or hs-cTnT significantly improved the sensitivity and reduced the specificity compared to either cTnI or hs-
cTnT alone. Adding copeptin to cTnI significantly improved the NPV compared to cTnI alone, but adding copeptin to hs-cTnT significantly decreased the NPV. The effect of copeptin on the NPV is different when copeptin is combined with hs-cTnT from cTnI; the addition of copeptin could be useful when applied with cTnI. The fact that only hs-cTnT was included in this study should be considered, because it is not obvious that hs-cTnT and hs-cTnI can lead to the same diagnostic accuracy, given that the analytical performances of these assays can differ significantly.

A study by Reinstadler et al. on the usefulness of copeptin in patients with suspected AMI in comparison with routine biomarkers indicated that the advantages of the dual marker strategy appear insignificant when hs-cTnT assays are used [41]. Meanwhile, Potocki et al. showed that when copeptin is used in combination with hs-cTnT, it significantly improved the diagnostic and prognostic accuracy [42]. This study assessed for patients with pre-existing coronary artery disease. These specific patients may show different diagnostic performances of the biomarker. Other studies concluded that the dual strategy should be applied to clinically selected patients with low to intermediate risk of AMI, so as to maximize the NPV if hs-cTnT assays are not available or approved for clinical use [43,44]. Future studies about the diagnostic performance of the adding copeptin to hs-cTnT are necessary.

As shown in the pooled AUC, adding copeptin to cTn showed lower diagnostic accuracy for NSTEMI compared to cTn alone. Emergency physicians involved in the management of older patients encounter the diagnostic challenges of improved sensitivity but decreased specificity of hs-cTnT assays on a daily basis [45]. Reiter et al. revealed that the best cut-off value to rule in AMI varies substantially with age; older patients have nearly four times higher cut-off values with hs-cTnT [46]. As a result of the sensitivity analysis, except for one study that enrolled patients aged ≥70 years [15], adding copeptin to cTn showed lower diagnostic accuracy (0.91 vs. 0.83, p < 0.001) compared to cTn alone, but improved the sensitivity (0.79 vs. 0.91, p < 0.001) and the NPV (0.96 vs. 0.98, p = 0.001). In this setting, the use of copeptin may be helpful in the diagnostic work-up for NSTEMI patients.

This meta-analysis has several important limitations. First, the between-study statistical and clinical heterogeneity was still unresolved in this study. The reasons for heterogeneity in estimates were related to variations of proportions of underlying disease and risk factors of AMI, timing of enrollment, copeptin and cTn assays, and the cut-points across the original studies. This may restrict the quality and interpretation of data. Second, a major methodological concern exists in the included studies. There is the potential for incorporation bias with the baseline cTn value serving as the index test and being part of the reference standard of NSTEMI, based on indirect comparison. This may result in overestimating the diagnostic accuracy for cTn and, therefore, decrease the diagnostic value of copeptin. Third, most included studies were performed in Europe. Hence, these findings may not apply to patients from other regions.

Conclusions

The addition of copeptin to cTn improved the sensitivity and NPV for the diagnosis of NSTEMI compared to cTn alone. Thus, adding copeptin to cTn might help to detect NSTEMI early upon admission to the ED. The addition of copeptin to hs-cTnT could be a useful alternative if hs-cTnT assays are not available or approved for clinical use.

Supporting information

S1 Table. Search strategy.
(PDF)
S2 Table. Number of true positives, true negatives, false positives, and false negatives based on the cardiac troponin I or high-sensitivity troponin T cut-point for studies providing these data.
(PDF)

S3 Table. Number of true positives, true negatives, false positives, and false negatives based on the addition of copeptin to cardiac troponin I or high-sensitivity troponin T cut-point for studies providing these data.
(PDF)

S4 Table. Characteristics of patients in the included studies.
(PDF)

S5 Table. Sensitivity analysis for diagnostic accuracy of cardiac troponin alone and adding copeptin to cardiac troponin for non-ST elevation myocardial infarction, except for one study that enrolled patients aged ≥70 years.
(PDF)

S1 Fig. Assessment risk of bias using Quality Assessment of Diagnostic Accuracy Studies—2 tool.
(PDF)

Author Contributions

Conceptualization: Bo-Hyoung Jang, Wonhee Kim.
Data curation: Hyungoo Shin, Bo-Hyoung Jang, Chiwon Ahn.
Formal analysis: Hyungoo Shin, Youngsuk Cho, Chiwon Ahn, Kyu-Sun Choi.
Funding acquisition: Tae Ho Lim.
Investigation: Hyungoo Shin, Bo-Hyoung Jang, Chiwon Ahn.
Methodology: Bo-Hyoung Jang, Tae Ho Lim, Kyu-Sun Choi.
Project administration: Juncheol Lee, Wonhee Kim.
Resources: Youngsuk Cho, Chiwon Ahn.
Software: Bo-Hyoung Jang, Juncheol Lee.
Supervision: Tae Ho Lim, Wonhee Kim, Kyu-Sun Choi.
Validation: Juncheol Lee, Youngsuk Cho.
Visualization: Tae Ho Lim, Youngsuk Cho, Kyu-Sun Choi.
Writing – original draft: Hyungoo Shin.
Writing – review & editing: Tae Ho Lim, Wonhee Kim.

References

1. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Circulation. 2012; 126:2020–2035. https://doi.org/10.1161/CIR.0b013e31826e1058 PMID: 22923432
2. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the management of acute coronary syndromes (ACS) in patients presenting without
Cardiac troponin and copeptin for NSTEMI

1. Kumar A, Cannon CP. Acute coronary syndromes: diagnosis and management, part I. Mayo Clin Proc. 2009; 84:917–938. https://doi.org/10.1016/S0025-6196(11)60509-0 PMID: 19797781

2. Holwerda DA. A glycopeptide from the posterior lobe of pig pituitaries. I. Isolation and characterization. Eur J Biochem. 1972; 28:334–339. PMID: 5079944

3. Maisel A, Mueller C, Neath SX, Christenson RH, Morgen thaler NG, McCord J, et al. Copeptin helps in the early detection of patients with acute myocardial infarction: primary results of the CHOPIN trial (Copeptin Helps in the early detection Of patients with acute myocardial Infarction). J Am Coll Cardiol. 2013; 62:150–160. https://doi.org/10.1016/j.jacc.2013.04.011 PMID: 23643955

4. Holwerda DA. A glycopeptide from the posterior lobe of pig pituitaries. I. Isolation and characterization. Eur J Biochem. 1972; 28:334–339. PMID: 5079944

5. Nickel CH, Bingisser R, Morgenthaler NG. The role of copeptin as a diagnostic and prognostic biomarker for risk stratification in the emergency department. BMC Med. 2012; 10:7. https://doi.org/10.1186/1710-1097-10-7 PMID: 22642200

6. Alqueizar A, Santaló M, Rizzi M, Gich I, Grau M, Sionis A, et al. Combined high-sensitivity copeptin and troponin T evaluation for the diagnosis of non-ST elevation acute coronary syndrome in the emergency department. Emergencias. 2017; 51:1307–1319. https://doi.org/10.1515/emergencias-2017-0036

7. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009; 151:264–269. PMID: 19622511

8. Thygesen K, Alpert JS, White HD, Jaffe AS, Apple FS, Galvani M, et al. Universal definition of myocardial infarction. Circulation. 2007; 116:2634–2653. https://doi.org/10.1161/CIRCULATIONAHA.107.187397 PMID: 17951284

9. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011; 155:529–536. https://doi.org/10.7326/0003-4819-155-8-2011101800009 PMID: 22007046

10. Bahrma nn P, Bahrmann A, Breithardt OA, Daniel WG, Christ M, Sieber CC, et al. Additional diagnostic and prognostic value of copeptin ultra-sensitive for diagnosis of non-ST-elevation myocardial infarction in older patients presenting to the emergency department. Clin Chem Lab Med. 2013; 51:1307–1319. https://doi.org/10.1515/cclm-2012-0401

11. Alqueizar A, Santaló M, Rizzi M, Gich I, Grau M, Sionis A, et al. Combined high-sensitivity copeptin and troponin T evaluation for the diagnosis of non-ST elevation acute coronary syndrome in the emergency department. Emergencias. 2017; 51:1307–1319. https://doi.org/10.1515/emergencias-2017-0036

12. Holwerda DA. A glycopeptide from the posterior lobe of pig pituitaries. I. Isolation and characterization. Eur J Biochem. 1972; 28:334–339. PMID: 5079944

13. Alqueizar A, Santaló M, Rizzi M, Gich I, Grau M, Sionis A, et al. Combined high-sensitivity copeptin and troponin T evaluation for the diagnosis of non-ST elevation acute coronary syndrome in the emergency department. Emergencias. 2017; 51:1307–1319. https://doi.org/10.1515/emergencias-2017-0036

14. Raskovalov a T, Tweno rbold R, Collinson PO, Keller T, Bouvaist H, Folli C, et al. Diagnostic accuracy of combined cardiac troponin and copeptin assessment for early rule-out of myocardial infarction: a systematic review and meta-analysis. Eur Heart J Acute Cardiovasc Care. 2014; 3:18–27. https://doi.org/10.1177/2048872613514015 PMID: 24562800

15. Eur J Biochem. 1972; 28:334–339. PMID: 5079944

16. Alqueizar A, Santaló M, Rizzi M, Gich I, Grau M, Sionis A, et al. Combined high-sensitivity copeptin and troponin T evaluation for the diagnosis of non-ST elevation acute coronary syndrome in the emergency department. Emergencias. 2017; 51:1307–1319. https://doi.org/10.1515/emergencias-2017-0036

17. Nickel CH, Bingisser R, Morgenthaler NG. The role of copeptin as a diagnostic and prognostic biomarker for risk stratification in the emergency department. BMC Med. 2012; 10:7. https://doi.org/10.1186/1710-1097-10-7 PMID: 22642200

18. Gandhi PU, Januzzi JL Jr. Can copeptin emerge from the growing shadow of the troponins? Eur Heart J. 2015; 36:333–336. https://doi.org/10.1093/eurheartj/ehu211 PMID: 24847154

19. Mueller C. Biomarkers and acute coronary syndromes: an update. Eur Heart J. 2014; 35:552–556. https://doi.org/10.1093/eurheartj/ehu211 PMID: 24847154

20. Maisel A, Mueller C, Neath SX, Christenson RH, Morgenthaler NG, McCord J, et al. Copeptin helps in the early detection of patients with acute myocardial infarction: primary results of the CHOPIN trial (Copeptin Helps in the early detection Of patients with acute myocardial Infarction). J Am Coll Cardiol. 2013; 62:150–160. https://doi.org/10.1016/j.jacc.2013.04.011 PMID: 23643955

21. Meune C, Zuluy S, Wahbi K, Claessens YE, Weber S, Chenevier-Gobeaux C. Combination of copeptin and high-sensitivity cardiac troponin T assay in unstable angina and non-ST-segment elevation

22. Dupuy AM, Chastang E, Cristol JP, Jreige R, Lefebvre S, Sebbane M. Analytical performances of the newly developed, fully automated Kryptor Copeptin assay: which impact factor for myocardial infarction rules out in the emergency department? Clin Lab. 2012; 58:635–644. PMID: 22999309

23. Eggers KM, Venge P, Lindahl B. High-sensitive cardiac troponin T outperforms novel diagnostic biomarkers in patients with acute chest pain. Clin Chim Acta. 2012; 413:1135–1140. https://doi.org/10.1016/j.cca.2012.03.011 PMID: 22594355

24. Jacobs LH, van Boren M, Gemen E, van Eck M, van Son B, Glatz JF, et al. Rapidly rule out acute myocardial infarction by combining copeptin and heart-type fatty acid-binding protein with cardiac troponin. Ann Clin Biochem. 2015; 52:550–561. https://doi.org/10.1177/0004563215578189 PMID: 25732130

25. Collinson PO, Gaze DC, Thokala P, Goodacre S. Randomised Assessment of Treatment using Panel Assay of Cardiac markers—Contemporary Biomarker Evaluation (RATPAC CBE). Health Technol Assess. 2013; 17:1–122.
myocardial infarction: a pilot study. Arch Cardiovasc Dis. 2011; 104:4–10. https://doi.org/10.1016/j.acvd.2010.11.002 PMID: 21276572

23. Ricci F, Di Scala R, Massacesi C, Di Nicola M, Cremonese G, De Pace D, et al. Ultra-Sensitive Copeptin and Cardiac Troponin in Diagnosing Non-ST-Segment Elevation Acute Coronary Syndromes—The COPACS Study. Am J Med. 2016; 129:105–114. https://doi.org/10.1016/j.ajmed.2015.06.033 PMID: 26169889

24. Sebbane M, Lefebvre S, Kuster N, Jreige R, Jacques E, Badiou S, et al. Early rule out of acute myocardial infarction in ED patients: value of combined high-sensitivity cardiac troponin T and ultra-sensitive copeptin assays at admission. Am J Emerg Med. 2013; 31:1302–1308. https://doi.org/10.1016/j.ajem.2013.04.033 PMID: 23816196

25. Thelin J, Borna C, Erlinge D, Öhlín B. The combination of high sensitivity troponin T and copeptin facilitates early rule-out of ACS: a prospective observational study. BMC Cardiovasc Disord. 2013; 13:42. https://doi.org/10.1186/1471-2261-13-42 PMID: 23777442

26. Vafei M, Biener M, Mueller M, Abu Sharar H, Hartmann O, Hertel S, et al. Addition of copeptin improves diagnostic performance of point-of-care testing (POCT) for cardiac troponin T in early rule-out of myocardial infarction—A pilot study. Int J Cardiol. 2015; 198:26–30. https://doi.org/10.1016/j.ijcard.2015.06.122 PMID: 26149334

27. Wildi K, Zellweger C, Twerenbold R, Jaeger C, Reichlin T, Haaf P, et al. Incremental value of copeptin to highly sensitive cardiac Troponin I for rapid rule-out of myocardial infarction. Int J Cardiol. 2015; 190:170–176. https://doi.org/10.1016/j.ijcard.2015.04.135 PMID: 25918073

28. Lipinski MJ, Escarcérga RO, D’Ascenzo F, Magalhães MA, Baker NC, Torguson R, et al. A systematic review and collaborative meta-analysis to determine the incremental value of copeptin for rapid rule-out of acute myocardial infarction. Am J Cardiol. 2014; 113:1581–1591. https://doi.org/10.1016/j.amjcard.2014.01.436 PMID: 24731654

29. Morgenthaler NG. Copeptin: a biomarker of cardiovascular and renal function. Congest Heart Fail. 2010; 16:S37–44. https://doi.org/10.1111/j.1751-7133.2010.00177.x PMID: 20653710

30.Slagman A, Searle J, Müller C, Möckel M, et al. Temporal release pattern of copeptin and troponin T in patients with suspected acute coronary syndrome and spontaneous acute myocardial infarction. Clin Chem. 2015; 61:1273–1282. https://doi.org/10.1373/clinchem.2015.240580 PMID: 26341999

31. Bohyn E, Dubie E, Lebrun C, Jund J, Beaune G, Lesage P, et al. Serial changes in highly sensitive troponin I assay and early diagnosis of acute coronary syndrome by combined measurements of copeptin, high-sensitivity troponin, and GRACE score. Am J Emerg Med. 2014; 32:293–296. https://doi.org/10.1016/j.ajem.2013.11.043 PMID: 24480311

32. Sanchez M, Llorens P, Herrero P, Martin-Sanchez FJ, Pinera P, Miro O. The utility of copeptin in the emergency department as a predictor of adverse outcomes in non-ST-elevation acute coronary syndrome: the COPED-PAO study. Emerg Med J. 2014; 31:286–291. https://doi.org/10.1136/emermed-2012-201996 PMID: 23731777

33. Khan SQ, Dhillon OS, O’Brien RJ, Struck J, Quinn PA, Morgenthaler NG et al. C-terminal provasopressin (copeptin) as a novel and prognostic marker in acute myocardial infarction: Leicester Acute Myocardial Infarction Peptide (LAMP) study. Circulation. 2007; 115:2103–2110. https://doi.org/10.1161/CIRCULATIONAHA.106.685503 PMID: 17420344

34. Reinstadler SJ, Klug F, Feistritzer HJ, Mayr A, Harrasser B, Mair J, et al. Association of copeptin with myocardial infarct size and myocardial function after ST segment elevation myocardial infarction. Heart. 2013; 99:1525–1529. https://doi.org/10.1136/heartjnl-2013-303975 PMID: 23697651

35. Vargas KG, Kassem M, Mueller C, Wojta J, Huber K. Copeptin for the early rule-out of non-ST-elevation myocardial infarction. Int J Cardiol. 2016; 223:797–804. https://doi.org/10.1016/j.ijcard.2016.08.304 PMID: 27573613

36. Akobeng AK. Understanding diagnostic tests 1: sensitivity, specificity and predictive values. Acta Pae diatr. 2007; 96:338–341. https://doi.org/10.1111/j.1651-2227.2006.00180.x PMID: 17407452

37. Reichlin T, Hochholzer W, Stelzig C, Laule K, Freidank H, Morgenthaler NG, et al. Incremental value of copeptin for rapid rule out of acute myocardial infarction. J Am Coll Cardiol. 2009; 54:60–68. https://doi.org/10.1016/j.jacc.2009.01.076 PMID: 19558442

38. Keller T, Zeller T, Ojeda F, Tzikas S, Lillpopp L, Sinning C, et al. Serial changes in highly sensitive troponin I assay and early diagnosis of myocardial infarction. JAMA. 2011; 306:2684–2693. https://doi.org/10.1001/jama.2011.1896 PMID: 22203537

39. de Lemos JA. Increasingly sensitive assays for cardiac troponins: a review. JAMA. 2013; 309:2262–2269. https://doi.org/10.1001/jama.2013.5809 PMID: 23736735

40. Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med. 2009; 361:858–867. https://doi.org/10.1056/NEJMoa0900428 PMID: 19710484
41. Reinstadler SJ, Klug G, Feistritzer HJ, Metzler B, Mair J. Copeptin testing in acute myocardial infarction: ready for routine use? Dis Markers. 2015; 2015:614145. https://doi.org/10.1155/2015/614145 PMID: 25960596

42. Potocki M, Reichlin T, Thalmann S, Zellweger C, Twerenbold R, Reiter M, et al. Diagnostic and prognostic impact of copeptin and high-sensitivity cardiac troponin T in patients with pre-existing coronary artery disease and suspected acute myocardial infarction. Heart. 2012; 98:558–565. https://doi.org/10.1136/heartjnl-2011-301269 PMID: 22337952

43. Korley FK, Jaffe AS. Preparing the United States for high-sensitivity cardiac troponin assays. J Am Coll Cardiol 2013; 61:1753–1758. https://doi.org/10.1016/j.jacc.2012.09.069 PMID: 23395074

44. Mueller C. Use of high-sensitivity troponin for the diagnosis of acute myocardial infarction. Coron Artery Dis. 2013; 24:710–712. https://doi.org/10.1097/MCA.0000000000000049 PMID: 24145764

45. Christ M, Bertsch T, Popp S, Bahrmann P, Heppner HJ, Müller C. High-sensitivity troponin assays in the evaluation of patients with acute chest pain in the emergency department. Clin Chem Lab Med. 2011; 49:1955–1963. https://doi.org/10.1515/CCLM.2011.695 PMID: 21892907

46. Reiter M, Twerenbold R, Reichlin T, Haaf P, Peter F, Meissner J, et al. Early diagnosis of acute myocardial infarction in the elderly using more sensitive cardiac troponin assays. Eur Heart J. 2011; 32:1379–1389. https://doi.org/10.1093/eurheartj/ehr033 PMID: 21362702