Observational Study

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Chest pain in the emergency department

From score to core—A prospective clinical study

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Abstract

High-sensitivity troponin assay brought new challenges as we detect elevated concentration in many other diseases, and it became difficult to distinguish the real cause of this elevation. In this notion, diagnosis of acute coronary syndrome (ACS) remains a challenge in emergency department (ED).

We aim to examine different approaches for rule-in and rule-out of ACS using risk scores, copeptin, and coronary computed tomography angiography (CCTA).

A prospective observational study was designed to evaluate chest pain patients. Consecutive adult patients admitted to the ED with a chief complaint of chest pain due to any cause were included.

All patients were followed-up for 6 months after discharge for major adverse cardiovascular events and readmissions. Admission data, ED processes, and diagnoses were analyzed.

One hundred forty-six patients were included, average age was 63 ± 13.4 years, and 95 (65.1%) were male. Global Registry of Acute Coronary Events (GRACE) and History, ECG, Age, Risk factors, Troponin (HEART) scores showed good prognostic abilities, but HEART combination with copeptin improves diagnoses of myocardial infarction (area under the curve [AUC] 0.764 vs AUC 0.864 $P = .0008$). Patients with elevated copeptin were older, had higher risk scores, and were more likely to be admitted to hospital and diagnosed with ACS in ED. For copeptin, AUC was 0.715 (95% confidence interval 0.629–0.803), and for combination with troponin, AUC of 0.770 (0.703–0.855) did not improve rule-in of myocardial infarction. High-sensitivity troponin I assay alongside prior stroke, history of carotid stenosis, dyslipidemia, use of diuretics, and electrocardiogram changes (left bundle branch block or ST depression) are good predictors of myocardial infarction ($\chi^2 = 52.29$, AUC = 0.875 [0.813–0.937], $P < .001$). The regression analysis showed that combination of copeptin and CCTA without significant stenosis can be used for ACS rule-out ($\chi^2 = 26.36$, $P < .001$, AUC = 0.772 [0.681–0.863], negative predictive value of 96.25%).

For rule-in of ACS, practitioner should consider not only scores for risk stratification but carefully analyze medical history and nonspecific electrocardiogram changes and even with normal troponin results, we strongly suggest thorough evaluation in chest pain unit. For rule-out of ACS combination of copeptin and CCTA holds great potential.

Abbreviation: ACS = acute coronary syndrome, AUC = area under the curve, AVP = arginine vasopressin, CCTA = coronary computed tomography angiography, CTA = computed tomography angiography, CI = confidence interval, ECG = electrocardiogram, ED = emergency department, LBBB = left bundle branch block, ROC = receiver operating characteristic, SD = standard deviation.

Keywords: biomarker, chest pain, copeptin, coronary CT angiography.

1. Introduction

Cardiovascular diseases remain the top cause of death in the world accounting for 17.9 million death per year.[1]

Assessment of patients with a chief complaint of chest pain remains an old challenge. New era with high-sensitivity troponin I assay brought us new challenges as we detect elevated concentration in many other diseases or other conditions, and it

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became difficult to distinguish the real cause of this elevation.[2] With coronavirus disease 2019 worldwide pandemic, new challenges for patient safety as well as faster rule-in and rule-out protocols became of new importance. We want patients to remain isolated from potential harm and spend less time in the emergency department (ED) but nevertheless to go home safely. In some countries, to see a specialist even before pandemic was a demanding task, so the new consideration when dealing with chest pain patients is how safely one can be discharged when there is a good chance that a patient will not be able to see specialist soon.

Chest pain can be a symptom of life-threatening disease, although most patients will go home after spending several hours in the ED. According to the European Society of Cardiology Guidelines, it is safe to use 0/1 hour algorithm to rule-in acute coronary syndrome (ACS) without any additional markers.[3] But in a time of fast decisions in ED, does 1 high-sensitivity troponin assay is enough?

Copeptin is called a stress hormone as it releases as a response to endogenous stress in human body. It is investigated broadly in different acute settings such as acute heart failure and ACS.

In our study, we decided to examine different approaches for rule-in and rule-out as well as levels of copeptin, coronary computed tomography angiography (CCTA) in a cohort of patients with chest pain due to multiple causes and its relationship with clinical signs and outcome.

2. Methods

2.1. Study design

Prospective observational study was performed at Vilnius University Hospital Santaros Klinikos. The study was designed to determine the clinical impact of CCTA and copeptin concentration to rule-in or rule-out ACS in patients with chest pain in ED. The study was approved by The Vilnius Regional Biomedical Research Ethics Committee (no. 158200-18-985-491) and conducted in accordance with the Declaration of Helsinki. All participants provided their written informed consent.

2.2. Inclusion criteria

Consecutive adult patients admitted to the ED with a chief complaint of chest pain due to any cause were included.

2.3. Exclusion criteria

Patients with ST-elevation on initial electrocardiogram (ECG) were excluded. Further exclusion criteria were inability to provide informed consent, patients who did not complete full follow-up (could not be reached by provided contacts), pregnant woman, and patients with active III to IV stage cancer or with history of psychiatric disease.

2.4. Data collection

Patient demographic data, comorbidities, baseline medication, clinical signs and laboratory findings admission, early in-hospital treatment, and in-hospital death and subsequent ambulatory cardiologist consultation data were recorded. Patient gender was self-reported. Global Registry of Acute Coronary Events (GRACE)[4] and History, ECG, Age, Risk factors, Troponin (HEART)[5] scores were calculated for every included patient.

2.5. Biomarkers

Blood samples were taken upon admission to the ED by peripheral intravenous catheter. Samples were collected into plastic ethylenediaminetetraacetic acid tubes (BD, USA). After the sampling, tubes were placed on ice and centrifuged at 3000*g* for 10 minutes to separate plasma within 1 hour from sample collection. Plasma was frozen at –80°C until test was done. Copeptin concentrations were measured by sandwich immunoluminometric assay (BRAHMS Copeptin-proAVP KRYPTOR, BRAHMS GmbH, Germany).

2.6. Coronary computed tomography angiography

The CCTA imaging was performed with Brilliance-64 scanner (Brilliance Pro, Philips Medical Systems, Cleveland, OH). The standard scanning parameters for this study were set to 120 kVp with 600 mAs per slice. In preparation for the scan, patients with a heart rate over 60 beats/min received an intravenous beta-blocker (metoprolol tartrate, 2.5–30 mg) and their systolic blood pressure was monitored during procedure. In addition, sublingual nitroglycerin spray (800 μg) was administered briefly before scanning. Intravenous access was obtained by placement of an 18- or 20-gauge intravenous line in peripheral vein. The patient was asked to take a small breath before starting the scan and to remain completely still during the scan. A biphasic injection protocol was employed. Dedicated CCTA scans started at the carina and utilized 70 mL of ioversol (optiray-350 Mallinckrodt Medical, St Louis, MO) followed by 40 mL of saline injected at 5.5 mL/s. Prospective ECG-based tube current modulation was used for dose reduction more than appropriate. Coronary arteries were evaluated with images reconstructed using 0.8-mm slice thickness and 22-cm field of view with the cardiac sharp C reconstruction kernel. Images were reconstructed from multiple phases of the cardiac cycle to obtain the best quality images of each coronary artery. If an initial evaluation of images reconstructed at the 75% phase was optimal, no further reconstructions were obtained.

2.7. Diagnosis adjudication

Physician in the ED diagnosed ACS according to hospital protocols and standard care and blinded from copeptin and CCTA results. After patient data and hospital records were reviewed independently by 2 cardiologists and 1 emergency medicine physician blinded to postdischarge outcomes adjudicated the cause of acute chest pain. All available patient records including medical history, symptoms and signs at admission, routine laboratory measurements, stress tests, and CCTA results were reviewed. Final diagnoses were classified as myocardial infarction or non–myocardial infarction; the latter included musculoskeletal causes, pulmonary embolism, pulmonary/non-pulmonary infections, cancer, and others.

2.8. Readmission and mortality

All patients were followed-up for 6 months after discharge. Lithuanian administrative databases provided data on mortality and unplanned all-cause readmissions coded by the 10th revision of the International Classification of Diseases. Lithuania's national administrative databases capture all of the events since there are no private hospitals that admit acute patients and are not covered by Health care insurance. Therefore, there were no patients lost to follow-up. Patients were also contacted by telephone at 1, 3, and 6 months after the index episode.

2.9. Statistical analysis

Values are expressed as counts and frequencies for qualitative variables and as means and standard deviations or medians with interquartile range for quantitative variables, depending on the distribution.

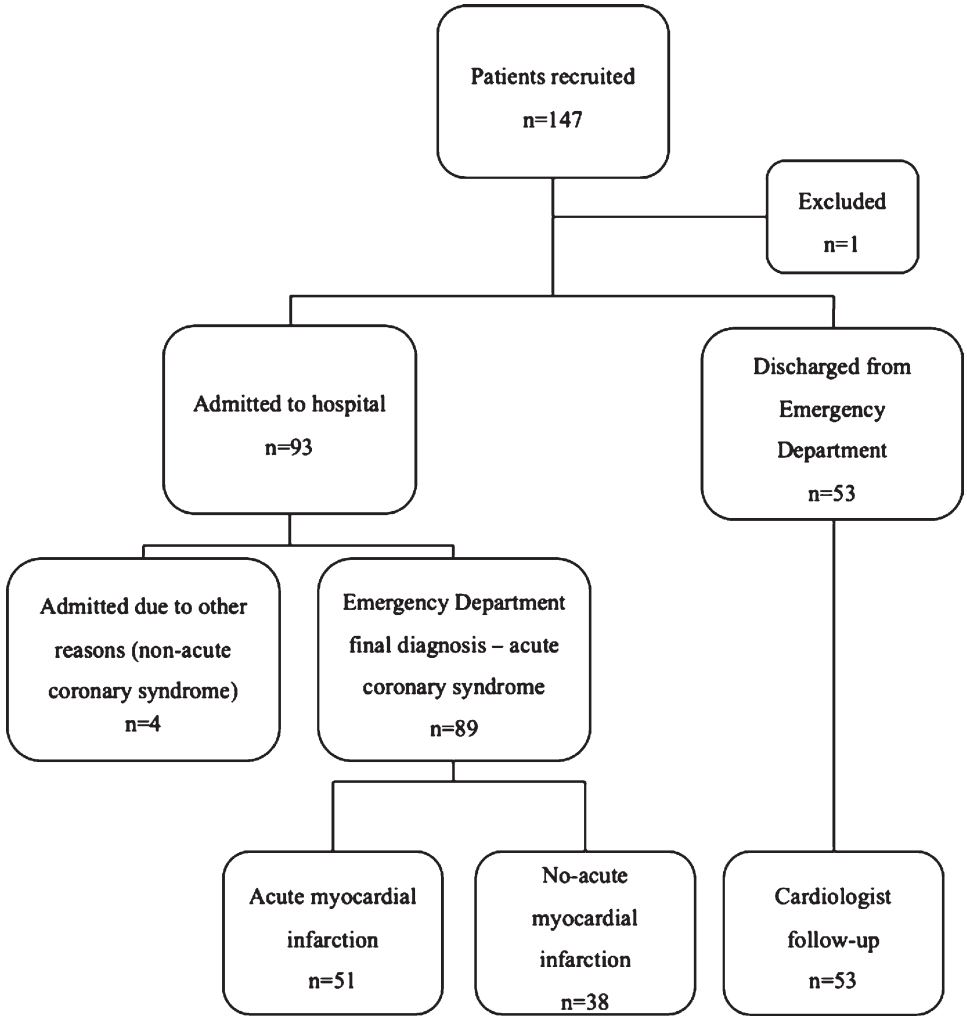

Figure 1. Patient flow diagram.

All study parameters were compared between 2 groups, based on copeptin laboratory cutoff value for a more detailed description of the biomarker in an acute chest pain cohort.

The χ^2 test was used to compare categories. The means of continuous nonparametric variables were compared using the Mann–Whitney *U* or Kruskal–Wallis *H* test when appropriate.

In order to assess a statistically significant influence of relevant independent variables on the dependent variable, we created models based on linear regression equations.

Performance of copeptin and CCTA in the prediction of acute myocardial infarction was assessed in a receiver operating characteristics (ROC) analysis using the area under the ROC curve (AUC). Change in 2 AUC was tested by DeLong et al.[6]

The analysis was carried out using R statistical software package Version 4.0.2 (© The R Foundation for Statistical Computing), RStudio Version 1.3.959 (© 2021–2020 RStudio), PBC, IBM SPSS Statistics Version 23, G*Power Version 3.1.9.4, and Jamovi software, Version 1.8.4.

Relationships between variables were considered statistically significant when the *P* value was <.05 ($P < .05$) and a statistical test power of 1 – ß was equal to 0.95 (1 – ß = 0.95).

3. Results

3.1. Study population

In this analysis, 146 patients were included, who underwent full workup for chest pain in ED following 6 months of follow-up. Eighty-nine patients (61.0%) were diagnosed with ACS at ED, but only 57% of them was diagnosed with acute myocardial infarction (n = 51). (Patient flow diagram of the study see **Fig. 1**). One patient developed ST-segment elevation in ECG during ED stay and was excluded from the study.

Baseline characteristics of the study population are shown in **Table 1**. The patients' average age was 63 ± 13.4 years; 95 (65.1%) were male.

The patients had higher risk of myocardial infarction if their medical history included hypertension, dyslipidemia, prior stroke, and carotid stenosis (>50%; $P < .05$; Fig. 1, Supplemental Digital Content, http://links.lww.com/MD/G950).

3.2. Risk scores in the study population

GRACE and HEART risk scores were calculated for every included patient. GRACE median value was 87.5 (67.5–108), HEART score 4.00 (3.00–6.00) points. Areas under the ROC curves were calculated for each score independently and in combination with copeptin for diagnosis of myocardial infarction. For GRACE area under the ROC curve (confidence interval [CI] 95%) was 0.720 (0.638–0.802), and HEART score was 0.831 (0.765–0.897). Copeptin alone AUC was 0.715 (0.626–0.803). For risk stratification, we combine GRACE and HEART score with copeptin, and we find out that combination with HEART score can improve diagnoses of myocardial infarction (AUC 0.764 vs AUC 0.864 $P = .0008$; **Fig. 2**).

Table 1

Baseline characteristics of the study population stratified by final diagnosis.

Variables	Total, n = 146	MI, n = 51	Non-MI, n = 95	*P* value
Demographics				
Age, yr	63.6 ± 13.4	66.5 ± 10.7	62.1 ± 14.5	.055
	63.0 (19.8)	68.0 (16.6)	62.0 (21.5)	.089
Male	95 (65.1)	34 (66.7)	61 (64.2)	.856
Risk factors				
Family history of coronary artery disease	58 (40.3)	22 (44.0)	36 (38.3)	.593
Smoking	35 (24.1)	14 (28.0)	21 (22.1)	.541
Obesity	45 (30.8)	45 (30.8)	29 (30.5)	1
Arterial hypertension	122 (83.6)	48 (94.1)	74 (77.9)	.011
Diabetes mellitus	20 (13.7)	9 (17.6)	11 (11.6)	.322
Dyslipidemia	98 (67.1)	46 (90.2)	51 (54.7)	<.001
Examination				
Heart rate, BPM	75.9 ± 16.9	76.7 ± 18.8	75.5 ± 15.9	.684
	72.0 (19.8)	75.0 (20.0)	70.0 (19.5)	.887
SBP, mm Hg	153.0 ± 30.9	151.9 ± 31.7	153 ± 30.6	.764
	147.5 (42.0)	145.0 (37.0)	150 (46.5)	.701
DBP, mm Hg	84.1 ± 14.2	83.8 ± 13.4	84.3 ± 14.7	.846
	82.5 (15.0)	80.0 (15.0)	83.0 (15.)	.701
Medical history				
CHF	37 (25.3)	14 (27.5)	23 (24.2)	.693
Previous MI	32 (21.9)	15 (29.4)	17 (17.9)	.142
Previous PCI	36 (24.7)	17 (33.3)	19 (20.0)	.106
Coronary angiography without PCI	8 (5.5)	2 (3.9)	6 (6.3)	.714
CABG	11 (7.5)	3 (5.9)	8 (8.4)	.748
Chronic kidney disease	6 (4.1)	0 (0.0)	6 (6.3)	.092
Carotid artery disease	8 (5.5)	6 (11.8)	2 (2.1)	.022
Stroke	12 (8.2)	9 (17.6)	3 (3.2)	.004
ECG				
SR	133 (91.1)	45 (88.2)	88 (92.6)	.585
ST depression	22 (15.1)	13 (25.5)	9 (9.5)	.010
T inversion	30 (20.5)	11 (21.6)	19 (20.0)	.823
LBBB	7 (4.8)	1 (2.0)	6 (6.3)	.240
Patient logistics				
Time spent in the ED, h	4.40 ± 2.44	4.30 ± 2.77	4.45 ± 2.26	.729
	3.58 (2.98)	3.02 (3.20)	3.80 (2.81)	.190
ED ACS	89 (61.0)	51 (100)	38 (40)	<.001
Admission to hospital	93 (64.1)	51 (100)	42 (44.2)	<.001
Coronary angiography	85 (58.2)	51 (100)	95 (100)	<.001
PCI	44 (30.1)	40 (78.4)	4 (4.2)	<.001
Follow-up				
Myocardial infarction in 6 mo	7 (4.8)	3 (5.9)	4 (4.2)	.206
Readmission in 6 mo	17 (11.6)	10 (19.6)	7 (7.4)	.028
Laboratory test results				
BNP	123 (353)	259 (51)	64.8 (54.7)	.02
Troponin I	17.4 (110)	206 (520)	5.50 (234)	<.001
Copeptin	8.59 (16.6)	15.2 (13.8)	4.95 (2.25)	<.001

Values are expressed as n, mean ± SD or n, % unless otherwise stated. Significant *P* values (<.05) are presented in bold.

ACS = acute coronary syndrome, BNP = B-type natriuretic peptide, BPM = beats per minute, CABG = coronary artery bypass graft surgery, CHF = chronic heart failure, COPD = chronic obstructive pulmonary disease, DBP = diastolic blood pressure, ECG = electrocardiogram, ED = emergency department, HR = heart rate, LBBB = left bundle branch block, MI = myocardial infarction, n = number of subjects with available data, PCI = percutaneous coronary intervention, SBP = systolic blood pressure, SR = sinus rhythm.

3.3. Copeptin in the study population

The median value of copeptin concentration in the study cohort was 8.69 (2.6–19.2) pmol/L. Comparison of patients with plasma copeptin concentration above and below laboratory cut-offs is shown in Table 1 (Supplemental Digital Content, http://links.lww.com/MD/G950). Patients, with elevated copeptin were older, had higher risk scores according to GRACE and HEART and were more likely to be admitted to hospital and diagnosed with ACS in ED.

Areas under the ROC were calculated for troponin I, copeptin, and combination of both (**Fig. 3A–C**). For copeptin, AUC was 0.715 (95% CI 0.629–0.803), and combination with troponin, AUC of 0.770 (95% CI 0.703–0.855) did not improve rule-in of myocardial infarction.

We divided patients who were finally diagnosed with myocardial infarction according to onset of symptoms into 3 groups. **Figure 4** clearly shows that high-sensitivity troponin I concentration are strongly dependent on time after onset of chest pain while copeptin remains the same (troponin median [interquartile range] 38.8 [78.4] vs 192 [907] vs 282 [977], $P = .013$; copeptin 25.6 924.70 vs 19.6 976.40 vs 10.6 [18.4], $P = .276$).

3.4. CCTA in the study population

CCTA was performed in 33 patients. CCTA revealed no or minimal (<20%) stenosis in 17 (12.1%) patients, 20% to 70% stenosis in 1 or more vessels in 14 (12.0%), and >70% stenosis in 2 (1.4%).

3.5. Evaluation of chest pain patients

We find out that with high-sensitivity troponin assay alongside prior stroke, history of carotid stenosis, dyslipidemia, ECG changes (ST depression) are good predictors of myocardial infarction ($\chi^2 = 52.29$, $P < .001$), area under the curve (AUC = 0.875 95% CI 0.813–0.937], $P < .001$; **Fig. 5A**).

We analyze model with CCTA and copeptin to optimize ED ACS rule-out.

The regression analysis showed that combination of copeptin and negative CCTA can be used for ACS rule-out ($\chi^2 = 26.36$, $P < .001$). A ROC curve analysis for model showed a modest AUC of 0.772 (0.681–0.863) but a high negative predictive value of 96.25% (**Fig. 5B**).

3.6. Prognostic role of model

Overall, there were 7 deaths during 6 months of follow-up (mortality rate 4.8%) and 17 readmissions due to various reasons. The number of cases was too small to evaluate mortality prediction of copeptin and CTA. There were no deaths, major adverse cardiac events, or readmission in the group of patients with both negative copeptin and troponin. That is true for CCTA without significant stenosis.

4. Discussion

The present study reveals the importance of risk assessment and medical history for rule-in and new possibilities to rule-out safely ACS using combination of copeptin and CCTA.

Ischemic heart disease is the number 1 cause of death and disability globally. Lithuania alongside with Bulgaria, Latvia, Estonia, and the Czech Republic has the highest prevalence.[7] According to the Health Information Centre of the Institute of Hygiene, preliminary statistics for 2020, cardiovascular disease remains the top cause of death, accounting for more than half (52.7%) deaths and 508.7 deaths per 100,000 population in 2020 from ischemic heart disease ischemic heart disease in Lithuania.[8]

Risk stratification for chest pain patients is important and more studies suggest it should start in prehospital care.[9,10] Other looks for triage nurse tool to assess self-reporting chest pain patients.[11] HEART score, although easy to use, has disagreements due to subjective components.[12] GRACE score is widely investigated[13] and recommended but in real-time settings, clinicians tend to go by their clinical gestalt instead. In

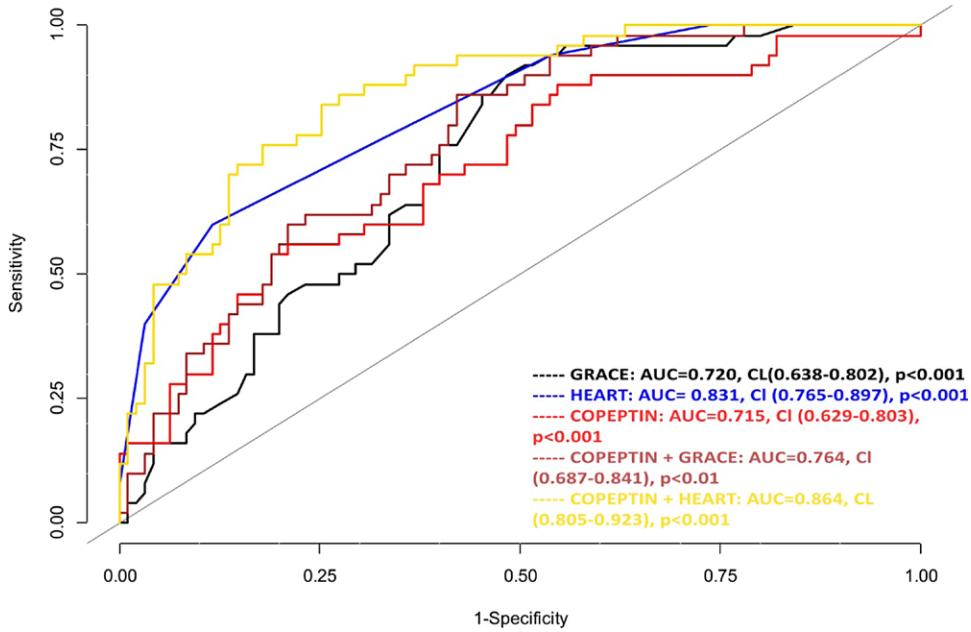

Figure 2. Receiver operating characteristic curves for GRACE, HEART, copeptin, and their combinations to predict myocardial infarction. **P* values < .001 for all variables. AUC = area under the curve, CI = confidence interval, GRACE = Global Registry of Acute Coronary Events score, HEART = History, ECG, Age, Risk factors, Troponin.

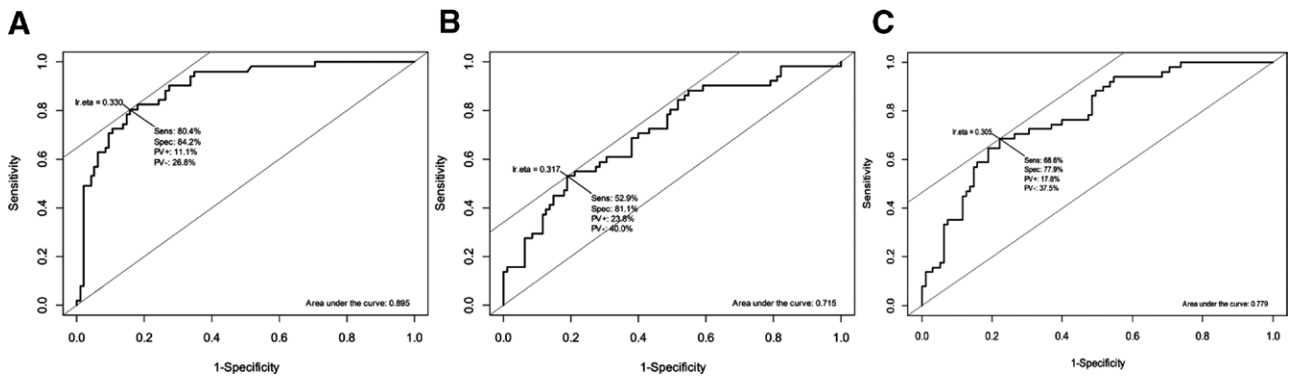

Figure 3. Receiver operating characteristic curves for (A) troponin I, (B) copeptin, and (C) combinations of both biomarkers to predict myocardial infarction. **P* values < .001 for all variables.

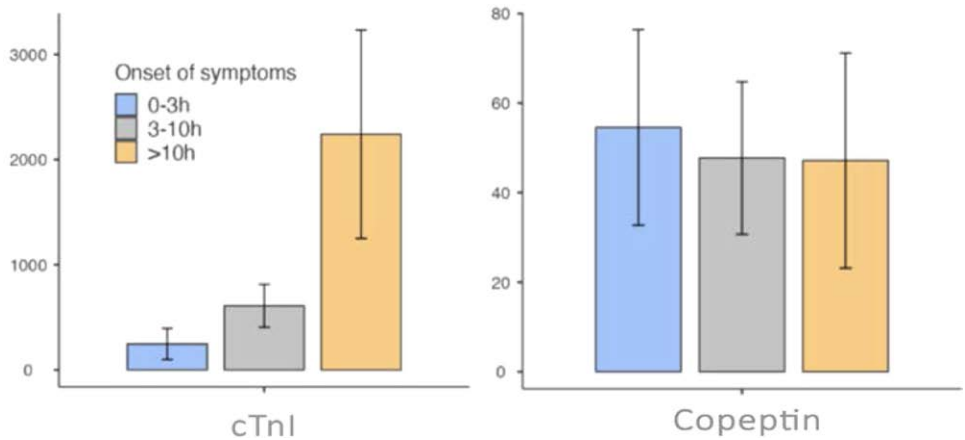

Figure 4. Hs-TnI and copeptin concentrations according to onset of symptoms. Hs-TnI = high-sensitive troponin I.

our study, we confirm that HEART and GRACE score are both equally good. Though we find out that medical history is very important for rule-in especially prior stroke, carotid stenosis, and history of dyslipidemia and should not be forgotten.

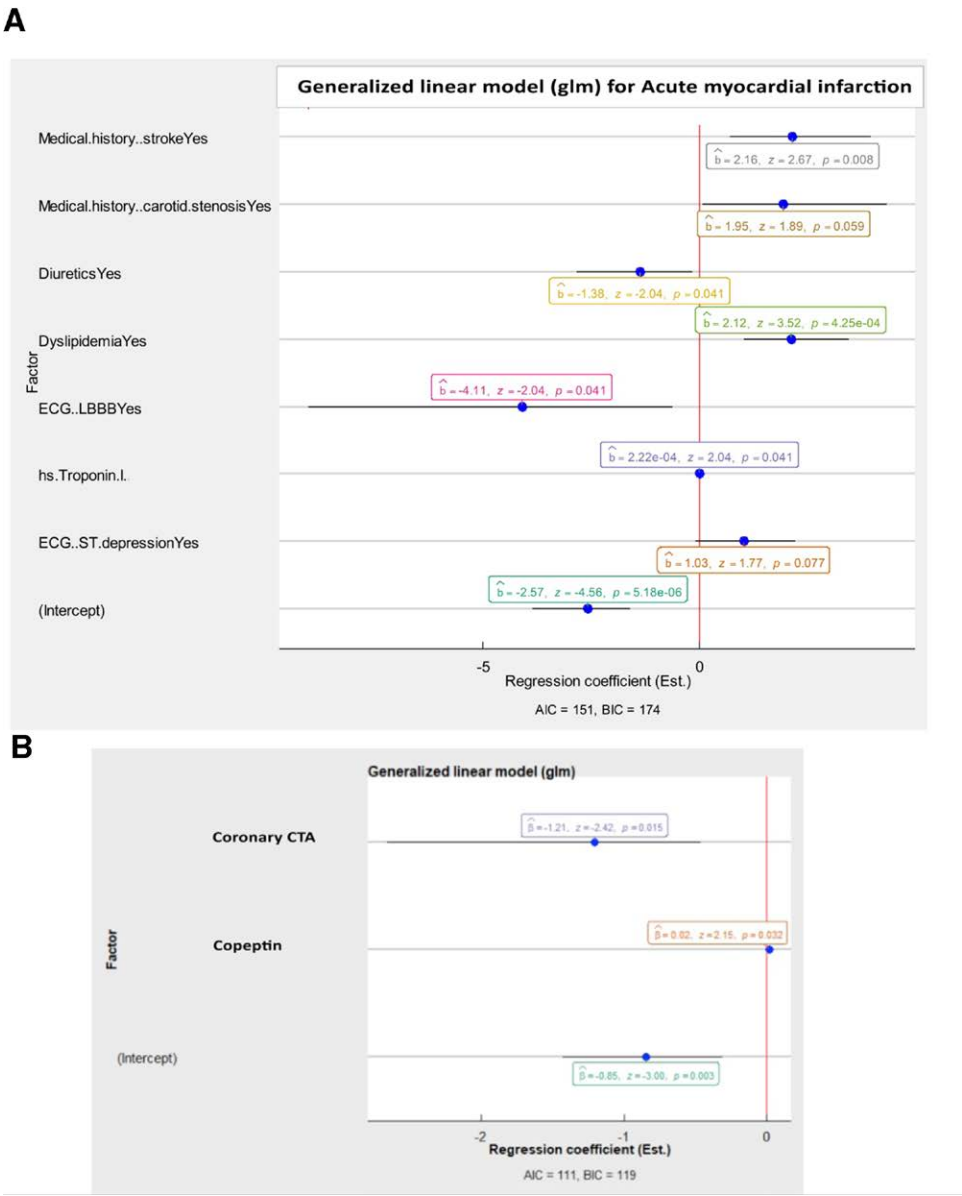

Figure 5. (A) Regression model for rule-in. (B) Regression model for rule-out. CTA = computed tomography angiography, ECG = electrocardiogram, LBBB = left bundle branch block.

Although with high-sensitivity troponin is easily available in almost every hospital, we should not forget that ECG changes (LBBB or ST depression) also hold greater risk for patients with acute chest pain.

Arginine vasopressin (AVP; known as antidiuretic hormone) is important in human physiological homeostasis of fluid balance and in regulation of the endocrine stress response and also known as antidiuretic hormone.[14] The structure of AVP was first described in 1953 by Roger Acher.[15] Therefore, clinical use of AVP has never entered daily practice because it is too complicated to measure.[16] Differently, copeptin, the C-terminal part of pro-AVP, was found to be simple to measure a surrogate marker of AVP release.[17] Copeptin as a biomarker is investigated in different clinical fields: diagnostic ability of diabetes insipidus,[18,19] prognostic marker in critically ill patients,[20,21] it is discussed in neonates,[22] and in chronic kidney disease.[23] Last decades copeptin has been investigated in a broad spectrum of cardiovascular and cerebral diseases, such as a potential biomarker in acute heart failure[24] and neurological disease.[25,26] European guidelines[3] suggest using copeptin for the early rule-out of ACS only in settings where Hs-TnI assays are not available, which is not very likely in European countries. On the other hand, studies find that copeptin is good for early diagnosis of myocardial infarction.[27] In our study, we as well showed that copeptin rises early and potentially can be useful in patients who arrives fast from the onset of symptoms. In addition, copeptin in combination with HEART score is good for short-term risk stratification. Pro-core registry states that copeptin in combination with troponin can be used for a safe discharge.[28] There was no death or major adverse cardiac event in both negative copeptin and troponin group in our study. In meta-analysis, copeptin was found to be good prognostic marker for ACS mortality,[29,30] and in the other study, elevated copeptin was independently associated with all-cause death (ACS and non-ACS related).[31]

CCTA plays significant role in the future vision of evaluation of coronary disease in patients with ACS symptoms but no troponin elevation. It holds the potential to be safe and applicable diagnostic method with the potential to reduce hospitalization rate.[32] In our study, it seems to be a safe method for ACS

rule-out. In the model with copeptin, CCTA showed best accuracy for ACS rule-out; also, there were no deaths in the negative CCTA group within 6 months. Though it is a safe method, it takes time to prepare a patient for CCTA, has contraindications, so it potentially can lead to longer ED times. Despite that, in low to intermediate risk group, patients would benefit from CCTA in ED, as it is safe and can rule-out not only ACS but potentially coronary artery disease.

5. Limitations

This study has several limitations. First, the sample size is limited as it was not always possible to perform CCTA. Second, longer follow-up time would be beneficial for long-term mortality assessment. Finally, we believe that chest pain unit would be beneficial for this kind of study, so patients would receive faster necessary diagnostic investigation (such as stress tests, cardiac ultrasound). Because in real-life settings, patients who were discharged from ED with an unknown cause of chest pain would wait for cardiologist consult and diagnostic test longer than they did when they agree to participate in this study and that potentially may lead to worse outcome. Lastly, the sample size was too small to investigate patients in detail with normal troponin values but with significant coronary stenosis.

6. Conclusion

The present study indicates that for rule-in of ACS, practitioner should consider not only scores for risk stratification but carefully analyze medical history and nonspecific ECG changes. For those patients (medical history, ECG nonspecific changes) but with normal troponin results, we strongly suggest thorough evaluation in chest pain unit. For rule-out of ACS combination of copeptin and CCTA holds great potential.

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