VILNIUS UNIVERSITY

Renata
JUKNEVIČIENĖ

Diagnosis of Non-ST-Segment Elevation Acute Coronary Syndromes by Testing Myocardial Injury and Stress Biomarkers in the Emergency Department

SUMMARY OF DOCTORAL DISSERTATION

Medicine and Health Sciences,
Medicine (M001)

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The dissertation was prepared between 2016 and 2021 at Vilnius University.

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VILNIAUS UNIVERSITETAS

Renata
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Ūminių vainikinių arterijų sindromų be ST segmento pakilimo diagnostika Priėmimo-skubios pagalbos skyriuje, naudojant miokardo pažeidimo ir streso žymenis

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ABBREVIATIONS

ABP	Arterial blood pressure
ACS	Acute coronary syndromes
AMI	Acute myocardial infarction
BMI	Body mass index
BNP	B-type natriuretic peptide
CABG	Coronary artery bypass grafting
CCTA	Coronary computed tomography angiography
COPD	Chronic obstructive pulmonary disease
CRP	High-sensitivity C-reactive protein
cTnI	Cardiac troponin I
DM	Diabetes mellitus
ECG	Electrocardiography
ED	Emergency department
HF	Heart failure
HR	Heart rate
LBBB	Left bundle branch block
MACE	Major adverse cardiovascular event
MI	Myocardial infarction
PAH	Primary arterial hypertension
PE	Pulmonary artery thromboembolism
PCI	Percutaneous coronary intervention
RBBB	Right bundle branch block
ROC	Receiver operating characteristics
SD	Standard deviation
ST segment	ECG segment between the end of the QRS complex and the beginning of the T wave
STE	ST segment elevation on ECG
VUH SK	Vilnius University Hospital Santaros Klinikos

CONTENTS

1. INTRODUCTION

1.1. The problem and relevance of the study

According to the World Health Organization, cardiovascular diseases are the leading global causes of death, resulting in the deaths of up to 17.9 million people annually [1]. According to the 2020 data of the Health Information Center of the Institute of Hygiene, 52.7% of all deaths in Lithuania resulted from cardiovascular diseases (9.8% more than in 2019) [2].

Chest pain is one of the most common complaints of non-traumatic origin in emergency departments. It is also one of the most common complaints (16%) that lead to emergency medical services calls [3]. Most often, these patients are not diagnosed with acute cardiovascular diseases at the emergency department, but with diseases of skeletal muscles, the digestive tract, or pulmonary or psychiatric diseases. The rest of these patients are ultimately diagnosed with other life-threatening conditions, such as aortic dissection or pulmonary artery thromboembolism (PE). About 10% of these patients are eventually diagnosed with an acute myocardial infarction (AMI) [4]. Even though chest pain is the main symptom of acute coronary syndrome (ACS), which is defined as an acute pain of a throbbing, pressing nature, other possible symptoms of ACS should be kept in mind as well: shortness of breath, epigastric pain, or pain spreading to the left arm.

Definition of acute coronary syndromes based on electrocardiogram (ECG) evaluation includes [5]:

- ***ST-segment elevation ACS.*** Patients complaining of chest pain and ST-segment elevation on ECG. These symptoms are usually indicative of total coronary artery occlusion and are treated with emergency percutaneous coronary intervention.
- ***Non-ST-segment elevation ACS.*** Based on ECG, patients may have no ST-segment elevation; ST-segment depression, T-wave inversion, or no variations are possible in the electrocardiogram.

Biomarkers have dramatically changed the diagnosis of acute

coronary syndromes. In the past, myoglobin, creatine kinase, and creatine kinase-MB used to be tested for; however, these markers are detected late when myocardial cells become necrotic. These markers also lacked specificity; therefore, the current gold standard in the diagnosis of ACS is the cardiac troponin (cTn) concentration test [6]. The latest recommendations of the European Society of Cardiology advise performing high-sensitivity cardiac troponin tests in patients complaining of chest pain and who are suspected of having ACS and repeating it in dynamic if necessary. However, although high-sensitivity cardiac troponin has accelerated the diagnosis of ACS, its specificity has decreased. Certain other diseases and conditions, including pulmonary artery thromboembolism, acute heart failure, severe sepsis, renal insufficiency, or the severe general condition of a patient, may cause high-sensitivity cardiac troponin to rise above the normal range [7].

The number of emergency department (ED) patients is increasing worldwide [8, 9]. Vilnius University Hospital Santaros Klinikos is no exception, where the ED performed 55,434 consultations in the first half of 2020, while in the first half of 2021 – as many as 89,120. Therefore, in order not to burden the work of the emergency department staff, new, speedy, and most importantly, safe algorithms for ruling out acute coronary syndrome are being sought. Currently, diagnosing patients by addressing chest pain and suspected ACS in the emergency department is complicated and time-consuming due to repeated cardiac troponin tests as well as occupied observation beds, as vital functions of patients complaining of chest pain must be observed on a monitor until the diagnosis of ACS is ruled out. On the other hand, a speedy diagnosis of acute myocardial infarction at the emergency department is crucial. From a patient's perspective, long waiting times at the emergency department are associated with stress, possible transmission of droplet infections from other patients and visitors, and dissatisfaction with the work of the emergency department. A study examining nearly 14 million patient visits to the emergency department found that long waiting times are a risk factor

for early death and hospitalization (within 7 days of ED examination) [10]. Another study showed that on days when the occupancy of the emergency department is high, not only the waiting time of patients in ED, but also the risk of death during the inpatient period and a longer period of hospitalization become increased [11]. Therefore, it is beneficial for both patients and physicians to rule out ACS quickly and safely.

One of the markers that can be used in conjunction with high-sensitivity cardiac troponin is the stress marker copeptin. It was first mentioned in the literature in 1972. It is a 39-amino acid peptide, a surrogate marker of vasopressin, which originates from a pre-hormone (prepro-vasopressin) and is released and detected in the blood as early as 10 minutes after physiological stress [12]. Patients with elevated blood levels of copeptin are at a higher risk group and may require more intensive monitoring and more detailed examinations [13]. Whereas if acute myocardial infarction is diagnosed after copeptin concentration increases, this biomarker predicts worse outcomes and death in these patients [14]. It is also important that the pathophysiology of troponins, natriuretic peptides, and copeptin reflects the different links of the homeostasis of the cardiovascular system. Therefore, a combination of biomarkers may be more beneficial compared to a single biomarker [15].

Coronary CT angiography (CCTA) is a costly, but non-invasive method of cardiovascular examination. The high negative prognostic value of this method is the reason why this examination is particularly useful in the emergency department. Furthermore, it provides additional information on coronary artery anatomy, atherosclerotic cardiovascular disease, and is important in identifying noncardiac pathology [16]. The literature indicates that this is a particularly suitable method for assessing the risk of low- and medium-risk patients being discharged from the emergency department. [17]. Another important aspect is that CCTA examination results can also be used in primary prevention; although there are not many studies and specific recommendations yet, it is believed that this examination would enable a cardiologist to

choose the optimal medicinal treatment or correction of risk factors [18]. According to the literature, if atherosclerotic variations are not detected during CCTA examination, the risk of cardiovascular disease in symptomatic patients is extremely low and equal to the baseline risk of healthy population [19].

When a patient complaining of chest pain arrives at the emergency department, detailed tests are performed, and the patient's risk is assessed. Despite a prolonged examination in ED, the cause of chest pain often remains unexplained. Therefore, a significant number of patients are hospitalized on suspicion of ACS, but after more detailed examinations, the diagnosis of non-ST-segment elevation acute myocardial infarction is not confirmed. On the other hand, although the lack of beds in the hospital is a very sore point, it is not always possible to discharge the patient for outpatient treatment safely, especially when the cause of chest pain does not become clear after the examinations are carried out in the emergency department. Also, high-risk patients are hospitalized, regardless of the results of the tests. Outpatient examination of these patients is complicated, as a patient may have to wait a long time for a consultation by both a family doctor and cardiologist, while the clinical consequences may be severe.

1.2. Research objective

Development of an algorithm to confirm and safely rule out the diagnosis of non-ST-segment elevation acute coronary syndromes by evaluating cardiovascular risk factors using high-sensitivity cardiac troponin, stress marker copeptin, and coronary CT angiography results.

1.3. Research tasks

1. To compare the risk assessment scales for acute coronary syndromes (*GRACE, HEART*) in practical emergency department work with patients who complained of chest pain.
2. To assess the differences in copeptin concentration between patients

with confirmed and unconfirmed non-ST-segment elevation acute coronary syndrome, as well as the diagnostic and prognostic potential of copeptin.
3. To assess the application possibilities of coronary CT angiography in patients for whom the cause of chest pain remains unexplained after an examination at the emergency department.
4. To develop a diagnostic tool suitable for patients with suspected non-ST-elevation acute coronary syndrome in the emergency department.

1.4. Novelty of the study

For the first time in Lithuania, we investigated the diagnostic actions of patients with suspected non-ST-segment elevation ACS in the emergency department. We performed a detailed assessment of patients' anamnesis, prescribed laboratory tests and instrumental examinations, examined time intervals and final outcomes of patients, following them up to 6 months after the first visit.

This study also used the copeptin concentration test in the diagnosis of non-ST-segment elevation acute coronary syndrome for the first time in the Lithuanian population.

We also evaluated CCTA results together with copeptin. To our knowledge there are no studies done where both copeptin and CCTA are analysed together for safely ruling out non-STE ACS.

We have developed a new mathematical diagnostic model that is not based on subjective estimates but rather on specific values of two biomarker concentrations and validated risk factors that could be used in the emergency department for patients with suspected non-ST-segment elevation ACS.

1.5. Statements to be defended

1. The HEART risk scale is more appropriate for risk assessment of patients with suspected non-ST-segment elevation acute coronary syndromes in the emergency department.
2. Copeptin concentration testing could shorten the time of examination of patients who arrive in the emergency department shortly after the onset of symptoms.
3. For patients whose cause of chest pain remains unexplained after the examination, it is appropriate to perform coronary computed tomography angiography.
4. The proposed diagnostic model can aid a physician to rule out or confirm the diagnosis of a non-ST-segment elevation acute myocardial infarction, reduce the frequency of unnecessary hospitalization in patients complaining of chest pain, and shorten the examination time of these patients in the emergency department.

2. METHODOLOGY

This study was conducted using a prospective monitoring methodology. The study was carried out at Vilnius University Hospital Santaros Klinikos (VUH SK). A permit was obtained from the Vilnius Regional Biomedical Research Ethics Committee to conduct biomedical research (No. 158200-18-985-491). This research complies with the principles of the Declaration of Helsinki [20].

Enrolled subjects were interviewed, and the anonymized data on their health records were stored in a database specially designed for the study. Epidemiological (age, gender, risk factors, data on co-morbidities) and laboratory and instrumental examinations data were collected.

The enrolment and monitoring protocol was developed by the supervisor Prof. Dr. Pranas Šerpytis and doctoral student Renata Juknevičienė. The selection of patients for the study and the monitoring of the patients were carried out by the doctoral student and physician researchers specified in the biomedical study protocol.

2.1. Enrolment protocol

Patients who were admitted to the emergency department and complained of chest pain:

A) Subjects who self-presented to the emergency department with a chief complaint of chest pain when a cardiologist suspected ACS.

B) Subjects who were brought by an emergency medical services (EMS) vehicle or with referral from other medical facilities with suspected non-STE ACS (the diagnosis was specified on EMS card or referral from another medical facility (ICD-10-AM code):

- Precordial pain (R07.2);
- Chest pain, unspecified (R07.4);
- Unstable angina pectoris (I20.0);
- Acute myocardial infarction (non-ST elevation, unspecified localization) (I21.9).

Patients who met the inclusion criteria were included in the study, and there were no exclusion criteria. All subjects signed personal information and personal consent forms before being included in the study. As the follow-up protocol is extended, the number of patients followed-up simultaneously was limited; therefore, not all patients who met the inclusion criteria were included in the study.

2.2. Study process and model

The study took place from January 2018 to September 2020 at the VUH Santaros Klinikos. The study scheme is presented in **Figure 1**.

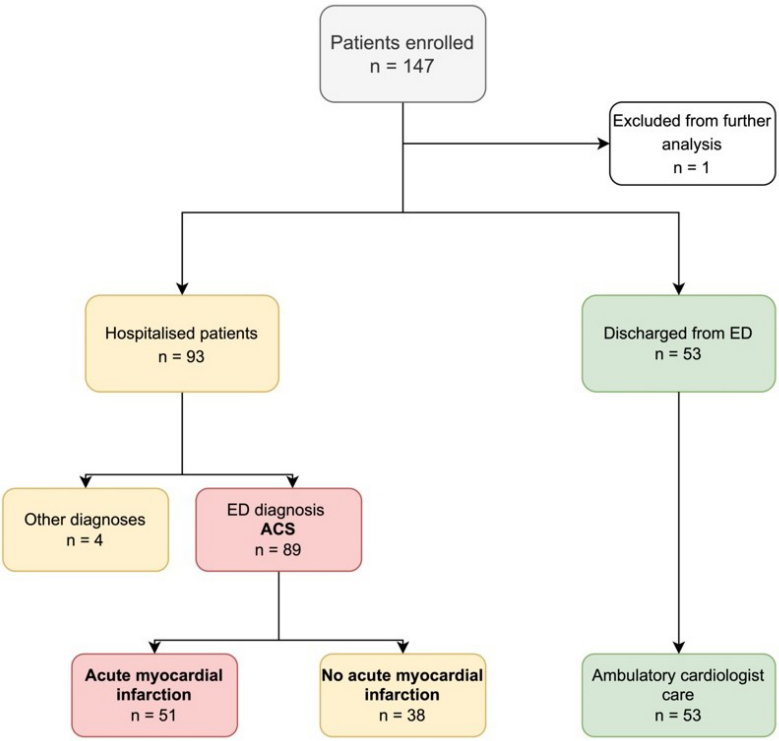

Figure 1. Study scheme.
ED – Emergency Department.

2.3. Patient inclusion criteria

1. Patients with suspected non-ST-segment elevation of acute coronary syndromes at the emergency department.
2. Informed, consenting patients who signed a personal information form and consent form.
3. Female and male patients aged > 18.

2.4. Patient exclusion criteria

1. Patients who have been informed but who have not consented and have not signed personal information and consent forms;
2. Patients diagnosed with ST-segment elevation acute myocardial infarction after recording ECG;
3. Patients who refused to continue participating in the ongoing study or who could not be contacted during follow-up;
4. Patients diagnosed with stage III–IV oncological diseases or diagnosed with a mental illness;
5. Pregnancy;
6. Hemodynamically unstable patients (after resuscitation, in cardiogenic or other shock, with systolic arterial blood pressure (sABP) < 90 mmHg, in life-threatening arrhythmias, unconscious patients).

2.5. Examination of patients in the emergency department

The patients were examined at the discretion of an attending cardiologist in the emergency department according to the valid procedures and recommendations of the institution. Patient examinations included, but were not limited to, ECG, complete blood count, high-sensitivity C-reactive protein (CRP), B-type natriuretic peptide (BNP), coagulogram, chest X-ray, and others. Also, at the discretion of the attending physician and based on the obtained examination results, consultations of other medical specialists were given. Patients were hospitalized or discharged at the discretion of the attending physician, without the intervention of the researcher.

2.6. Follow-up protocol

Patients who met the inclusion criteria and signed an informed consent form to participate in the study, and who were not hospitalized from the emergency department, were further examined (**Figure 2**). Patients came for a scheduled consultation with a cardiologist no later than one month after the discharge from ED; blood pressure measurements in the doctor's office, echocardiogram, ECG, and veloergometry examinations were performed. If after the examination the cause of chest pain remained unexplained or the veloergometry was noninformative, the patients additionally underwent CCTA.

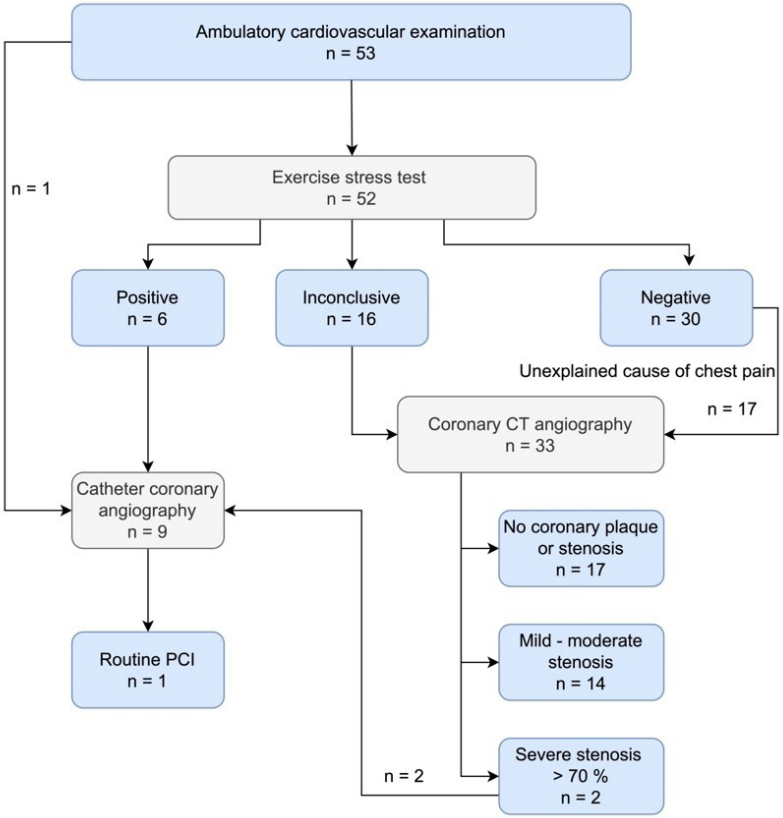

Figure 2. Follow up scheme.
n – number of subjects; CT – computed tomography; PCI – percutaneous coronary intervention.

All patients were followed up for 1 month, 3 months and 6 months after their visit at the emergency department. The following major adverse cardiovascular events (MACE) were recorded:

1. Death. A patient died of an unspecified cause after discharge from the hospital.
2. Myocardial infarction (MI). The diagnosis of MI was confirmed by medical record documentation.
3. Hospitalization for heart failure (HF) exacerbation. An episode of HF was documented in the medical record.
4. Percutaneous coronary intervention of the culprit vessel. Repeated percutaneous coronary intervention (PCI) was performed on the vessel that developed ACS.

3. RESULTS

3.1. General characteristics of study population

3.1.1. General characteristics of study population

One hundred forty-six subjects participated in the study, including 95 men (65%) and 51 women (35%). The youngest subject was 18 years old, the oldest – 91 years old. The average age of the subjects was 63.6 ± 13.4 years. Age was significantly different between men and women, with women being older (68.4 ± 11.3 and 61.1 ± 13.8 years, respectively, p = 0.0008). We divided the subjects into two groups according to the final clinical diagnosis. During the study, the diagnosis of non-ST-segment elevation acute myocardial infarction was confirmed in 51 (35%) subjects, and it was not confirmed in 95 subjects (65%). Both groups were of similar age and gender. The general characteristics of subjects according to the final clinical diagnosis are presented in **Table 1**.

Table 1. General characteristics of subjects according to the final clinical diagnosis.

Demographic data	**All, n=146**	**AMI, n=51**	**Non- AMI, n=95**	**p value**
Age, year	63.6±13,4 63.0 (19.8)	66.5 ± 10.7 68.0 (16.6)	62.1 ± 14.5 62.0 (21.5)	0.055 0.089
Male, yes (%)	95 (65.1)	34 (66.7)	61 (64.2)	0.856

AMI – acute myocardial infarction

3.1.2. Complaints

The median time from the onset of symptoms to the first medical contact was 9.5 (93) hours. The chief complaint of all subjects was chest pain. Apart from the chest pain, patients most complained of shortness of breath (23%), palpitations (8%), pain outside the chest (6%), nausea (3%), and upper abdominal pain (3%). Forty-nine percent of patients had no complaints other than chest pain. No statistically significant dependence was found between symptoms and ED diagnosis and final clinical diagnosis (p=0.868), and the effect size was extremely small (Cramer's V (φc) = 0.00). The dependence between symptoms, diagnosis of ED, and the final diagnosis is shown in **Figure 3**.

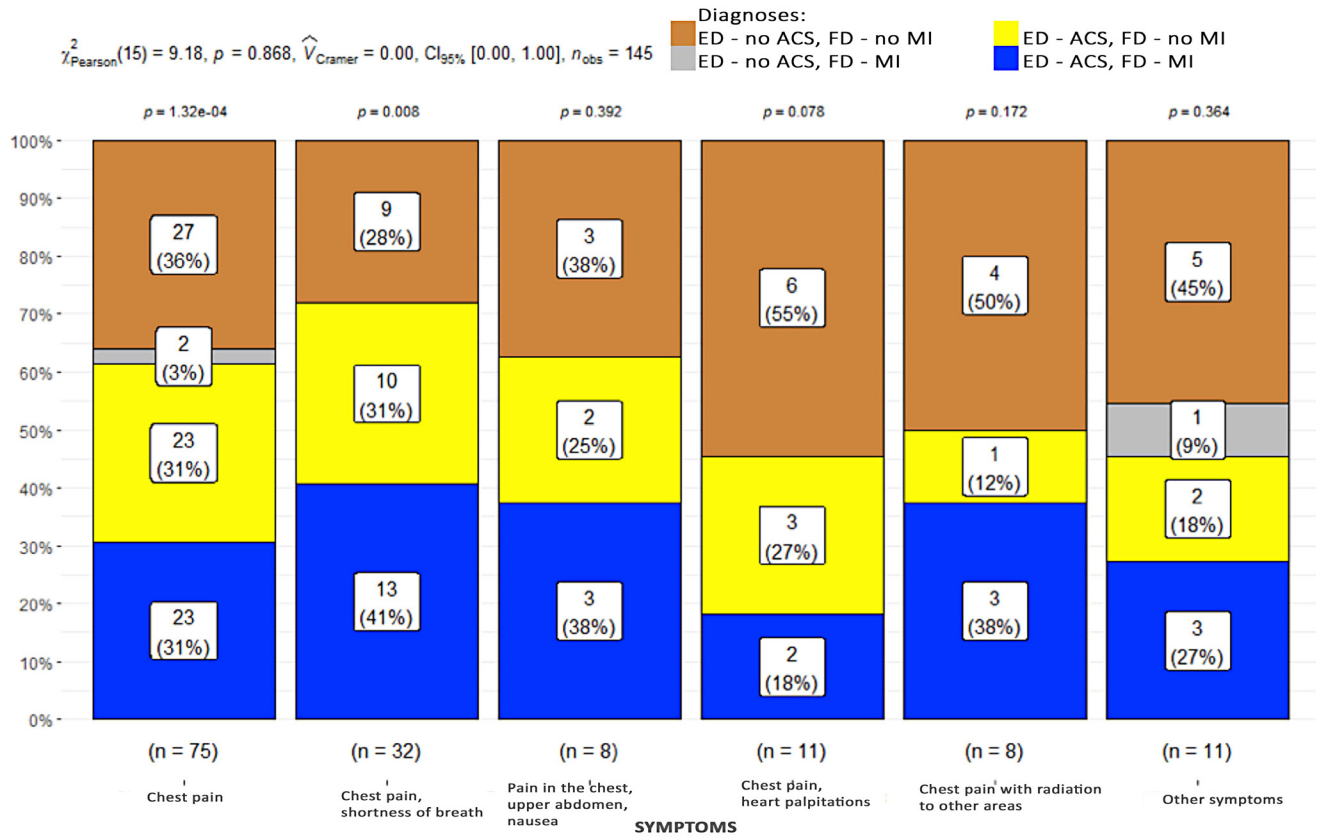

Figure 3. Dependence between symptoms, ED diagnosis, and final clinical diagnosis.

3.1.3. Anamnesis

When evaluating the anamnesis data of the subjects, 32 (22%) patients had a prior myocardial infarction, 12 (8%) had a stroke. Coronary artery bypass grafting (CABG) was performed in 11 (7.5%) patients, PCI – in 26 (25%), and invasive coronary angiography without PCI – in 8 (5.5%). Twenty (14%) patients had diabetes, bronchial asthma (BA) or chronic obstructive pulmonary disease (COPD) – 5 (3.4%), chronic kidney disease – 6 (4%), and carotid artery stenosis – 8 (5.5%) patients. Carotid artery stenosis and stroke were more frequent in patients in the MI group. Patient anamnesis characteristics are presented in **Table 2**.

Table 2. Patient anamnesis data.

Patient anamnesis data	**All, n = 146**	**AMI, n = 51**	**No AMI, n = 95**	**p value (Fisher)**
Prior MI, yes (%)	32 (21.9)	15 (29.4)	17 (17.9)	0.142
Heart failure: - with preserved LVEF - with moderately reduced LVEF - with reduced LVEF yes (%)	 27 (18.5) 7 (3.8) 3 (2.1)	 10 (19.6) 2 (3.9) 2 (3.9)	 17 (17.9) 5 (5.5) 1 (1.1)	0.693
Former PCI, yes (%)	36 (24.7)	17 (33.3)	19 (20.0)	0.106
Invasive coronary angiography without PCI, yes (%)	8 (5.5)	2 (3.9)	6 (6.3)	0.714
CABG, yes (%)	11 (7.5)	3 (5.9)	8 (8.4)	0.748
Chronic kidney disease, yes (%)	6 (4.1)	0 (0.0)	6 (6.3)	0.092
Carotid artery stenosis, yes (%)	8 (5.5)	6 (11.8)	2 (2.1)	**0.022**
BA/COPD, yes (%)	5 (3.4%)	4 (4.2)	1 (2.0)	0.658
Stroke, yes (%)	12 (8.2)	9 (17.6)	3 (3.2)	**0.004**

CABG – coronary artery bypass grafting; BA – bronchial asthma; DM – diabetes mellitus; LVEF – left ventricular ejection fraction; COPD – chronic obstructive pulmonary disease; MI – myocardial infarction; PCI – percutaneous coronary intervention.

3.1.4. Objective examination data

ABP mean value on admission to the emergency department was 153 ± 31/84 ± 13 mmHg, HR – 76 ± 17 bpm. BMI mean value was 29 ± 5 kg/m^2. The clinical data did not differ between subjects with and without confirmed MI and are presented in **Table 3**.

Table 3. Objective examination data of subjects.

Clinical data	All, n = 146	AMI, n = 51	No AMI, n = 95	P value (Fisher)
Heart rate, HR bpm	75.9 ± 16.9 72.0 (19.8)	76.7 ± 18.8 75.0 (20.0)	75.5 ± 15.9 70.0 (19.5)	0.684 0.887
sABP, mmHg	153.0 ± 30.9 147.5 (42.0)	151.9 ± 31.7 145.0 (37.0)	153 ± 30.6 150 (46.5)	0.764 0.701
dABP, mmHg	84.1 ± 14.2 82.5 (15.0)	83.8 ± 13.4 80.0 (15.0)	84.3 ±14.7 83.0 (15.0)	0.846 0.701
BMI, kg/m^2	28.6 ± 5.3 27.7 (7.8)	28.8 ± 5.5 27.8 (7.8)	28.5 ± 5.2 27.7 (7.8)	0.787 0.794

dABP – diastolic arterial blood pressure; BMI – body mass index; sABP – systolic arterial blood pressure.

3.1.5. Risk factors

The subjects had an average of 2.6 ± 0.7 risk factors. The most common risk factor was primary arterial hypertension (PAH), which was documented in 122 patients (83.6%), and dyslipidaemia, documented in 98 subjects (67.1%). MI patients were more likely to have PAH and dyslipidaemia; the frequency of risk factors is presented in **Table 4**.

Table 4. Risk factor data of subjects.

Risk factors	All, n = 146	AMI, n = 51	No AMI, n = 95	P value (Fisher)
Family history of coronary heart disease, yes (%)	58 (40.3)	22 (44.0)	36 (38.3)	0.593
Smoking, yes (%)	35 (24.1)	14 (28.0)	21 (22.1)	0.541
Obesity, yes (%)	45 (30.8)	45 (30.8)	29 (30.5)	1
PAH, yes (%)	122 (83.6)	48 (94.1)	74 (77.9)	**0.011**
DM, yes (%)	20 (13.7)	9 (17.6)	11 (11.6)	0.322
Dyslipidaemia, yes (%)	98 (67.1)	46 (90.2)	51 (54.7)	**<0.001**

DM – diabetes mellitus; PAH – primary arterial hypertension; AMI – acute myocardial infarction.

3.1.6. GRACE risk assessment scale

The average GRACE score in the studied sample was 87.8 ± 27.0 points, minimum – 24, maximum – 139. There were 111 (76%) subjects in the low-risk group, and 35 (24%) subjects in the medium-risk group. In the AMI group, the *GRACE* median was 100 (29.0) points, in the no AMI group – 77 (42.5) points, p <0.001. **Figure 4** shows the *GRACE* risk scale histogram and violin boxplot.

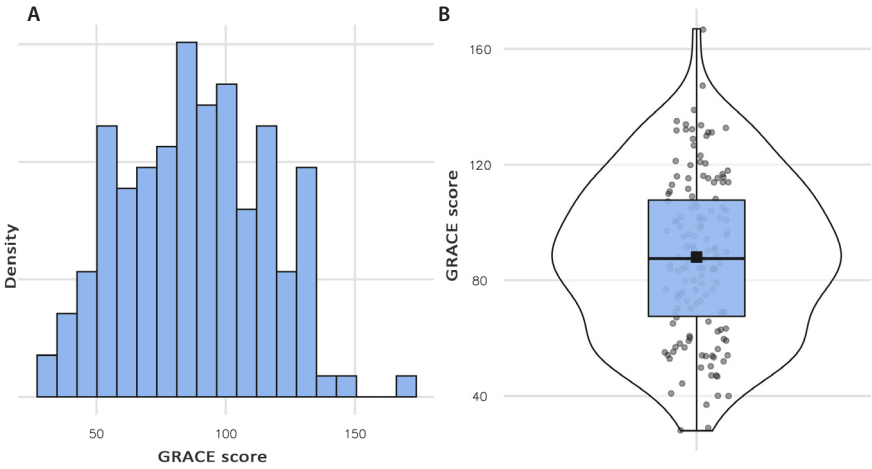

Figure 4. GRACE risk assessment scales for all subject: **A** histogram, **B** violin boxplot.

3.1.7. HEART risk assessment scale

The average *HEART* score in the studied sample was 4.45 ± 1.80 points, minimum – 0, maximum – 9. There were 47 (32%) subjects in the low-risk group, 76 (52%) subjects in the medium-risk group, and 23 (16%) subjects in the high-risk group. **Figure 5** shows the *HEART* risk scale histogram and violin boxplot.

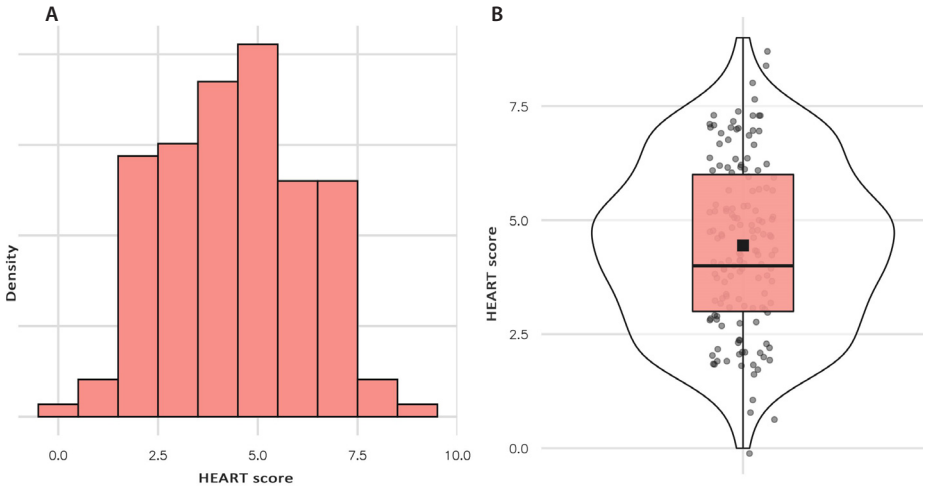

Figure 5. *HEART* risk assessment scales for all subjects: **A** histogram, **B** violin boxplot.

3.1.8. Laboratory blood tests

All patients with suspected ACS underwent standard tests at the emergency department according to the clinical assessment of an attending physician. When evaluating the laboratory data of blood tests, the most common were troponin I concentration test, complete blood count, and creatinine in blood serum; the least common was BNP. Total leukocyte count, BNP, CRP, and glucose medians were higher in the MI group; all study laboratory results (median (IQR)) are presented in **Table 5.** The average time from ordering tests to receiving a response for all laboratory tests was 1.48 ± 0.77 h.

Table 5. Laboratory test results between groups.

Indicators	**n**	**All, n = 146**	**AMI, n = 51**	**No AMI, n = 95**	**P value**
Total leukocyte count $\times 10^9$/l	146	7.37 (3.15)	8.76 (4.10)	6,83 (2.84)	**<0.001**
Haemoglobin, g/l	146	139,0 (21.0)	136 (25)	142 (18)	0.097
BNP (ng/L)	42	139,0 (21.0)	259 (373)	64.8 (150)	**0.02**

Indicators	n	All, n = 146	AMI, n = 51	No AMI, n = 95	P value
CRP (mg/L)	140	2.08 (4.62)	2.56 (9.16)	1.73 (4.19)	**0.022**
Serum glucose (mmol/l)	127	6.02 (1.2)	6.28 (1.55)	5.92 (0.95)	**0.02**
Potassium (mmol/L)	145	4.30 (0.50)	4.25 (0.48)	4.30 (0.50)	0.741
Sodium (mmol/L)	145	140,0 (3.5)	140 (2.75)	140 (4.00)	0.719
Creatinine (μmol/L)	146	82.0 (28.0)	82 (27.8)	81 (27.0)	0.917
D-dimers (μg/L)	108	163 (198)	203 (213)	148 (165)	0.129

BNP – B-type natriuretic peptide; CRP – high-sensitivity C-reactive protein.

Troponin I

High sensitivity cTnI was performed on all subjects in the study; the concentration median was 17.4 (111.9) ng/L, the minimum concentration was 0 ng/L, and the maximum concentration was 22159 ng/L. First and repeat troponin I results are presented in **Table 6**. The area under the ROC curve for the first performed troponin I to confirm the diagnosis of non-ST-segment elevation myocardial infarction was AUC – 0.895 (95% CI 0.765–0.897) (based on the first troponin estimate suggested by the 0/1-hour algorithm). **Figure 6** shows the first troponin I concentration histogram, rectangular plot, and ROC curve. In 40 (27.4%) subjects, the troponin concentration test was repeated in dynamics.

Table 6. Laboratory test results for troponin I.

Biochemical indicators	n	Mean ± SD	Median (IQR)
Troponin I (ng/L)	146	655.67 ± 2894	17.4 (111.9)
Troponin I (ng/L) unrepeated in dynamics	100	870 ± 3375	15.6 (110)
Troponin I (ng/l) repeated in dynamics	40	398 ± 1138	77.3 (319)

IQR – interquartile range; n – number of subjects; SD – standard deviation.

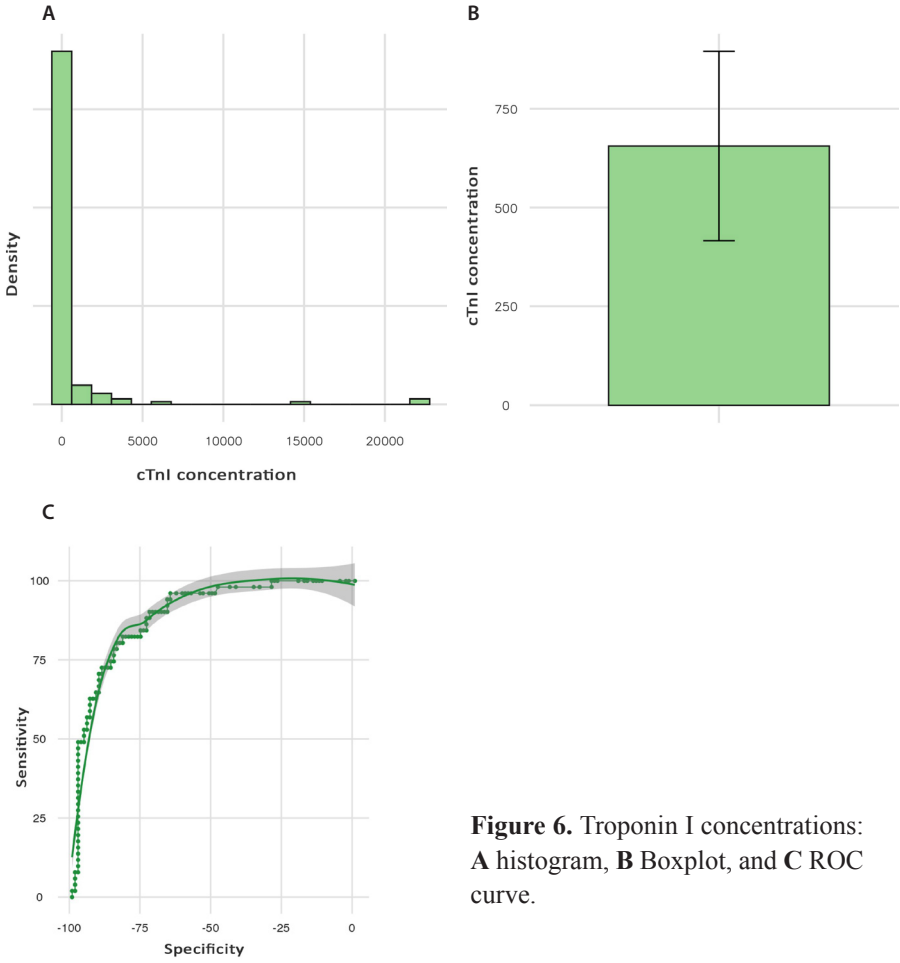

Figure 6. Troponin I concentrations: **A** histogram, **B** Boxplot, and **C** ROC curve.

Copeptin

Copeptin concentration was measured for all subjects participating in the study; its mean concentration was 25.48 ± 62.67 pmol/L, minimum concentration – 0.75 pmol/L, maximum – 237 pmol/L. Copeptin concentration results are presented in **Table 7**. The copeptin area under the ROC curve for confirming the diagnosis of non-ST-segment elevation myocardial infarction was 0.715 (95% CI 0.626–

0.803). The chosen threshold value is selected according to the normal value determined by the laboratory. **Figure 7** shows the copeptin concentration histogram, boxplot, and ROC curve.

Table 7. Laboratory test results for copeptin.

Biochemical indicator	n	Mean ± SD	Median (IQR)
Copeptin, (pmol/l)	146	22.8 ± 41.9	8.48 (17.0)

IQR – interquartile range; n – number of subjects; SD – standard deviation.

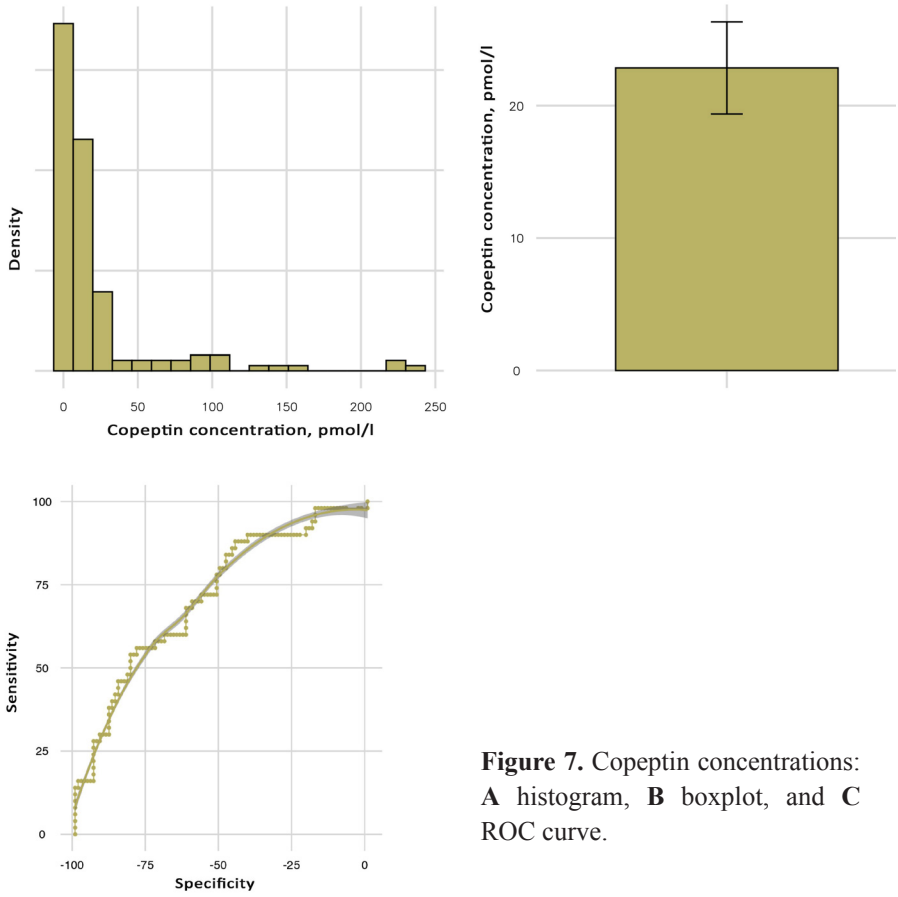

Figure 7. Copeptin concentrations: **A** histogram, **B** boxplot, and **C** ROC curve.

3.1.9. Instrumental examinations

The ECG test was performed on all the subjects who participated in the study; 9 of them had the ECG test repeated in the emergency department. Most of the subjects were diagnosed with sinus rhythm (91.1%). ST segment depression (p= 0.01) is more common in the AMI group. All ECG readings are listed in **Table 8**.

Table 8. ECG readings of subjects.

ECG readings	All, n = 146	AMI, n = 51	No AMI, n = 91	P value
SR, yes (%)	133 (91.1)	45 (88.2)	88 (92.6)	0.585
ST segment depression, yes (%)	22 (15.1)	13 (25.5)	9 (9.5)	**0.010**
T wave inversion, yes (%)	30 (20.5)	11 (21.6)	19 (20.0)	0.823
LBBB, yes (%)	7 (4.8)	1 (2.0)	6 (6.3)	0.240
RBBB, yes (%)	13 (8.9)	5 (9.8)	8 (8.4)	0.769
Other variations yes (%)	37 (25.3)	18 (35.3)	19 (20.0)	**0.048**

RBBB – right bundle branch block; ECG – electrocardiography; LBBB – left bundle branch block; n – number of subjects; MI – myocardial infarction; SR – sinus rhythm.

For subjects who complained of chest pain, the second most frequent instrumental examination was a chest X-ray. Echocardiogram is rarely performed in the emergency department, and was performed only in 3.4% of all cases. Other examinations (abdominal ultrasound examination, computed tomography other than chest CTA) were performed in 5 patients. **Table 9** shows instrumental examinations performed on the subjects at ED.

Table 9. Instrumental examinations performed on subjects at ED.

Instrumental examinations	n	%
Chest X-ray	18	12.3
Echocardiogram	5	3.4
Chest CTA	6	4.1
Other instrumental examinations	5	3.4

CTA – computed tomography angiograph.; n – number of subjects; ED – emergency department.

3.1.10. Subjects' time spent in the emergency department, final diagnoses, and subjects' outcomes

The average time spent in the emergency department was 4.40 ± 2.44 hours (the shortest time – 1 hour, the longest – 12.9 hours); 41.8% of subjects complaining of chest pain spent more than 4 hours at the ED.

At the emergency department, 61% (89) of subjects were diagnosed with ACS, 94 subjects were hospitalized (89 for ACS, 4 for other conditions); 52 subjects were hospitalized in the general cardiology department, 28 in the department of interventional cardiology, and 13 were hospitalized in the intensive care unit. Eighty-five subjects underwent invasive coronary angiography, of which 44 (51.8%) underwent PCI. In 27 subjects, the culprit vessel was the anterior interventricular branch of the left coronary artery (Latin *ramus interventricularis anterior a. coronariae sinistrae*). The mean time from arrival at ED to invasive coronary angiography was 44.3 ± 42.7 hours. In the non-acute myocardial group (n = 38), the diagnoses differed as follows: atherosclerotic cardiovascular disease, stable angina pectoris was diagnosed in 26 (67%), heart rhythm disorders – in 4 (10%), primary arterial hypertension – in 4 (10%), other diseases (PE, connective tissue, musculoskeletal diseases, bile duct obstruction, chronic kidney disease) – in 5 patients (13%).

Subjects ruled out for ACS and discharged from ED (53) for outpatient treatment were referred to a cardiologist for a scheduled outpatient examination as soon as possible, but no later than within the first month of discharge from ED. Fifty-two subjects underwent an exercise tolerance test (veloergometry) on an outpatient basis; it was evaluated as negative for 30 (58%) subjects, non-informative for 16 subjects (31%), and positive for 6 (11%) subjects. Among subjects with an uninformative or negative exercise stress test, for whom the cause of chest pain remained unexplained from the point of view of an attending cardiologist, 33 (22.7%) underwent CCTA. Nine (6.2%) patients underwent planned coronary angiography, with one of them undergoing PCI.

The final clinical diagnosis of non-ST-segment elevation acute myocardial infarction (AMI group) was confirmed in 51 patients (1 in the outpatient unit and 50 in hospitalized patients). It should be noted that the diagnosis of the absence of acute myocardial infarction is determined quite accurately by ED. However, impatient diagnosis of AMI is only confirmed in 56% of cases after the diagnosis of ACS by ED. The number of subjects and the correspondence of the final clinical diagnosis to the diagnosis by ED are shown in **Figure 8**. We see a statistically significant ($p<0.0001$) and moderate association between ACS ED and final clinical diagnosis after re-evaluation ($\varphi_c = 0.49$).

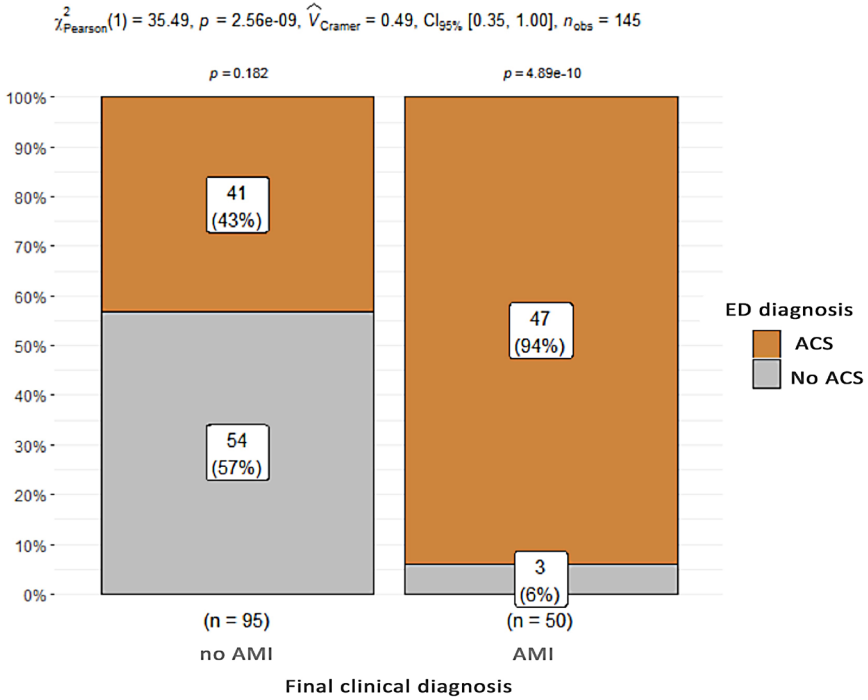

Figure 8. Correspondence between final diagnosis and ED diagnosis.
AMI – acute myocardial infarction; ED – emergency department; ACS – acute coronary syndrome.

The follow-up of the subjects continued for 6 months after their visit to ED. Within 6 months, major adverse cardiovascular events were documented in 7 patients (5 died, 5 underwent repeat PCI), 17 subjects were re-hospitalized for various causes.

3.2. Comparison of prognostic risk assessment scales

3.2.1. Assessment of the effectiveness of GRACE risk scale

To assess the prognostic values of the GRACE risk scale more accurately, we plotted an approximating curve, calculated the optimal threshold value using Youden's index, and calculated the prognostic accuracy of this threshold value for MACE.

The approximating curve for the *GRACE* indicator describing the dependence of the risk of the presence of MACE is shown in **Figure 9**.

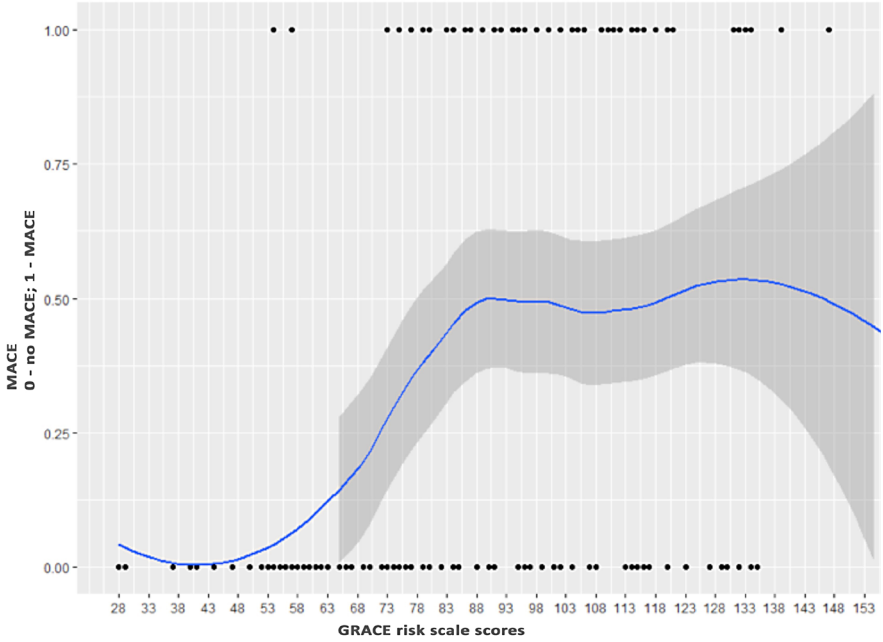

Figure 9. Approximating curve for the GRACE risk scale.
MACE – major adverse cardiac events.

The optimal threshold value for *GRACE* is 79.00. The value of 79.00 on the abscissa rises to the 0.42 mark on the ordinate. As we can see, the approximating curve does not rise above the 0.52 mark on the ordinate axis, which indicates that we could diagnose MACE according to the *GRACE* indicator with a probability no higher than 0.52.

Figure 10 shows the dependence between risk groups according to the *GRACE* risk assessment scale and the final clinical diagnose. Cramer's effect size demonstrates a statistically significant (p=0.003) yet weak dependence between the *GRACE* risk group and the final clinical diagnosis (φ=0.24). In the low-risk group, there is a statistically

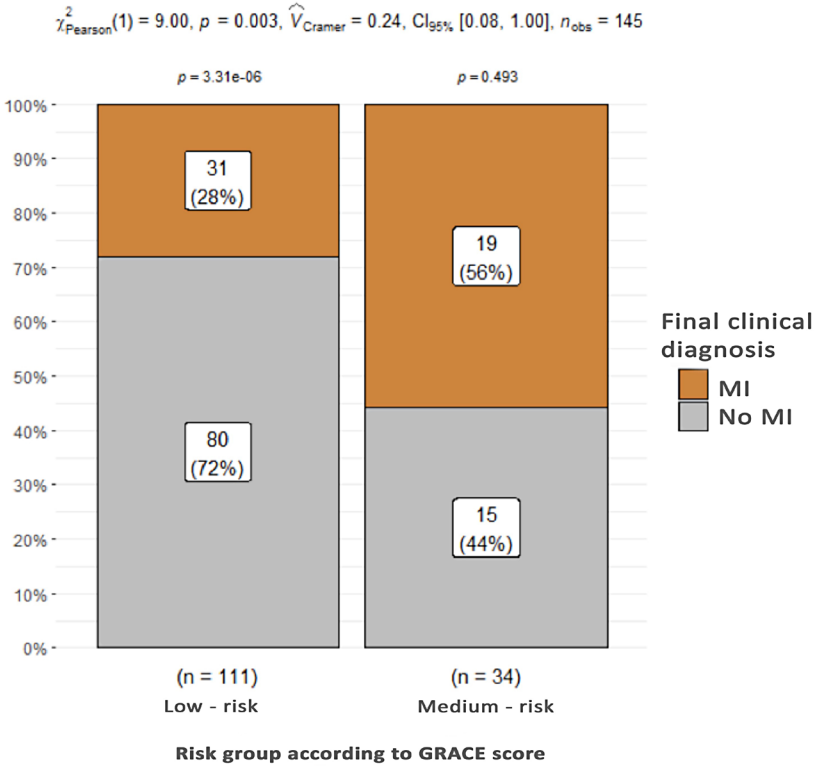

Figure 10. Dependence between the GRACE risk scale and final clinical diagnosis.

AMI – acute myocardial infarction.

significant relationship between the MI and non-MI groups ($p < 0.001$). In the medium-risk group, there is no statistically significant relationship between MI and non-MI ($p = 0.493$).

3.2.2. Assessment of the effectiveness of HEART risk scale

To assess the prognostic values of the HEART risk scale more accurately, we drew an approximating curve, calculated the optimal threshold value using Youden's index, and calculated the prognostic accuracy of this threshold value for the diagnosis of MACE.

The approximating curve for the *HEART* risk scale indicator, describing the dependence of the risk of MACE presence on the *HEART* risk scale scores, is shown in **Figure 11**. The optimal threshold value of the *HEART* indicator for diagnosing MACE equals 6.00 points.

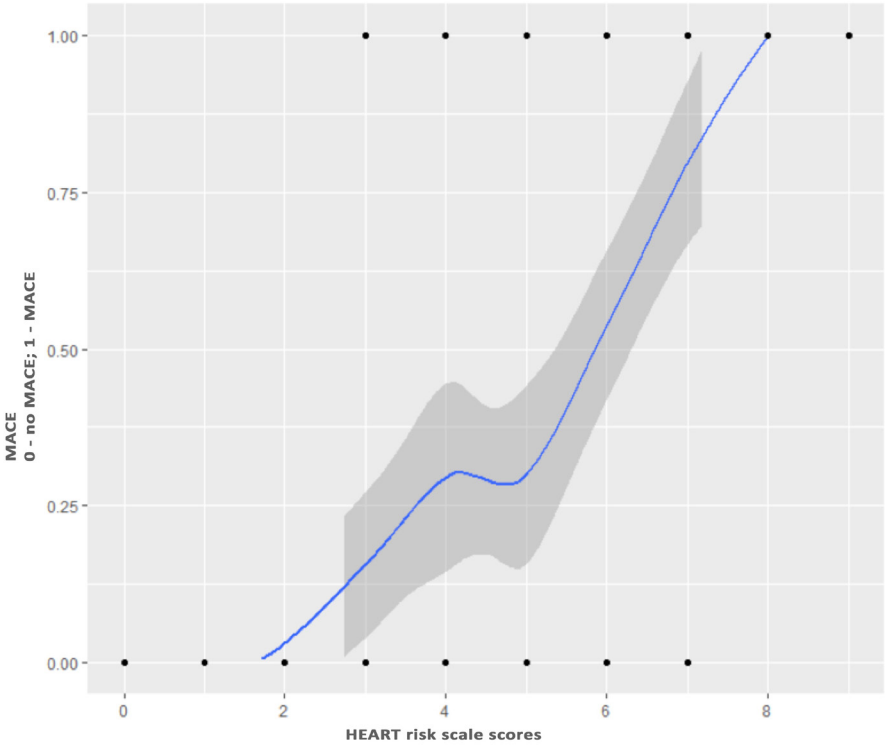

Figure 11. Approximating curve for HEART indicator.
MACE – major adverse cardiac events.

The value on the abscissa axis 6.00 rises to the 0.52 mark on the ordinate axis. As we can see, the approximating curve from the value on the abscissa axis 4.8 rises rather sharply, which indicates that we could diagnose MACE according to the *HEART* indicator with a fairly high probability (0.7381).

Figure 12 shows the dependence between *HEART* risk scale points and the final clinical diagnosis. Cramer's effect size demonstrates a statistically significant (p=0.0000001), and a moderate dependence between the *HEART* risk score and MI diagnosis (φ=0.53). There is a statistically significant dependence between MI and non-MI for all *HEART* risk scale scores except score 6.

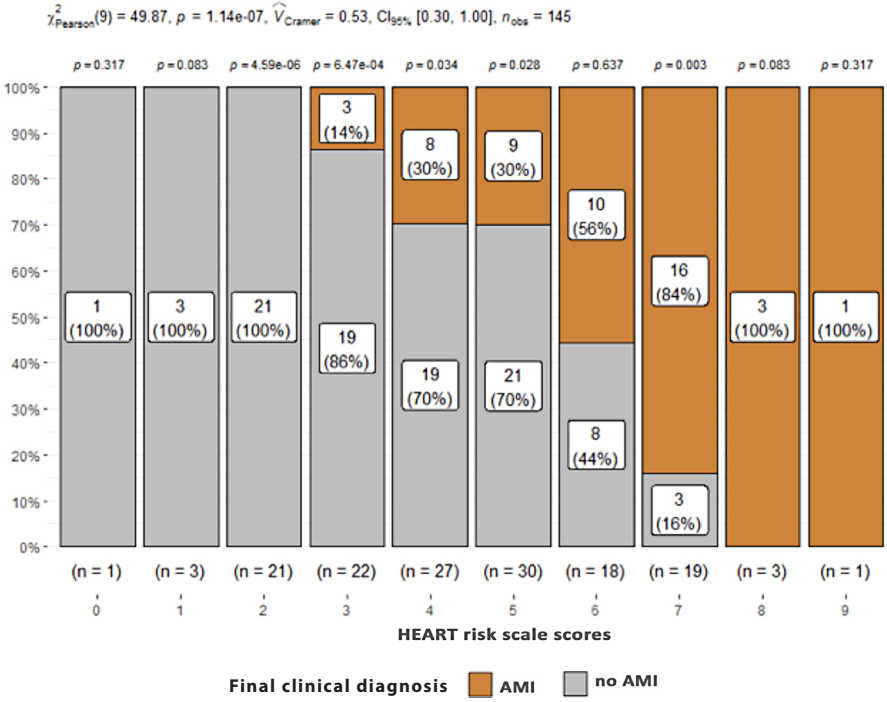

Figure 12. Dependence between HEART risk scale scores and final clinical diagnosis.

AMI – acute myocardial infarction.

3.3. Copeptin efficacy assessment

Subjects were compared according to the upper limit of the normal range for copeptin concentration according to laboratory recommendations (10 pmol/l). In 75 (51.4%) subjects, copeptin concentration was within normal range limits, while in 71 (48.6%) it was elevated. Copeptin concentration was higher in older patients, as well as in patients with previous MI, stroke, and diagnosed with dyslipidaemia, with higher *GRACE* and *HEART* risk scores. These patients were also more often hospitalized, they were diagnosed with ACS in the emergency department, and the final clinical diagnosis was non-ST-segment elevation acute myocardial infarction.

A moderate correlation was found between copeptin and the first cTnI concentrations ($r=0.5$, $p<0.001$). Copeptin and troponin results were concordant in 70.5% of cases when evaluated according to threshold diagnostic concentrations. Elevated copeptin levels but not cTnI levels were found in 22 subjects; the opposite discrepancy of elevated cTnI but normal copeptin levels was found in 21 subjects. A comparison of copeptin and cTnI according to laboratory normal ranges is presented in **Table 10**.

Table 10. Comparison of copeptin and cTnI according to threshold diagnostic concentrations.

Copeptin concentration	**cTnI concentration**	
	< normal ranges	**> normal ranges**
< normal ranges	52 (35.6%)	21 (14.4%)
> normal ranges	22 (15.1%)	51 (34.9%)

cTnI normal ranges: female <15.6 ng/L, male < 35.4 ng/L. Copeptin normal range <10 pmol/L

We examined in detail the differences between subjects with mismatched tests of copeptin and troponin I concentration. Their grouping into four groups according to troponin and copeptin laboratory normal ranges is presented in **Figure 13**.

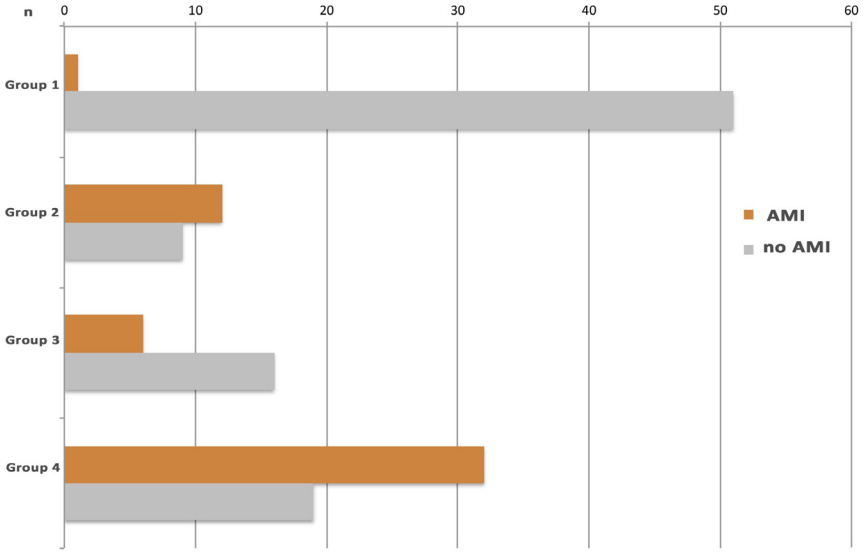

Figure 13. Final diagnoses based on normal range limits of concentrations of both biomarkers.
AMI – acute myocardial infarction, n – number of subjects.

Group 1: Subjects with non-elevated levels of copeptin and troponin I within laboratory normal ranges. In total, there were 52 (35.6%) subjects in this group: AMI was denied in 51 patients. Of these, AMI was diagnosed at ED in 1 subject. After re-reviewing the final clinical diagnosis, for this subject with normal biomarker values, we found that it was non-ST-segment elevation subacute myocardial infarction (the most severe chest pains had begun a month prior, but the patient was referred to the hospital only after returning from abroad).

Group 2: Subjects with normal value copeptin but elevated cTnI. In total, there were 21 subjects in this group (14.4%): of them, 12 subjects were diagnosed with AMI, 9 were not.

Group 3: Subjects with elevated copeptin but normal cTnI value. In total, there were 22 (15.1%) subjects in this group: of them, 6 subjects

were diagnosed with AMI, 16 were not. We further examined the AMI group:

- In 4 subjects, cTnI concentration in dynamics increased after repetition (all these subjects were male, for whom the time from the onset of symptoms was less than 4 hours).
- For 1 subject, 2 hours had passed since the onset of pain, the concentration of copeptin was extremely high (200 pmol/l); cTnI was not repeated in dynamics, but due to variations in the ECG examination the patient was hospitalized.
- 1 subject was hospitalized due to typical complaints of myocardial infarction 3 hours after the onset of pain.

Group 4: Patients with increased levels of copeptin and cTnI. In total, there were 51 (34.9%) patients in this group: of them, 32 subjects were diagnosed with AMI, 19 were not. For the latter, the increase of both biomarkers was usually caused by severe concomitant diseases or their exacerbation.

To evaluate of the prognostic values of copeptin more accurately in non-STE ACS, we plotted an approximating curve, calculated the optimal threshold value using Youden's index, and assessed the prognostic accuracy of this threshold value for the diagnosis of MI.

The approximate curve for the copeptin indicator, describing the dependence of the risk of MI presence on copeptin concentration, is shown in **Figure 14**. VUH SK laboratory reference ranges of copeptin is 10 pmol/l. However, our study showed that the optimal threshold value for copeptin in assessing MI risk is 14.68 pmol/l.

In **Figure 15**, we see that dependence between copeptin and final clinical diagnosis using a threshold value of 14.68 pmol/l increases: Cramer's effect size increases from 0.27 to 0.35.

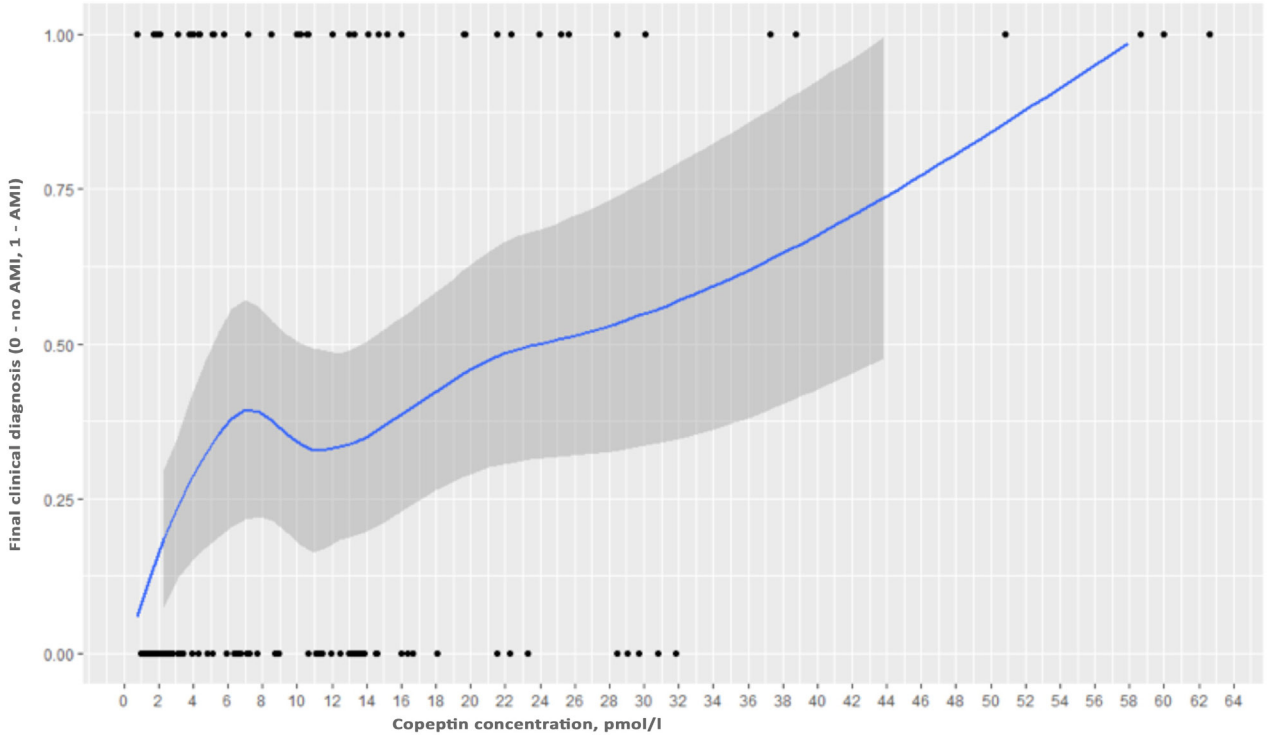

Figure 14. Approximating curve for copeptin concentration.
AMI – acute myocardial infarction.

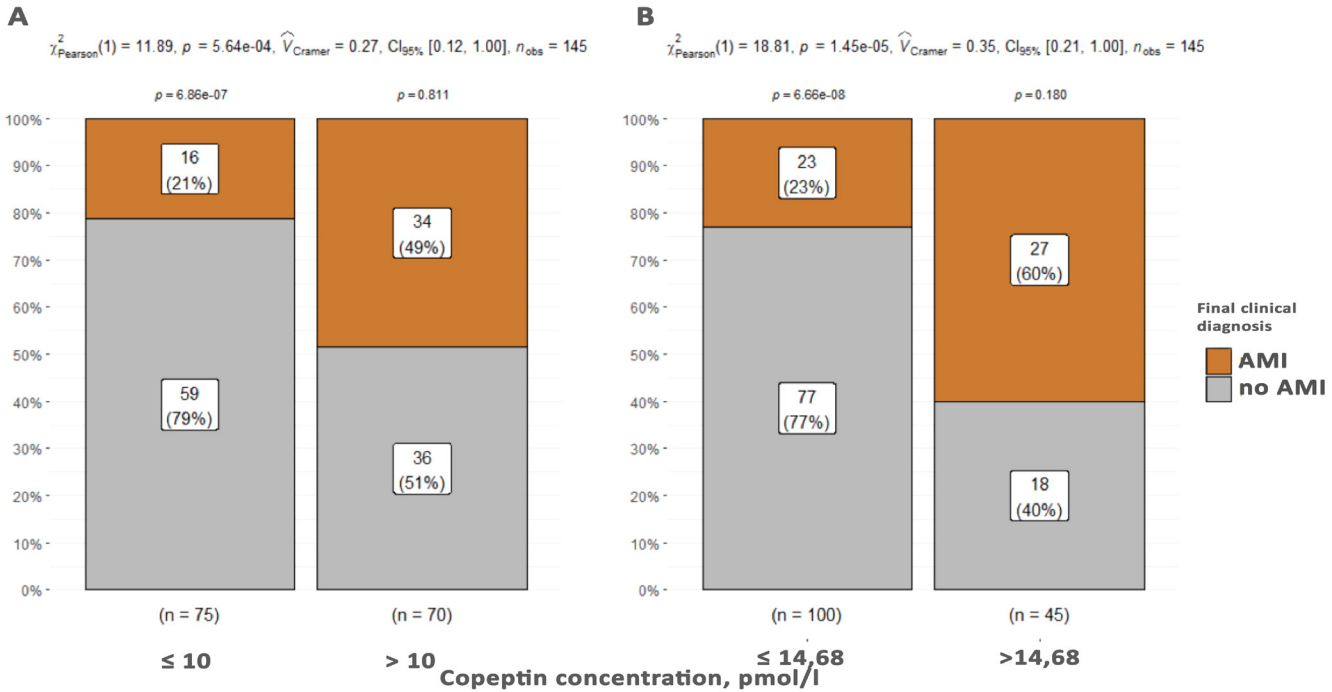

Figure 15. Dependence between copeptin and final clinical diagnosis: **A** for threshold value 10 pmol/l, **B** for threshold value 14.68 pmol/l.

AMI – acute myocardial infarction.

3.3.1. Comparison of prognostic indicators of non-ST-segment elevation acute myocardial infarction

To determine the possibilities of combinations of copeptin and risk scales to predict non-STE AMI at ED in patients who complained of chest pain, we performed an ROC analysis. The area under ROC was calculated for each risk scale separately and in combination with the copeptin concentration test. The area under ROC curve calculated for the *GRACE* risk scale was 0.720 (95% CI 0.638–0.802), while for the *HEART* risk scale – 0.831 (95% CI 0.765–0.897). The area under the ROC curve for copeptin concentration was 0.715 (95% CI 0.626–0.803). The area under the ROC curve of the combination of copeptin concentration and the *HEART* risk scale was statistically significantly higher than that of the combination with the *GRACE* risk scale (AUC 0.864 and AUC 0.764, p = 0.0008). Areas under the ROC curve for all scales are shown in **Figure 16** and compared by the DeLong's method, with p-values in **Table 11**.

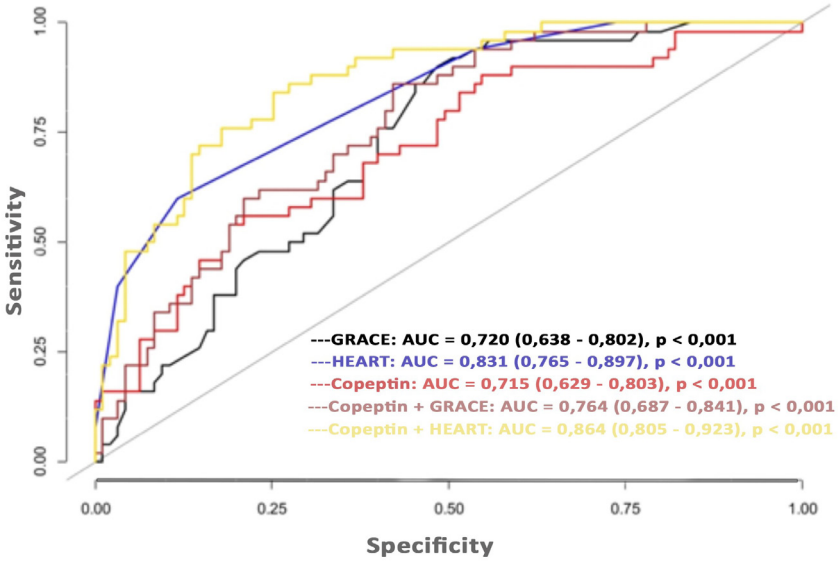

Figure 16. Comparison of risk scales and copeptin and specificity and sensitivity of their combinations by ROC curves, *p-value < 0.001 for all variables.

Table 11. Comparison of risk scales and copeptin and their AUC-based combinations using DeLong's method.

Variables	AUC	GRACE	HEART	Copeptin	Copeptin and GRACE	Copeptin and HEART
GRACE	0.720	x	**0.003**	0.9	**0.02**	**0.00002**
HEART	0.831	**0.003**	X	**0.04**	0.09	**0.06**
Copeptin	0.715	0.9	**0.04**	X	0.2	**0.0007**
Copeptin and *GRACE*	0.764	**0.02**	0.09	0.2	X	**0.0008**
Copeptin and *HEART*	0.864	**0.00002**	0.06	**0.0007**	**0.0008**	x

3.3.2. *Comparison of copeptin concentration and troponin I concentration in the diagnosis of non-ST-segment elevation acute myocardial infarction*

To determine the accuracy of copeptin in identifying which subjects have non-ST-segment elevation acute myocardial infarction, ROC analysis and its comparison with the gold standard were performed by testing troponin I concentration. The first test of troponin I concentration was analysed. The area under ROC curve was calculated for each laboratory test individually and in combination. The estimated area under the ROC curve was 0.895 (95% CI 0.829-0.961) for cTnI and 0.715 (95% CI 0.626-0.803) for copeptin. In this testing, cTnI had a sensitivity of 80.4%, a specificity of 84.2%, and copeptin – 52.9% and 81.1%, respectively. The sensitivity of the combination of troponin I and copeptin – 68.6%, specificity – 77.9%. However, when comparing the combination of cTnI with the concentration of copeptin and these two biomarkers separately, the overall accuracy of the tests in distinguishing between subjects diagnosed with AMI and those without AMI, a statistically significant difference was higher in the troponin I group ($p < 0.001$). Hence, copeptin concentration did not attach additional value to the diagnosis of AMI. However, the

negative prognostic value of troponin was 0.94 (0.93–0.95) and the combination was 0.96 (0.95–0.98), so the combination of these two markers could be beneficial for a more accurate ruling out of ACS. The combination area in the ROC curve was 0.779 (0.703–0.855). The comparison of specificity and sensitivity according to ROC curves is shown in **Figure 17**.

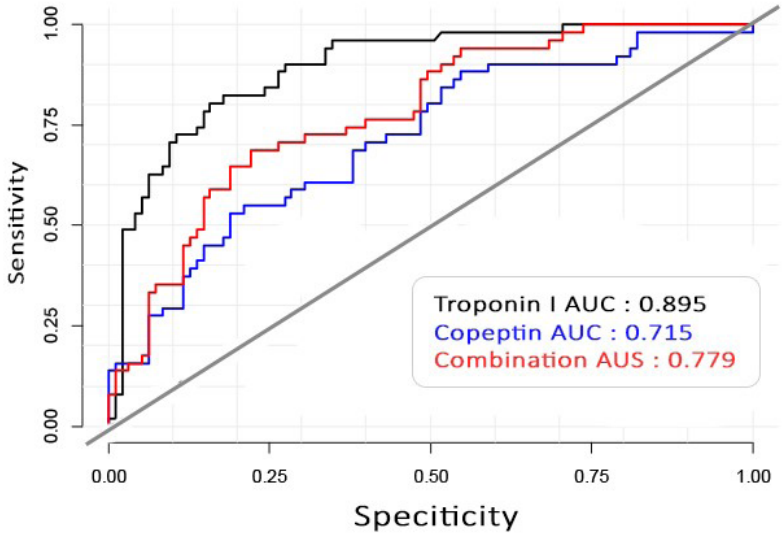

Figure 17. Comparison of troponin I, copeptin and their combination by ROC curves.

The subjects were divided into three groups according to time from the onset of symptoms to the arrival at ED. Group 1 had subjects with chest pain lasting for up to 3 hours, Group 2 – from 3 to 10 hours, and in Group 3 the symptoms lasted longer than 10 hours. **Figure 18** shows that cTnI concentrations are time-dependent, with copeptin concentrations remaining the same since the onset of symptoms (cTnI mean concentration in the groups, respectively: 97.8 ± 320 ng/L, 224 ± 488 ng/L, 1132 ± 3973 ng/L, p = 0.013); copeptin mean concentration

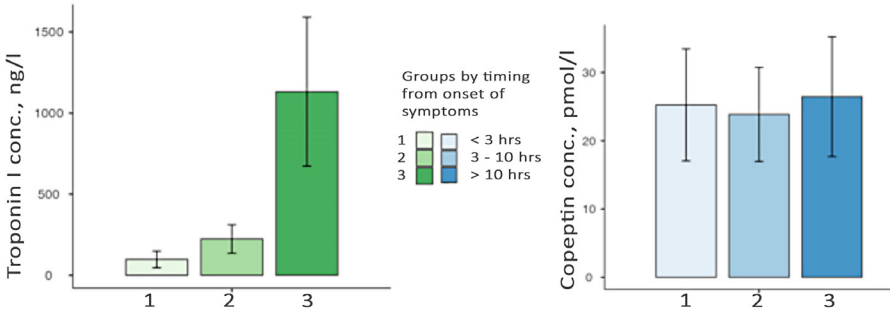

Figure 18. Troponin I and copeptin concentrations among groups by timing of onset of symptoms (1 – chest pain lasting up to 3 hours, 2 – chest pain lasting from 3 to 10 hours, 3 – chest pain started more than 10 hours ago).
conc. – concentration; hrs – hours

in the groups, respectively: 25.2 ± 51.2; 23.9 ± 38.3; 26.4 ± 75.8, p = 0.276). Most often, cTnI was repeated in subjects of Group 1 (20, 9, and 11 subjects, respectively).

If we were to use the copeptin concentration test as an alternative to repeat the cTnI concentration test in dynamics, time spent at the ED would be shortened for some patients, the accuracy would remain similar, and the negative prognostic value would increase. Currently, the average time spent at ED is 4.40 ± 2.44 hours, but patients with repeat cTnI concentration test in dynamics spend an average of about 6.86 ± 2.36 hrs at the ED (median 6.60 (2.88)).

Figure 19 shows how time spent at ED would theoretically be reduced to 3.47 ± 1.73 hrs (median 2.98 (1.71), p<0.001).

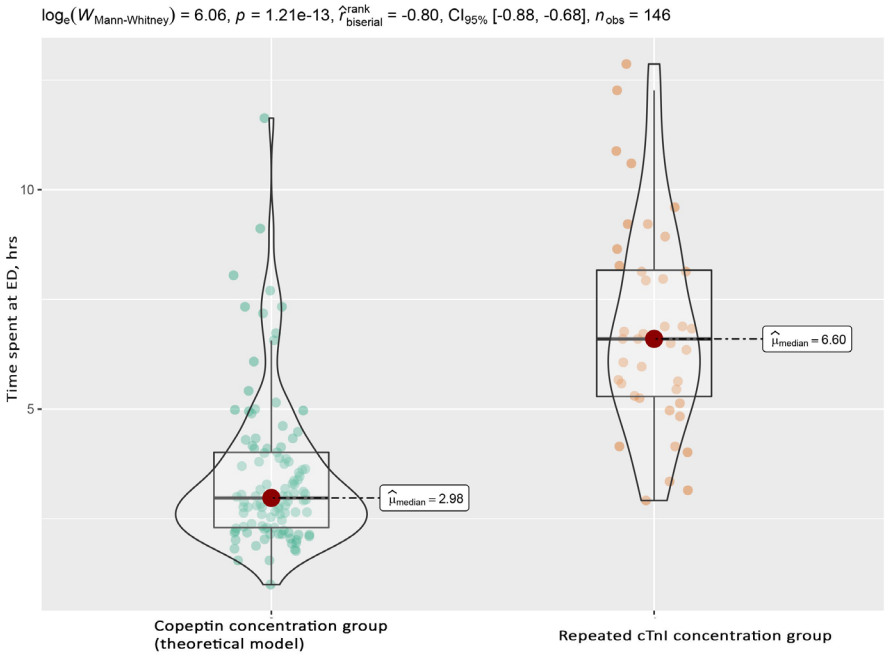

Figure 19. Boxplot of time spent at ED in two groups (theoretical model with copeptin concentration test and repeated cTnI concentration test).
ED – emergency department; cTnI – cardiac troponin I; hrs – hours.

3.3.3. The role of copeptin concentration in the evaluation of prognosis and final outcomes

Five patients died during the study. The proportion of deaths was too small to analyse survival; as a result, a more detailed analysis was not applied. **Figure 20** shows the curves for predicting death and rehospitalisation by cTnI and copeptin concentrations. However, these were noninformative due to the small sample size.

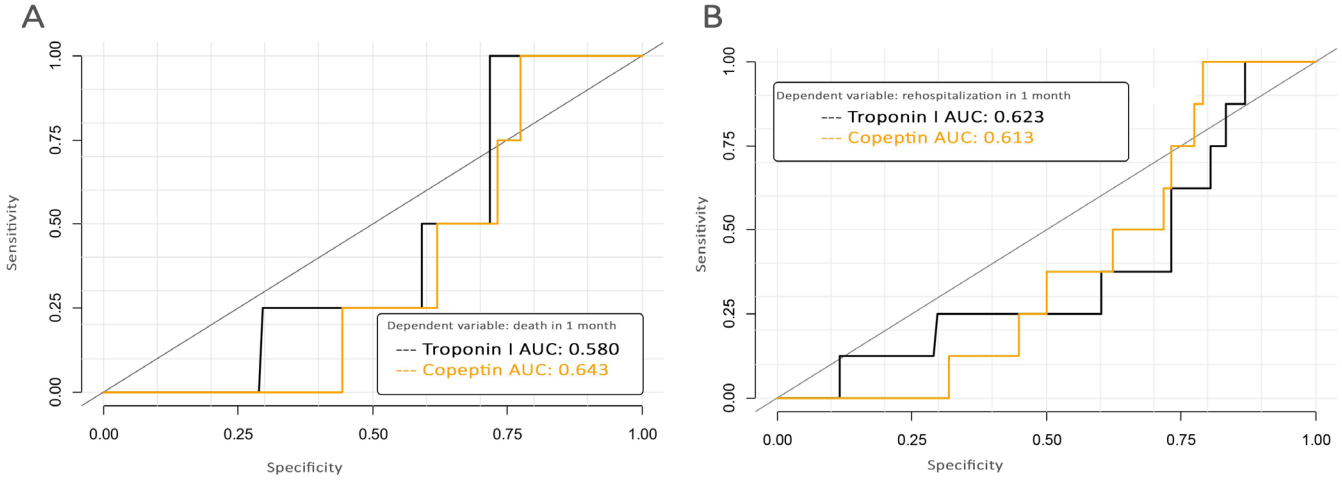

Figure 20. Survival (**A**) and rehospitalisation (**B**) curves for copeptin and troponin concentrations.

3.4. Coronary CT angiography results in the study group

CCTA was performed in 33 (22.7%) low-risk subjects: 17 of them had no variations in coronary heart vessels, 14 showed clinically insignificant variations and stenoses up to 70%, with more than 70% detected in 2 subjects. CCTA was performed in 13 women, 20 men; variations in the coronary vessels were found more often in them than in women. Sixteen (48%) patients had their treatment regimen modified according to CCTA findings.

Table 12 shows mean copeptin, cTnI concentrations, and mean *GRACE* scores among CCTA findings. The mean age was 55.5 ± 9.69 years, mean *GRACE* score was 64.7 ± 17.3, *HEART* score – 2.79 ± 1.11., mean cTnI concentration – 16.8 ± 72.4 ng/ L, copeptin – 5.14 ± 7.83 pmol/L. Two patients underwent a scheduled invasive coronary angiography after CCTA due to variations found.

None of the subjects who underwent CCTA experienced major adverse cardiovascular events, and 1 subject was hospitalized for another pathology within 6 months.

Table 12. CCTA findings and mean GRACE score, mean troponin I and copeptin concentrations.

	All, n=33	***GRACE*, score**	**cTnI, ng/L**	**Copeptin, pmol/L**
CCTA				
No variations	n = 17 (12.1%)	62 ± 13.9	5.6 ± 9.99	4.9 ± 8.1
Up to 70%, Stenosis	n = 14 (10%)	64.9 ± 20,1	32.4 ± 111	5.64 ± 8.36
>70%, stenosis	n = 2 (1.4%)	86.5 ± 13.4	3.25 ± 1.77	3.52 ± 0.59

n – number of subjects; cTnI – cardiac troponin I; CCTA – coronary CT angiography.

3.5. Diagnostic model of non-ST-segment elevation acute myocardial infarction

We assessed which variables best predicted the final diagnosis of a non-ST-segment elevation acute myocardial infarction. We compiled an odds conversion table and determined the odds ratio for the diagnosis of non-ST-segment elevation myocardial infarction. From the data in this table, the most important indicators providing the highest risk of developing an acute myocardial infarction are dyslipidaemia (odds ratio 6.99 (CI 2.22-27.74), p=0.002) and carotid artery stenosis in anamnesis (odds ratio 20.8 (CI 2.51-246.12), p=0.008). The odds ratios of independent indicators for the dependent variable "AMI" are presented in **Table 13.**

We used binary logistic regression to assess which variables best predicted MI in all risk groups. The dependent variable was named as "AMI present": the event probability value is 1 when the final clinical diagnosis is acute myocardial infarction, 0 when AMI is not confirmed. Independent variables assessed were gender, age, risk scales, and others. Correlated variables were not entered into a single model. The parameters of the different regression models are presented in **Table 14.**

Table 13. Odds ratios of independent indicators for the dependent variable "Acute myocardial infarction [present]".

Indicator	Value	No AMI	AMI	Univariate odds ratio (95% CI, p value)	Multivariate odds ratio (95% CI, p value)
Age	Mean (SD)	62.1 (14.5)	66.5 (10.7)	1.03 (1.00 – 1.06, p = 0.057)	1.04 (1.00 – 1.09, p = 0.073)
Gender	Female (%)	34 (66.7)	17 (33.3)	-	-
	Male (%)	61 (64.2)	34 (35.8)	1.11 (0.55 – 2.31, p = 0.767)	1.08 (0.39 – 3.00, p = 0.886)
Family history of coronary heart disease	No (%)	58 (67.4)	28 (32.6)	-	-
	Yes (%)	36 (62.1)	22 (37.9)	1.27 (0.63 – 2.54, p = 0.507)	1.24 (0.52 - 2.93, p = 0.624)
Smoking	No (%)	74 (67.3)	36 (32.7)	-	-
	Yes (%)	21 (60.0)	14 (40.0)	1.37 (0.62 – 2.99, p = 0.431)	2.79 (0.91 – 9.27, p = 0.080)
Obesity	No (%)	66 (65.3)	35 (34.7)	-	-
	Yes (%)	29 (64.4)	16 (35.6)	1.04 (0.49 – 2.16, p = 0.916)	1.10 (0.40 – 2.97, p = 0,851)
Primary arterial hypertension	No (%)	21 (87.5)	3 (12.5)	-	-
	Yes (%)	74 (60.7)	48 (39.3)	4.54 (1.46 - 19.96, **p = 0.019**)	2.17 (0.50 – 12.23, p = 0.329)
Diabetes mellitus	No (%)	84 (66.7)	42 (33.3)	-	-
	Yes (%)	11 (55.0)	9 (45.0)	1.64 (0.62 - 4.26, p = 0.312)	1.80 (0.49-6.56, p = 0.372)
Dyslipidaemia	No (%)	43 (89.6)	5 (10.4)	-	-
	Yes (%)	52 (53.1)	46 (46.9)	7.61 (3.01-23.43, **p<0.001**)	6.99 (2.22-27.74, **p=0.002**)
Heart rate	Median (IQR)	75.5 (15.9)	76.7 (18.8)	1.00 (0.98-1.02, p=0.682)	0.99 (0.96-1.02, p=0.565)
sABP	Median (IQR)	153.6 (30.6)	151.9 (31.7)	1.00 (0.99-1.01, p=0.762)	0.99 (0.96-1.01, p=0.277)
dABP	Median (IQR)	84.3 (14.7)	83.8 (13.4)	1.00 (0.97-1.02, p=0.845)	1.03 (0.97-1.09, p=0.347)
Chronic heart failure	No (%)	72 (66.1)	37 (33.9)	-	-
	Yes (%)	23 (62.2)	14 (37.8)	1.18 (0.54-2.55, p=0.668)	0.46 (0.13-1.50, p=0.208)
Prior MI	No (%)	78 (68.4)	36 (31.6)	-	-
	Yes (%)	17 (53.1)	15 (46.9)	1.91 (0.85-4.26, p=0.112)	2.42 (0.33-20.06, p=0.391)
Carotid artery stenosis	No (%)	93 (67.4)	45 (32.6)	-	-
	Yes (%)	2 (25.0)	6 (75.0)	6.20 (1.37-43.48, **p=0.029**)	20.83 (2.51-246.12, **p=0.008**)
prior stroke	No (%)	92 (68.7)	42 (31.3)	-	-
	Yes (%)	3 (25.0)	9 (75.0)	6.57 (1.85-30.76, **p=0.007**)	3.96 (0.79-25.00, p=0.108)

AMI – acute myocardial infarction; dABP – diastolic arterial blood pressure; IQR – interquartile range; sABP – systolic arterial blood pressure.

Table 14. Regression models of AMI dependence on study parameters.

	Parameter estimate (logarithmized)	**95% CI**	**P value**
Model 1			
$\chi 2(7) = 52.29$, p=0.00 Pseudo-R^2 (Cragg-Uhler) = 0.42, Pseudo-R^2 (McFadden) = 0.28 AIC = 150.53, BIC = 174.34			
Intercept	-2.57	-3.68 –1.47	0.000
ECG: ST depression	1.03	-0.11 – 2.17	0.08
cTnI conc.	0.00	0.00 – 0.00	0.04
ECG: LBBB	-4.11	-8.05 –0.17	0.04
Dyslipidaemia	2.12	0.94 – 3.30	0.00
Diuretics	-1.38	-2.70 –0.60	0.04
Carotid artery stenosis	1.95	-0.08 – 3.98	0.06
Prior stroke	2.16	0.58 – 3.74	0.01
Model 2			
$\chi 2(2) = 26,36$, p=0,00 Pseudo-R^2 (Cragg-Uhler) = 0.30, Pseudo-R^2 (McFadden) = 0.20 AIC = 111.13, BIC = 119.26			
Intercept	0.43	0.02 – 0.74	0.00
Copeptin	1.02	1.00 – 1.03	0.03
CCTA	0,30	0.11 – 0.79	0.02
Model 3			
$\chi 2(6) = 37.26$, p=0.00 Pseudo-R^2 (Cragg-Uhler) = 0.31, Pseudo-R^2 (McFadden) = 0.20 AIC = 165.67, BIC= 186.56			
Intercept	-3.57	-5.69 –1.44	0.00
Age	0.03	-0.00 – 0.06	0.06
Prior MI	0.86	-0.06 – 1.78	0.07
ECG ST segment depression	1.36	0.31 – 2.41	0.01
ECG: paced rhythm	-17.25	-29.5 – 21.34	0.99
Non-specific ECG variations	1.07	0.19 – 1.95	0.02
Copeptin	0.01	0.00 – 0.03	0.01

	Parameter estimate (logarithmized)	95% CI	P value
Model 4			
$\chi 2(5) = 53.35$, p=0.00 Pseudo-R^2 (Cragg-Uhler) = 0.43, Pseudo-R^2 (McFadden) = 0.29 AIC = 144.61, BIC = 162.43			
Intercept	0.02	0.00 – 0.10	0.00
Total leukocyte count	1.19	1.02 – 1.38	0.03
Copeptin	1.02	1.00 – 1.03	0.01
Dyslipidaemia	7.52	2.44 – 23.20	0.00
Use of diuretics	0.21	0.06 – 0.73	0.01
Prior stroke	7.33	1.62 – 33.24	0.01
Model 5			
$\chi 2(5) = 85.18$, p = 0.00 Pseudo-R^2 (Cragg-Uhler) = 0.61, Pseudo-R^2 (McFadden) = 0.46 AIC = 113.63, BIC= 131.49			
Intercept	0.01	0.00 – 0.06	0.00
Copeptin >14.68 pmol/l	5.52	1.85 – 16.44	0.00
Dyslipidaemia: yes	11.16	2.47 – 50.43	0.00
Prior stroke: yes	6.28	1.10 – 35.88	0.04
TnI conc. 1-3 times exceeds normal range	3.12	0.84 – 11.53	0.09
TnI conc. >3 times exceeds normal range	22.73	7.17 – 72.07	0.00

ECG – electrocardiogram; LBBB – left bundle branch block; MI myocardial infarction; TnI conc. – troponin I concentration; CCTA - coronary CT angiography.

Model 1 and Model 3 were constructed by selecting the indicators measured in the emergency department, but both were rejected as several parameters were statistically insignificant according to the Wald test – p>0.05.

Pseudo-coefficients for determining Model 2 McFadden R^2=0.2 and Cragg-Uhler R^2=0.3 (both R^2>=0.20) show a good fit of the model to the data of "patients". Further analysis of the model found that 22.58% of patients with a diagnosis of MI and 96.25% with an

unconfirmed diagnosis of AMI were correctly identified (accuracy of the model 75.7%), with area under the ROC curve of the model 0.772 (CI 95% 0.681, 0.863), $p<0.001$. Estimated model sensitivity was 0.23%, and specificity 96.26%, (PPV 0.70, NPV 0.76). Therefore, this model, although having high specificity, was rejected due to low sensitivity.

Although Model 4 would be statistically optimal according to its indicators, it was rejected following a logical principle: diuretics were prescribed in the anamnesis by a family doctor, a patient was not always diagnosed with HF and was not related to the risk of AMI. After excluding this indicator, the coefficient of determination decreased significantly; as a result, this model was rejected.

Model 5 was selected for further analysis.

During the study, based on logistic regression equations, we managed to create a model that quite accurately diagnoses non-ST-segment elevation acute myocardial infarction. After applying this model, the coefficients of the variables or odds ratios (ORs) are as follows:

Intercept OR = 0.01;
"Troponin >3 times exceeds normal range: yes" OR = 5.31;
"Troponin 1-3 times exceeds normal range: yes" OR = 3.12;
"Prior stroke: yes" OR = 6.28;
"Dyslipidaemia: yes" OR = 11.16;
"Copeptin > 14,68 pmol/l" OR = 5.52.

Figure 21 shows the influence of model 5 indicators to determine AMI.

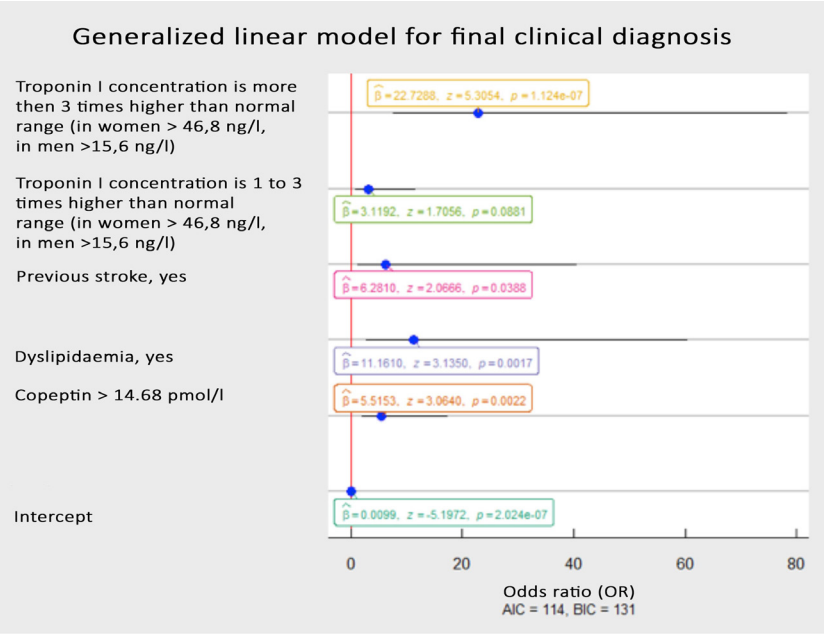

Figure 21. Influence of indicators on the likelihood of MI (odds ratios).

The model's representation:

$$\text{Ln}\ \frac{P(\text{Myocardial infarction})}{P(\text{no Myocardial infarction})} = -4.6126 +$$

$$\left\{\begin{array}{c} 0.00,\ \text{Coceptin} \le 14{,}68\ \text{pmol/l} \\ 1.7075,\ \text{Coceptin} > 14{,}68\ \ \text{pmol/l}) \end{array}\right\} + \left\{\begin{array}{c} 0.00,\ \text{Dyslipidaemia: No} \\ 2.4124,\ \text{Dyslipidaemia:Yes} \end{array}\right. +$$

$$+ \left\{\begin{array}{c} 0.00,\ \ \text{Previous stroke:No} \\ 1.8375,\ \text{Previous stroke:Yes} \end{array}\right. +$$

$$\left\{\begin{array}{c} 0.00,\ \text{Troponin of normal range} \\ 1.1376,\ \text{Troponin is 1-3 times higher than normal range} \\ 3.1236,\ \text{Troponin is more than 3 times higher than normal range} \end{array}\right.$$

By marking $\text{Ln}\frac{P(\text{Myocardial infarction})}{P(\text{no Myocardial infarction})} = z$, we easily determine the probabilities:

$$P(\text{Myocardial infarction}) = \frac{e^z}{1+e^z} = \frac{1}{1+e^{-z}}$$

$$P(\text{no Myocardial infarction}) = 1 - P(\text{Myocardial infarction}) =$$

$$= 1 - \frac{1}{1+e^{-z}} = \frac{1}{1+e^z}.$$

The effectiveness of the model was evaluated by creating a classification table and applying the model to the calculated and actually determined results. It is presented in **Table 15**. The model's sensitivity was 76%, specificity – 88.4%, positive prognostic value – 77.6%, negative prognostic value – 87.5%, accuracy – 84.1%. Blind guess and model results were statistically significantly different in favour of the model ($p<0.001$). The kappa test value – 0.647 and McNemar's test value was $p=1.0$ (no statistically significant difference between observed values and modelled values). The prevalence of the model was 0.345, detection rate – 0.262, detection prevalence – 0.338; balanced accuracy – 0.822. In addition, calculating the prognostic properties of the model and plotting the ROC curve yielded AUC of 0.911 (95% CI 0.864-0.959, $p<0.01$). The presented model has excellent prognostic performance based on AUROC estimate, > 0.8. A graphic representation of the developed model is presented in **Figure 22.**

Table 26. Classification table for a comparison of the results calculated and observed by the logistic regression model.

	Model results		
Observed	Acute myocardial infarction	No acute myocardial infarction	TOTAL:
Myocardial infarction: yes	38	12	50
Myocardial infarction: no	11	84	95
TOTAL:	49	96	145

Blind guess: Myocardial infarction: yes = 34.48%; Myocardial infarction: no = 65.52%.

Model results: Myocardial infarction: yes = 76.00%; Myocardial infarction: no = 88.42%.

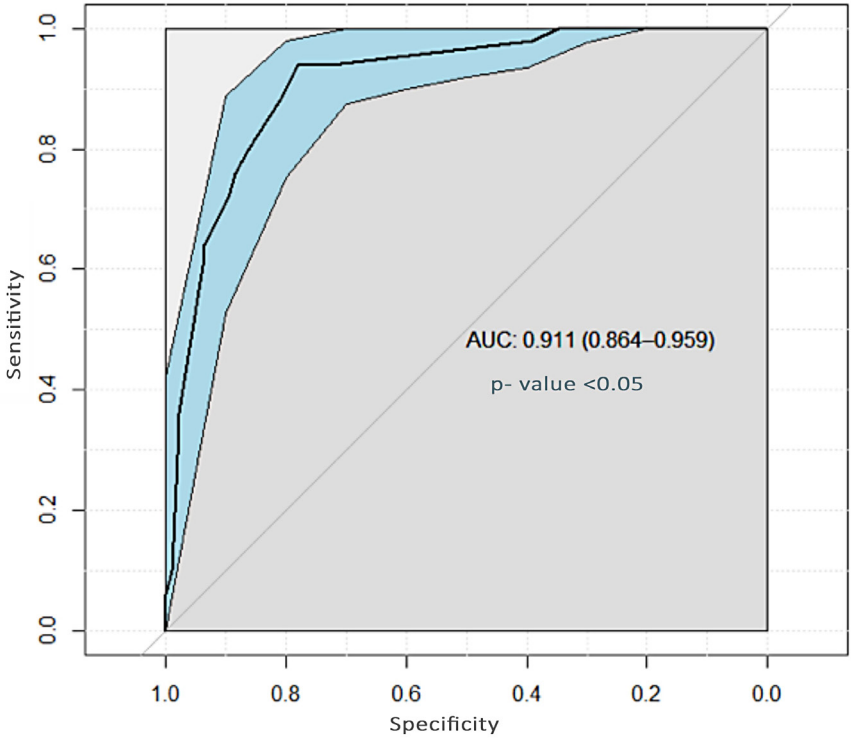

Figure 22. ROC (Receiver Operating Characteristics) curve with 95% confidence interval (CI 95%) for regression model estimation. P value <0.005.

Figure 23 shows the dependence between the model and the final clinical diagnosis. Following the model, we obtain a statistically significant ($p<0.0001$) and strong dependence between the MI diagnostic model and the final clinical diagnosis after re-evaluation ($\varphi_c=0.64$). In addition, we have a statistically significant dependence

between predicted AMI and no AMI in the group with diagnosed AMI at the final clinical diagnosis after re-evaluation (p=0.000236) and a statistically significant dependence between predicted AMI and no AMI in the group with no diagnosed AMI at final clinical diagnosis after re-evaluation ($p=6.91*10^{-14}$).

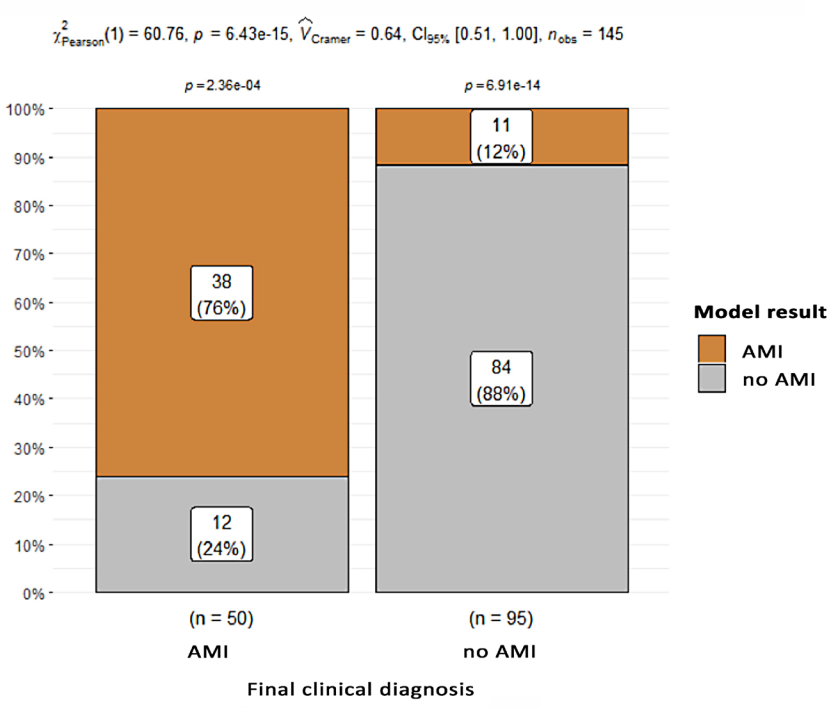

Figure 23. Dependence between binary logistic regression model and final clinical diagnosis.

4. DISCUSSION OF RESULTS

The diagnosis of non-ST-segment elevation acute coronary syndromes remains relevant worldwide. With the development of new diagnostic technologies, an attempt is made to find a balance between safely ruling out the diagnosis of non-ST-segment elevation ACS and conducting a full examination of a patient. In this dissertation, we reviewed ACS risk assessment scales, the stress biomarker copeptin, and the benefit of coronary CT angiography in the complex diagnostic pathway of patients with suspected non-ST-segment elevation ACS. We have also developed a diagnostic tool based on a mathematical model that has the potential to be used in clinical decision-making in the emergency department.

4.1. Risk assessment scales for patients complaining of chest pain in the emergency department

Patient complaints, anamnesis, and clinical symptoms are crucial in the examination and treatment of these patients. Yet, the results of our study showed that there was no statistically significant dependence between the symptom combinations and the final clinical diagnosis. Key clinical parameters (HR, ABP, BMI) of patients with suspected non-ST-segment elevation ACS were not statistically significantly different between those in whom this diagnosis was confirmed and in those whom it was not. Therefore, ACS cannot be diagnosed based on complaints, anamnesis, and clinical symptoms alone. The assessment of risk factors is important. In our study, subjects had an average of 2.6 cardiovascular risk factors. Non-ST-segment elevation acute myocardial infarction was statistically more often diagnosed in patients with primary arterial hypertension and dyslipidaemia.

The lengthy and complex examination of patients in the ED led to the emergence of risk assessment scales. And even though the emerging rapid diagnostic algorithms have shortened these processes, they still remain lengthy, as usually at least two cardiac troponin concentration

results will be needed, and in case the alternative cause of chest pain is not found, even longer observation in the ED is needed. Thus, risk scales can not only accelerate the examination of patients in EDs, but also become a supporting evidence-based tool for physicians working at the ED. Risk stratification scales can also help in the communication among physicians in describing a patient, as well as being a waymark at a sorting point, early treatment, and hospitalization processes. Some scales (*TIMI*, *GRACE*, *HEART*) are validated and recommended by major cardiology societies [5, 21] for the prediction of adverse cardiovascular events (including MI) in patients. However, despite the vast selection of these scales, they are not widely used in clinical practice. One reason is that the scales were developed to assess the risk of already diagnosed acute coronary syndromes (*TIMI*, *GRACE*) and not to assess patients with chest pain at the ED. On the other hand, the *HEART* risk scale was developed for use in EDs, and although it showed better prognostic properties than *TIMI* or *GRACE* [22–26], it was not established due to its possible subjectivity. The subjectivity factor arises from patients' anamnesis, which is not always clearly expressed, and risk factors, which are not always fully documented. Also, identifying low-risk patients and discharging them directly from the ED without extensive interventional cardiovascular examinations is beneficial financially as well; a good risk assessment scale helps to identify these patients [27]. With increased patient flows in the emergency department, it has also become very important to quickly identify high-risk ACS patients to provide them with effective and timely treatment. In the medical records of our study, only one subject had a *GRACE* risk score estimate documented.

In our study, the mean *GRACE* risk assessment scale score in the study sample was 87.8 points and was significantly different between those with and without a final clinical diagnosis of AMI (100 and 77 points, $p<0.001$). For the *GRACE* risk scale, the estimated area under the ROC curve for MACE events was 0.720 (95% CI 0.638–0.802). The following results were obtained in similar studies: *GRACE* area under the ROC curve was 0.717 [28], 0.830 [29], 0.570 [30], 0.620

[22]; our result is similar to those of the above studies. The negative prognostic value of the *GRACE* scale was 90.74%. Therefore, in our study, the *GRACE* risk scale showed good prognostic properties in differentiating low-risk patients. In our study, the mean *HEART* risk score was 4.45. For the *HEART* risk scale, the estimated area under the ROC curve was 0.831 (95% CI 0.765–0.897). Results obtained in similar studies by other authors: *HEART* area under the ROC curve was 0.816 [31], 0.830 [25], 0.753 [24], 0.820 [32]. Thus, the literature data are similar. The *HEART* risk assessment scale showed better prognostic properties for *MACE* in our study. As *HEART* risk scores increased, the number of *MACE* (including myocardial infarctions) increased. Also, no major adverse cardiovascular events (MACE) occurred in any patient at low risk according to te *HEART* risk scale.

Risk scales are a useful tool in the emergency department, where speedy decisions are required to ensure the optimal treatment of patients. Both risk scales identified low-risk patients well. However, further studies are needed to stratify patients with medium risk. Therefore, further research is needed for the economic benefits and cost analysis of these scales in Lithuanian emergency departments.

4.2. Possibilities of using copeptin in the diagnosis of non-ST-segment elevation acute coronary syndromes

In this work, we aimed to evaluate the possibilities of using copeptin in the diagnosis of non-ST-segment elevation acute coronary syndromes. The mean time from the order of examinations to the response of all laboratory examinations was 1.48 ± 0.77 hours. The mean concentration of the copeptin test was 25.28 ± 62.67 pmol/L. In 75 subjects, copeptin concentration corresponded to normal ranges, while in 71 subjects it was elevated. Increased concentrations were seen in older adults with comorbidities and higher risk scores according to *GRACE* and *HEART* risk scales (15%). It is worth noting that, as well as in other studies, this thesis found the concentration of copeptin to be higher in patients with AMI (41.3 pmol/l) than in those in whom the diagnosis was not confirmed (13.1 pmol/l). In the study

performed by Afzali et al., copeptin concentration differed between those with and without MI, 20.83 and 12.2 pmol/L, respectively, $p < 0.0001$ [33]. A meta-analysis of more than 14,000 patients also found a significant difference in copeptin levels between those with and without MI, 68.7 ± 74.7 and 14.8 ± 19.9 pmol/L, respectively ($p < 0.001$) [34].

We wanted to analyse the prognostic properties of copeptin and its combinations with risk stratification scales to predict MACE. The copeptin concentration test showed good prognostic properties for predicting *MACE* (ROC 0.715); similar data found by other authors established the copeptin concentration ROC value at 0.703 [35]. We combined copeptin testing and prognostic properties of the two risk scales and found that the area under the ROC curve of the combination of copeptin and the *HEART* risk scale was statistically significantly higher than that of the combination with the *GRACE* risk scale (0.864 and 0.764, respectively, $p < 0.001$). Thus, the combination of copeptin with risk scales could improve the prognostic properties of these scales for *MACE*. There are no studies combining one copeptin concentration with these scales for prognosis; however, similar studies combining high-sensitivity troponin have shown good prognostic properties for these events [36].

To evaluate the diagnostic values of copeptin more accurately, we drew approximating curves using Youden's index and calculated the optimal threshold value, which was 14.68 pmol/l. Using this threshold value, the accuracy of clinical diagnosis increases (Cramer's effect size increases from 0.27 to 0.35). The area under the ROC curve of copeptin for confirming the diagnosis of non-ST-segment elevation myocardial infarction was 0.715 (95% CI 0.626–0803), and we can describe the performance of this study as good. However, ROC for troponin was 0.895 (95% CI 0.829–0.961), and ROC for the combination of troponin and copeptin was 0.779 (95% CI 0.703–0.855), when comparing this combination with the accuracy of the troponin concentration test, the accuracy was statistically significantly higher in favour of troponin I ($p <0.001$). Therefore, the copeptin/troponin combination did not

attach additional benefit in the diagnosis of a non-ST-segment elevation acute myocardial infarction. In a study by American researchers from 2021, the obtained data were different – according to their study, this combination was superior for the diagnosis of AMI (combination ROC – 0.975, cTnI ROC – 0.888, $p < 0.001$) [37]. On the other hand, the results of our work showed that the negative prognostic value of troponin was 0.94 (0.93–0.95), and that of the combination – 0.96 (0.95–0.98), meaning that the combination of these two markers could be beneficial for ruling out ACS more accurately. The works of other researchers also showed a large negative prognostic value [37–41]. Another study found a high negative prognostic value of the combination of these two biomarkers not only for ruling out ACS, but also for ruling out other life-threatening diseases (aortic dissection, PE, severe sepsis, etc.) [39].

Copeptin, but not troponin I concentration, was found to be elevated in some of the subjects. A general trend was found for those diagnosed with acute myocardial infarction in this sample to arrive early from the onset of symptoms. Therefore, we grouped patients according to the time since symptom onset. As described in the literature, the concentration of copeptin in our study was increased already in the subjects of the first group (those who arrived earliest from the onset of symptoms) and remains the same across all groups when the concentration of troponin increases over time. The mean time spent in ED was 4.40 ± 2.44 hours. More than 40% of patients who complained of chest pain spent more than 4 hours in the emergency department. For those whom the troponin concentration test was repeated in dynamics, these patients spent 6.86 ± 2.36 hours in the ED. Data from other studies are similar and support the conclusion that copeptin concentration testing is useful in patients who arrive early from the onset of symptoms, before other biomarkers are potentially still unresponsive [37, 42, 43]. Copeptin testing would thus be useful in patients who arrive early from symptom onset and could offer an alternative to repeat troponin testing, thus shortening the ED testing of these patients. In a study by Mockel, this early discharge tactic was

shown to be safe and having a low probability of major cardiovascular events [44]. In another study, copeptin, cTnI, and the GRACE scale showed a high negative prognostic value of 99%, and this combination is suggested for rapid and safe ruling out of ACS [45]. Also, foreign studies claim that this speedy tactic would reduce the costs of ED [46]; however, we did not perform such an analysis.

4.3. Possibilities of using coronary CT angiography in the emergency department

The future challenge is to implement all innovations in clinical practice as widely as possible, especially in a health system with limited resources. CCTA was performed in 33 (22.7%) low-risk subjects, 13 women and 20 men, in whom variations in coronary vessels were more often found. The mean age of these patients was 55.5 ± 9.69 years, and according to the *GRACE* and *HEART* risk scores, these patients belonged to the low-risk group. The mean concentration of cTnI was 16.8 ± 17.3 ng/L, copeptin – 5.14 ± 7.83 pmol/L. Clinically insignificant variations were found in 14 patients, and stenoses of more than 70% in 2 patients. The latter underwent planned invasive coronary angiographies due to these variations. Almost half (48.5%, n=16) of low-risk patients were found to have coronary artery variations. And although these variations were not significant, we believe that the results of CCTA could serve for further lifestyle correction of these patients, education about their health status, and possible actions for stricter correction of risk factors. As in one study, statins were more likely to be prescribed and continued in patients with a diagnosis of atherosclerotic cardiovascular disease after a performed CCTA in the emergency department [47]. Also, we used the CCTA test in the model together with the copeptin concentration test and found a high negative prognostic value – 96.25%. Similar results have been reported by other researchers who combine troponin testing and CCTA for the safe ruling out of ACS [48] . Three large randomized examinations: CT – STAT [49], ACRIN – PA [50], and ROMICAT II [51] with a larger sample of patients and data from

our study confirm that CCTA is a reliable test for ruling out the diagnosis of non-ST-segment elevation acute myocardial infarction by excluding atherosclerotic cardiovascular disease. During our follow-up period, none of the subjects who underwent CCTA experienced major cardiovascular events. The literature data is also similar in this regard [52], the follow-up period of which was longer – 1 year [53].

4.4. Practical applications of the diagnostic model

It should be noted that physicians working in EDs are quite accurate in ruling out the diagnosis of non-ST-segment elevation ACS, but when ACS is detected in the ED, its diagnosis is confirmed in the hospital in only 56% of cases. In this thesis, our objective was to find an objective diagnostic model for patients with suspected non-STE ACS. We used the method of binary logistic regression, which enabled us to evaluate the importance of parameters in determining non-STE ACS. The selected optimal model contains the concentration values of the two biomarkers and a subject's risk factors, so there are no subjective indicators. Model ROC curve – 0.911 (95% CI 0.864–0.959). Therefore, the presented model exhibits excellent prognostic performance in terms of the AUROC estimate. This method equals and surpasses other diagnostic methods and risk assessment scales in its accuracy ($p < 0.01$). According to our data, no such models have been described in the literature to use these two biomarkers in the diagnosis of non-STE ACS.

4.5. Study limitations

It should be acknowledged that this thesis has several limitations. First of all, the study is monocentric, which means that in another centre, due to various factors – like the experience of the researchers, as well as logistical or technical features – the results may differ from those presented here. Second, the sample size of the present study is small, so some parameters, such as 30-day mortality, cannot be well estimated due to their rarity. The small CCTA sample and

heterogeneous sets of variables limited the interpretation of the results of this study in diagnostic models. Patient selection was biased, as we included only patients with suspected non-STE ACS, and not all patients who complained of chest pain. Questions arising from these limitations may be answered by a larger scope, multicentred study.

CONCLUSIONS

1. In patients presenting to the emergency department complaining with chest pain and suspected non-ST-elevation acute coronary syndrome, the *HEART* risk score showed better prognostic properties compared to *GRACE*.
2. Copeptin concentration testing is not specific for acute myocardial infarction; however, determining its concentration would allow reducing the time patients spend at the emergency department and safely discharge them to outpatient treatment.
3. For patients who are at the low-risk group after examination at the emergency department, and with the cause of chest pain remaining unexplained, it is appropriate to undergo coronary CT angiography.
4. The proposed diagnostic tool would improve the diagnosis of non-ST-segment elevation acute myocardial infarction and the ruling out of the diagnosis at the emergency department. More detailed studies are needed for the validation of this model and its applicability for analysis at the emergency department.

PRACTICAL RECOMMENDATIONS

1. The HEART risk assessment scale can be used for a speedy identification of patients with a low risk of adverse cardiovascular events at the emergency department and to safely discharge them to outpatient care.
2. The copeptin concentration test is beneficial for patients, especially those who arrived at the emergency department within the first 3 hours after the onset of chest pain.
3. Coronary CT angiography is recommended for patients with a persistent, unexplained cause of chest pain.
4. The new diagnostic model is effective both for the diagnosis of non-ST-segment elevation acute myocardial infarction and for a safe ruling out of the diagnosis.

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PUBLICATIONS

List of publications on the dissertation topic

1. **Ruseckaitė, Renata**; Matuliauskaitė, Lina; Juknevičius, Vytautas; Šerpytis, Pranas. Šiuolaikinis požiūris į didelio jautrumo troponino koncentracijos padidėjimą = Modern aproach to increased high-sensitivity troponin concentration // *Sveikatos mokslai*. Vilnius : *Sveikatos mokslai*. ISSN 1392-6373. eISSN 2335-867X. 2019, t. 29, Nr. 4, p. 79–93. DOI: 10.35988/sm-hs.2019.061.
2. **Juknevičienė, Renata**; Juknevičius, Vytautas; Jasiūnas, Eugenijus; Raščiūtė, Beatričė; Barysienė, Jūratė; Matačiūnas, Mindaugas; Vitkus, Dalius; Laucevičius, Aleksandras; Šerpytis, Pranas. Chest pain in the emergency department: from score to core – a prospective clinical study // *Medicine*. Philadelphia : Lippincott Williams & Wilkins. ISSN 0025-7974. eISSN 1536-5964. 2022, vol. 101, no. 29, art. no. e29579, p. [1–7]. DOI: 10.1097/MD.0000000000029579.

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3. **Juknevičienė R,** Simonavičius J, Mikalauskas A, Čerlinskaitė-Bajorė K, Arrigo M, Juknevičius V, Alitoit-Marrote I, Kablučko D, Bagdonaitė L, Vitkus D, Balčiūnas M, Zuozienė G, Barysienė J, Žaliaduonytė D, Stašaitis K, Kavoliūnienė A, Mebazaa A, Čelutkienė J. Soluble CD146 in the detection and grading of intravascular and tissue congestion in patients with acute dyspnoea: analysis of the prospective observational Lithuanian Echocardiography Study of Dyspnoea in Acute Settings (LEDA) cohort. *BMJ Open*. 2022 Sep 1;12(9):e061611. DOI: 10.1136/bmjopen-2022-061611. PMCID: PMC9438196.

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