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Copeptin for risk stratification and medium-term mortality prediction in patients with non-ST-segment elevation acute coronary syndrome

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Summary. *The study estimates prognostic value of copeptin level in assessing medium-term mortality risk in patients with non-ST-segment elevation acute coronary syndromes (NSTE ACSs) measured during first 3 hours from pain syndrome manifestation compared with troponin T.*

The study included 128 patients (52 patients with non-ST-elevation myocardial infarction (NSTEMI), 58 with unstable angina (UA), 18 with unconfirmed coronary event), who were selected using inclusion and exclusion criteria and voluntarily signed written informed consent in order to participate in the study. All patients underwent diagnostic examinations, laboratory tests, including the determination of quantitative troponin T level and quantitative human peptide copeptin level. The use of extended set of predictors including copeptin increases the accuracy of short-term and medium-term prognosis of fatal and non-fatal cardiovascular events up to almost 100%. At the same time, it does not depend on gender, age and condition severity and can indicate mortality in patients with NSTE ACSs up to 180 days of follow-up.

Key words: *copeptin, non-ST-segment elevation acute coronary syndrome, acute myocardial infarction, mortality, troponin T.*

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According to a large number of epidemiological studies, coronary heart disease (CHD) is one of the leading causes of morbidity, mortality and disability in adult population [1,2]. One of the most severe manifestations of CHD include myocardial infarction (MI) and unstable angina (UA) — the most common mortality causes in patients with CHD. Over the last years, the concept of acute coronary syndrome (ACS) has been developed in order to unify medical and diagnostic measures at the stage when an accurate diagnosis cannot be established [3, 4].

According to WHO, ACS can be defined as any group of clinical signs and symptoms that make it possible to suspect acute myocardial infarction (AMI) or unstable angina (UA) and includes MI with ST segment elevation, MI without ST segment elevation, and MI diagnosed by changes in enzymes level, by the presence of biomarkers and late ECG signs [2, 5]. Among patients with acute coronary syndrome without ST segment elevation, it is important to identify groups of patients with myocardial necrosis who have increased risk of complications and death. This group of patients need the most aggressive management strategy including percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Biomarkers play an important role in diagnosing and predicting the risks of adverse events in patients with non-ST-segment elevation acute coronary syndromes (NSTE ACSs) and affect diagnostic and therapeutic management strategies. The method of troponin T and I levels determination currently has the highest sensitivity and specificity. An increase of troponin level is defined as the value exceeding the 99th percentile of the normal population-based reference range, however, its use is limited by relatively late increase in blood after MI onset (3–6 hours after the onset of necrosis), as well as possible increase that not associated with myocardial ischemia, for example, in sepsis, pulmonary embolism, subarachnoid hemorrhage, severe cardiac and renal failure [2, 6]. In this regard, it is necessary to search for new biomarkers in order to optimize treatment strategies. For example, Copeptin is 39-amino acid glycopeptide acid that is the C-terminal part of pro-vasopressin. It is secreted by the posterior pituitary gland along with vasopressin and reflects the amount of vasopressin involved in biochemical processes.

Endogenous stress leads to antidiuretic hormone (ADH) activation and release of copeptin, independent of cardiomyocyte necrosis [7, 8]. S. Neuhold and M. Huelsmann (2008) [9] demonstrated in their study that copeptin is more valuable prognostic factor compared with brain natriuretic peptide (BNP) in predicting mortality risk in patients with II–III NYHA functional class of heart failure (HF). Large multicenter randomized study that included 1273 patients with HF showed that the level of copeptin is an independent outcome prognostic factor with 3.9 years median of follow-up [4]. Copeptin level in patients with HF independently or in combination with a wide range of biomarkers [10], including BNP and troponins, can significantly contribute to outcomes prediction [11,12].

Materials and methods

The study included 128 patients who were admitted to the hospital with NSTE ACSs in the first 3 hours after pain onset, with CHD development risk factors and signed written informed consent to participate in the study. They were divided into 3 groups during the study depending on the ACS: group 1 — with the development of acute myocardial infarction, group 2 — with unstable angina, group 3 — with excluded coronary pathology. Groups did not differ significantly by age ($p > 0.05$); the average age of the sample was 64.4±10.8. The distribution by gender between groups was approximately the same: 42.3 % of women in the 1st group, 51.7 % — in the second group and 33.3 % — in the third, the results between women and men did not differ significantly ($p > 0.05$). All the groups were examined according to guidelines with the determination of copeptin and troponin T levels at the time of admission and repeated troponin T determination after 12–72 hours in cases of negative or uncertain results. Diagnostic TnT Test Kit was used to identify cardiac troponin, intended for use with the RADIOMETR AQT90 FLEX analyzer. The study of blood plasma samples for copeptin was performed using a set of reagents manufactured by Phoenix pharmaceuticals according to the manufacturer's instructions and protocol using a competitive enzyme-linked immunosorbent assay.

Statistical analysis

Statistical analysis was done using SPSS STATISTIKA 10 program, version 10/11. Quantitative variables were expressed as mean (standard deviation) or median, depending on the type of distribution, qualitative variables — as frequencies, absolute and relative. The significance of differences between two independent samples was estimated using Mann-Whitney test and Student's t-test. Two independent samples with qualitative characteristics were compared using chi-square test. The analysis of the relationship between characters was done using contingency tables, chi-square test and correlation regression analysis. The correlation between copeptin and nonparametric variables was evaluated using Spearman's rank correlation. The survival function analysis was carried out using the Kaplan-Meyer method. Sensitivity, specificity, positive prognostic and negative values were evaluated by analyzing the area under the curve receiver operating characteristics curve (AUC ROC); the cut-off point of copeptin effectiveness in predicting the risk of HF was determined using AUC ROC. P-value less than 0.05 was considered statistically significant.

Results

The risks of repeated acute cardiovascular complications development and mortality were assessed during the stay (short-term prognosis) and long-term follow-up (medium-term prognosis, observation period 180 days). Examined patients with NSTE ACSs had copeptin level rise > 2.95 ng / ml during the stay that was associated with significant mortality and repeated acute cardiovascular events risk increase RR 96.86 [13.60; 689.68 p <0.00001], with a positive prognostic value of 100.00 % (95 % CI 75.75 % —100.00 %).

Significant level of hospital mortality was observed in group 1 (p <0.0001), groups 2 and 3 had no fatal outcomes (Figure 1). The level of copeptin directly correlated with the development of repeated acute coronary events during short- and medium-term follow-up (rs = + 1, p <0.0001) and with hospital mortality (rs = + 0.7, p <0.0001). 12 patients (23.1 %) from group1 died, 6 of them were diagnosed with repeated myocardial infarction, 5 patients with acute left ventricular failure and 1 patient developed cardiogenic shock. All deceased patients had significant copeptin level increase compared with other patients from group 1. Average copeptin level was 5.1±2.28 ng / ml (median 4.12; 2.91–9.24).

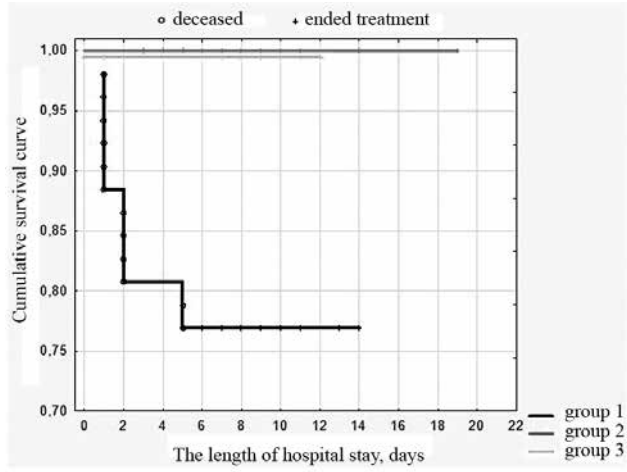

Figure 1. Inpatient Survival Analysis

General survival rate was 90.6 % (116 people) after the hospital stay. During the long-term observation period the number of endpoints (death, the development of repeated acute cardiovascular complications) was 31 % (36 people). By the end of 180 days follow-up, total mortality rate was 6.9 % (8 people). The analysis of mortality showed that 6 participants had repeated AMI with the development of severe heart failure, another 2 patients died from acute left ventricular failure. Mortality rate was equal in the 1st (4 people) and 2nd group (4 people), while there were no deaths 3rd (Figure 2).

Long-term survival analysis showed statistically significant differences between survival curves of the groups (p <0.00022). When comparing the risks of nosocomial and 6-month mortality in patients included in the study, only the difference between the risk of nosocomial mortality was statistically significant. Using the Gehan's criterion we revealed significant differences between groups 1 and 2 (p <0,00063) and groups 1 and 3 (p <0,00858). There were no statisti-

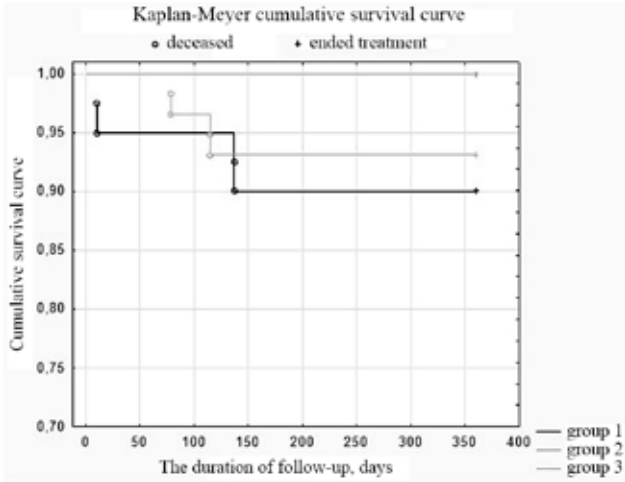

Figure 2. Long-term follow-up survival curves

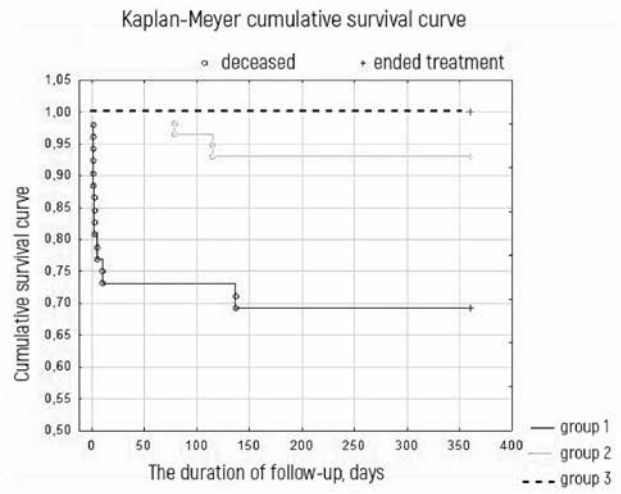

Figure 3. Survival curves during total follow-up (180 days)

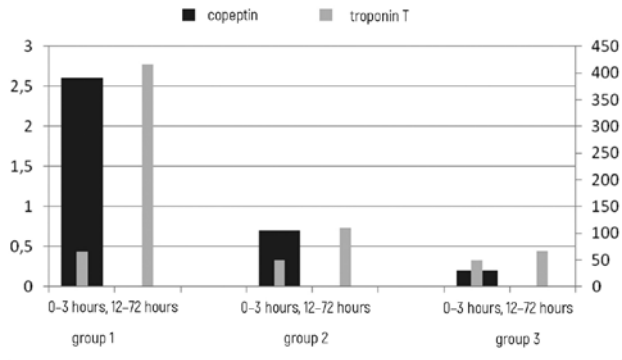

Figure 4. The association between the level of copeptin (ng/ml) and troponin T (ng/l) and mortality, mean values

cally significant differences between groups 2 and 3 (p> 0.05), (Figure 3).

Multivariate analysis (logistic regression) showed that copeptin during the first 3 hours after pain onset — the odds ratio (OR) — 5.27 [1.13–2.46], was stronger independent predictor of primary endpoints achievement during the admission period after MI compared with troponin T, OR 1.02 [0.99; 1.04], (Figure 4).

Positive predictive value of troponin T, as predictor of hospital mortality and recurrent MI, significantly increased after 12–72 hours, OR 4.93, and the cut-off point of troponin T> 147.5 ng / l, determined using ROC analysis, increased the risk of hospital mortality by almost 18 times (RR 17.8 [2.38–131, p <0.0001]) with sensitivity 24 % (95 % CI 14.3–37.4), specificity 100 % (95 % CI 95–100), a positive predictive value of 100 % (95 % CI 75.8–100) and an accuracy of 69.4 % (95 % CI 59–78.1), (Figure 5)

Areas under receiver operating characteristics curves (AUC ROC) after first 3 hours from pain syndrome manifestation were: 0,99 for copeptin (95 % CI 0,99–1,0) and 0,67 (95 % CI 0,5–0,83) for troponin

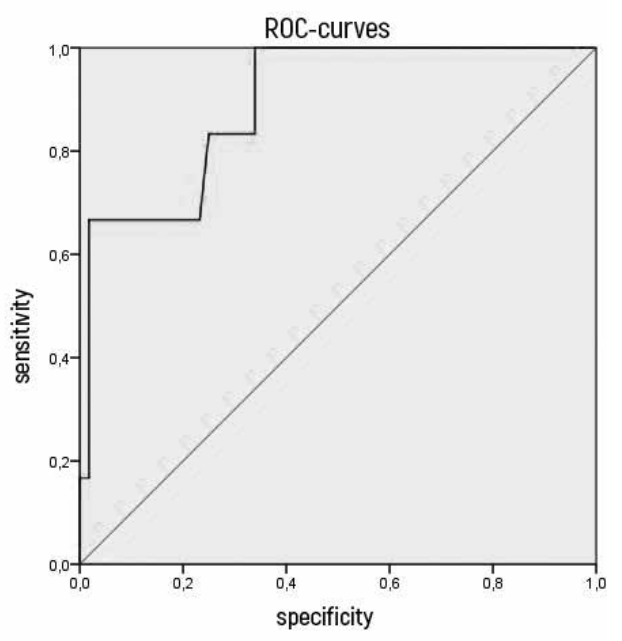

Figure 5. ROC-curve of troponin T level after 12–72 hours ng/l

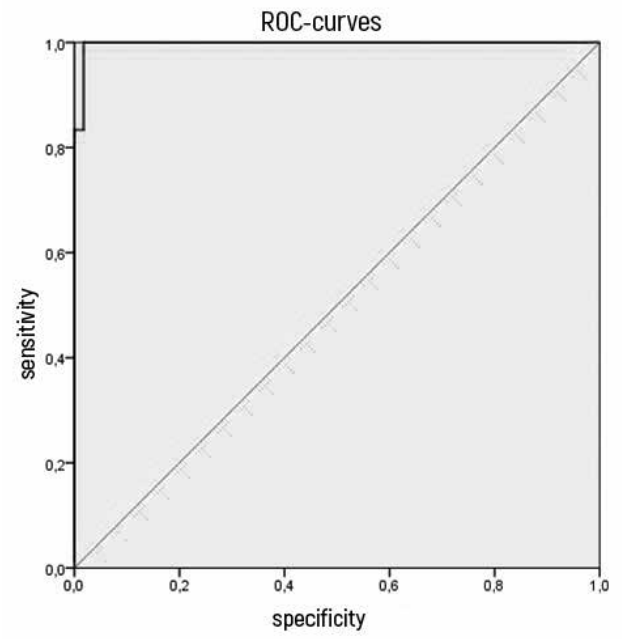

Figure 6. ROC-curve of copeptin level first 3 hours from pain syndrome manifestation

T, respectively (Figure 6, 7). The combination of copeptin and troponin T as recurrent MI and acute cardiovascular complications predictors during first 3 hours after pain syndrome manifestation (the dynamics during 12–72 hours) increased receiver operating characteristics curves to 0,9 (95 % CI 0,81).

The analysis of copeptin possibilities in order to predict the risk of recurrent AMI during 7-day follow-up showed that patients with significantly high copeptin level (median — 4,12 ng/ml, 2,91–9,24) had increased risk of recurrent MI (p < 0,01), when patients

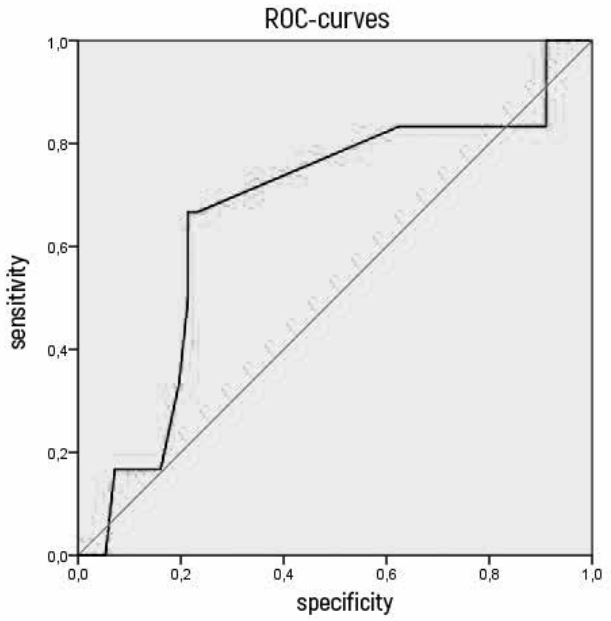

Figure 7. ROC-curve of troponin T (ng/l) level first 3 hours from pain syndrome manifestation

without recurrent MI during 7-day follow-up had significantly lower copeptin level.

According to ROC-curve analysis, copeptin level >2,95 was an independent predictor of AMI, recurrent acute cardiovascular complications and mortality. Therefore, it is possible to use it as predictive marker of acute coronary event during 7-day follow-up after AMI with 85,7% sensitivity (95% CI 60,06–95,9) and 100% specificity (95% CI 96,74–100,00). High sensitivity and specificity of this investigation can be explained by small sample of respondents.

In order to predict mortality, several models of binary logistic regression and algorithms for obtained results processing were developed, coefficients for copeptin were calculated, that are necessary for calculating and interpretation of the parameters.

According to the results of logistic regression analysis, copeptin level determined during the first 3 hours after pain syndrome manifestation, $p \leq 0.00\,001$, was more significant compared with troponin T determined during the same time period for the calculation of mortality risk (table 1).

Event (mortality) possibility was calculated using the formula

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

Where $z = b_1 * X_1 + b_2 X_2 + \ldots + b_n X_n + a$,

X1 — values of independent variables

b1 — coefficients that are calculated using binary logistic regression

a — constant value

In the classification table calculated using binary logistic regression the parameters of group membership (1=sick, 0=healthy) are opposed to predicted (p) parameters using calculated model. Negative prognosis group membership was $p > 0,5$, positive prognosis group membership — $p < 0,5$.

Developed during the investigation binary logistic regression method can be used in clinical practice for mortality prediction using copeptin and troponin levels estimated at the time of admission.

Conclusion

The results of current study showed that plasma copeptin level is valuable mortality risk and recurrent acute cardiovascular complications predictor in patients with NSTE ACSs. The use of extended set of predictors including copeptin increases the accuracy of short-term and long-term prognosis of fatal and non-fatal cardiovascular events up to almost 100%. At the same time, it is gender, age and condition se-

Table 1. **Multivariable model of factors analysis that affect mortality in patients included into the study**

	Constant B0	Troponin T 0–3 hours ng/l	Copeptin at admission 0–3 hours ng/ml
Coefficient estimation	- 5,723 252	0,11 580 045	1,661931E+00
Coefficient standard error	1,137 556	0,01 380 812	3,854260E-01
t (121) Student's t-test	- 5,031 182	1,844 287	4,311931E+00
p-value	0,000 001 714 155	0,0547 633	3,320181E-05
- 95%CL	- 7,975 345	0,01 153 637	8,988780E-01
+95%CL	- 3,471 159	0,04 313 727	2,424983E+00
χ^2 **Wald test**	25,31 279	1,309 392	1,859275E+01
p-value	0,000 000 490 102	0,06 525 132	1,623186E-05
Odds ratio (units of measure)	0,003 269 062	1,015 926	5,269474E+00
- 95%CL	0,0003 438 363	0,9885 299	2,456845E+00
+95%CL	0,03 108 097	1,044 081	1,130204E+01
Odds ratio (range)		5,254 304	3,760968E+06
- 95%CL		0,9978 044	3,600323E+03
+95%CL		92,7042	3,928781E+09

verity independent mortality indicator. Obtained copeptin values, as well as the calculated coefficients using binary logistic regression method, can be used to stratify patients into groups with low, intermediate and high risk. Methods developed during the study for predicting mortality and recurrent acute cardiovascular complications risks are approximate and require validation using larger group of patients, with the inclusion of obtained logistic regression parameters into the GRACE stratification scale for greater reliability.

Conflict of interests: None declared.

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