Cardiovascular Topics

Relationship between adiponectin and copeptin levels with long-term cardiovascular mortality in ST-segment elevation myocardial infarction after percutaneous coronary intervention

Ayça Türer Cabbar, Ersin Yıldırım, Özge Güzelburç Çalbayram, Mustafa A Şimşek, Servet Altay, Kazım S Özcan, M Muzaffer Değertekin

Abstract

Objective: The aim of this study was to determine adiponectin and copeptin levels that might be prognostic for cardiovascular mortality (CvsM) in ST-segment elevation myocardial infarction (STEMI) patients who had percutaneous coronary intervention (PCI).

Methods: Patients who underwent PCI between November 2010 and April 2011 were enrolled and followed for more than eight years. The baseline, demographic and angiographic findings, in-hospital follow up, laboratory results including adiponectin and copeptin levels, and echocardiographic data of the patients were evaluated.

Results: There were 78 males and 20 females. The CvsM rate was 26.66% at 112 months of follow up. Some factors were significantly related to CvsM and adiponectin level was an independent predictor of mortality. A cut-off value of ≥ 8 950 ng/ml for adiponectin and ≥ 7.41 ng/ml for copeptin was related to a 3.01- and 2.83-times higher CvsM risk, respectively.

Conclusion: Adiponectin level was a predictor for CvsM. Higher levels of adiponectin and copeptin could predict a higher risk of CvsM in STEMI patients.

Department of Cardiology, Faculty of Medicine, Yeditepe University, Istanbul, Turkey
Ayça Türer Cabbar, MD, turerayca@gmail.com
Mustafa A Şimşek, MD
M. Muzaffer Değertekin, MD

Department of Cardiology, Istanbul Umraniye Education and Research Hospital, University of Health Sciences, Istanbul, Turkey
Ersin Yıldırım, MD

Department of Cardiology, Dr Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, Istanbul, Turkey
Özge Güzelburç Çalbayram, MD
Kazım S Özcan, MD

Department of Cardiology, Faculty of Medicine, Trakya University, Edirne, Turkey
Servet Altay, MD

Keywords: ST-segment elevation myocardial infarction, mortality, adiponectin, copeptin

Submitted 23/5/23, accepted 6/9/23
Cardiovasc J Afr 2023; online publication www.cvja.co.za

DOI: 10.5830/CVJA-2023-046

ST-segment elevation myocardial infarction (STEMI) is regarded as a type of acute coronary syndrome, and it occurs by rupture or erosion of the atherosclerotic plaque, causing a thrombotic occlusion in the related artery.[1] The prognosis of STEMI patients was related to high risk for developing adverse events in the short or long term due to multiple factors.[2,3]

Although the mortality rates were higher in the study by Kristenson *et al.*,[4] the SAFARI trial, with a large population, reported lower mortality rates at 1.3 and 1.5% at a 30-day follow up.[5] For longer follow ups, the HORIZON-AMI trial reported mortality rates between 1.3 and 10.5% at three years of follow up in different countries.[6]

In the recent literature, copeptin is reported to be used as a novel biomarker to predict poor outcomes and all-cause mortality in MI patients, as an alternative to arginine vasopressin levels, due to its long-term stability and simplicity in measurement.[7] Furthermore, Zhang *et al*. reported that although copeptin could be used to predict clinical outcomes, the underlying mechanism of the relationship between this biomarker and mortality should be investigated further.[8] Moreover, the follow-up period of many studies was no longer than 12 months.

Adiponectin is a protein derived from adipocytes, and via its anti-atherogenic and anti-inflammatory abilities, it has cardioprotective effects.[9] The association between high adiponectin levels and low cardiovascular risk has been shown in healthy subjects.[10,11] However, just the opposite association was also reported for patients with cardiovascular disease.[12] In patients presenting with STEMI, adiponectin is shown to be a predictor for cardiovascular mortality (CvsM) in the long term.[13] Due to contradictory and paradoxical reports, further evaluation of the predictive role of copeptin and adiponectin on mortality in STEMI patients in the long term might be beneficial.

Therefore, this study aimed to determine serum adiponectin and copeptin levels predictive of CvsM in the long term, and

any possible cut-off values for adiponectin and copeptin that might be definitive for CvsM in patients who were all treated with primary percutaneous coronary intervention (PCI) within the first 12 hours of symptom development.

Methods

This retrospective study was designed according to the principles of the Helsinki Declaration and approved by the Yeditepe University ethics committee (no: 1129). All patients signed an informed consent.

Patients with STEMI, who were referred to the emergency department of the hospital and had emergency PCI between November 2010 and April 2011, were enrolled in the study. The inclusion criteria were: patients presenting within 12 hours from the beginning of symptoms (typical chest pain lasting at least 30 minutes), ST-segment elevation 1 mm or more in at least two contiguous ECG leads, or new onset of complete left bundle branch block. Once the STEMI diagnosis was verified, the patients were directly transferred to the primary PCI unit of the same centre. Since primary PCI is possible throughout 24 hours, no thrombolytic therapy was preferred. Patients who did not attend follow ups or could not be reached, who were pregnant, who had chronic renal disease stage 3, 4 or 5, or who died from non-cardiac reasons were excluded.

All patients underwent an initial clinical examination, including physical examination, family and medical history, 12-lead ECG, continuous bedside ECG monitoring, screening blood tests and saturation monitoring with pulse oximetry. The baseline demographics, clinical history, as well as the cause of admission, vital parameters and laboratory results were recorded.

The following baseline and demographic findings were included in the study. Diabetes mellitus was defined as a history of diabetes according to the diagnostic criteria of the World Health Organisation.[14] The patients were regarded as hypertensive if they were already on anti-hypertensive therapy. Hyperlipidaemia was defined as low-density lipoprotein cholesterol levels > 150 mg/dl (3.89 mmol/l), total cholesterol levels > 200 mg/dl (5.18 mmol/l), or triglyceride levels > 150 mg/dl (1.7 mmol/l).

Smoking was defined as the inhaled use of cigars, pipes or cigarettes at any quantity. Body mass index was calculated as the weight (kg) divided by the square of the height (m). Waist circumference was measured on the level of the umbilicus. Cardiogenic shock was defined according to the SHOCK trial.[15] The Killip classification was evaluated as described elsewhere.[16] The CADILLAC score was calculated from the patients' clinical, ECG and angiographic characteristics.

Angiographic findings and in-hospital follow up included hospitalisation period, contrast-induced nephropathy (CIN), inotropic period, in-hospital shock, intra-aortic balloon pump (IABP), in-hospital atrial fibrillation (AF), pre-PCI ST-elevation, post-PCI ST-elevation, DELTA ST-elevation, absence of reflow (no-reflow), intervened artery, pre-PCI thrombolysis in myocardial infarction (TIMI) flow grade, post-PCI TIMI flow grade and number of intervened arteries.

CIN was defined as impairment of renal function measured as either a 25% increase in the serum creatinine level from baseline or a 0.5 mg/dl increase in the absolute serum creatinine value within 48–72 hours after intravenous contrast administration.[17] Coronary flow was graded according to the TIMI criteria between 0 and 3. Lack of ST resolution by 50% was considered as an established marker of no-reflow, between the initial ECG and post-PCI first-hour follow-up ECG.[18]

Regarding laboratory results and echocardiographic data, the glomerular filtration rate (GFR) was estimated using the MDRD-4 formula, as described elsewhere.[19] Routine laboratory methods were used for other blood tests. Blood samples were collected at the admission after STEMI diagnosed on ECG, before the patients were sent to the catheterisation laboratory. The results of those blood tests were collected from the archives for this study.

Previous studies described the release pattern and structure of copeptin.[20] Copeptin plasma levels were evaluated from EDTA blood samples. Samples were centrifuged at 2 000 rpm for 20 minutes at 4°C. Platelet-poor plasma was separated and stored at –80°C until analysis. A commercial automated immunofluorescent assay (Copeptin, Hennings, BRAHMS, GmbH, Germany) was performed on a Kryptor analyser®.

For adiponectin measurements, venous blood was collected in EDTA tubes and centrifuged for 10 minutes at 2 000 rpm, so that the plasma was isolated and stored at −80°C. Total plasma adiponectin levels were measured by an enzyme-linked immunosorbent assay (Assaypro, MO, USA). The lower limit of detection of the assay was 0.246 ng/ml.

Two-dimensional transthoracic echocardiography was performed using a GE Vivid-3 ultrasound machine. The left ventricular ejection fraction (LVEF) was calculated from the modified Simpson method.[21]

All-cause mortality was obtained from the national death records. CvsM was assessed by telephone interviews with the patients, relatives or physicians between January and February 2020. Cardiovascular long-term mortality was identified as death associated with MI, arrhythmia, heart failure (HF), cardiac arrest (due to other unknown cause), or cerebrovascular accident.

Statistical Analyses

Statistical analyses were performed with the Number Cruncher Statistical System 2007 statistical software (Utah, USA) for Windows. Besides standard descriptive statistical calculations (mean and standard deviation, median, interquartile range), when the variables showed a normal distribution, the independent-samples *t*-test was used in the comparison of the groups, whereas, when the variables did not show a normal distribution, the Mann−Whitney *U*-test was used in the comparison of the groups, and the chi-squared test was performed during evaluation of the qualitative data.

Risk factors for mortality were examined in multivariate logistic regression analyses. The Hosmer−Lemeshow test was used for evaluating goodness of fit for logistic regression models. To calculate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and likelihood ratio (LR) (+) for the adiponectin and copeptin measurements at varying cut-off values, a conventional receiver operating characteristic (ROC) curve was generated, and the area under the curve (AUC) was calculated to test adiponectin and copeptin as biomarkers. From the AUC, the best adiponectin and copeptin cut-off values for the mortality groups were determined.

The Kaplan–Meier life-table method, estimating cardiac-related death, was used to summarise the follow-up experience in the patient population. The differences in the survival curves were tested using the log-rank test, adjusting for the adiponectin and copeptin prognostic risk factors. The results were evaluated within a 95% confidence interval (CI). The statistical significance level was established at $p < 0.05$.

Results

We selected 147 patients, of whom 42 could not be reached, resulting in 105 patients in the study. The results showed a total mortality rate of 33.33% (35 out of 105 patients). The CvsM rate was 26.66% (28 out of 105 patients). Among the mortalities, seven died because of non-cardiac reasons, and therefore, they were excluded from the study, resulting in a population of 98 patients (78 male, 20 female) (Fig. 1).

The mean ages of the survivors and the non-survivors were 54.69 ± 11.49 and 65.88 ± 12.29 years, respectively. The total follow-up period was 112 months (mean follow up 97.06 ± 28.83). The mean survival time for CvsM was 52.15 ± 41.12 months. Furthermore, 21.4% of the mortality was observed in the first month, and 30.8% was in the first six months. The baseline demographics and findings in relation to mortality status are shown in Table 1.

At the initial admission age, female gender, diabetes mellitus (DM), peripheral arterial disease, cerebrovascular accident, previous PCI, previous MI, cardiogenic shock and Killip classification score of 4, symptom-to-balloon time, heart rate and CADILLAC score were significantly higher among the non-survivors than the survivors ($p < 0.05$). No significant difference was observed between other baseline data ($p > 0.05$).

The angiographic findings are shown in Table 2. There was no significant relationship between the angiographic findings and mortality rate for most of the data. However, post-PCI TIMI flow grade 0 and 1 and no-reflow after performing intervention to the vein were significantly higher in the non-survivor group ($p < 0.05$). At the in-hospital follow up, the requirement of the inotropic period, in-hospital shock and IABP were significantly higher among the non-survivors ($p < 0.05$).

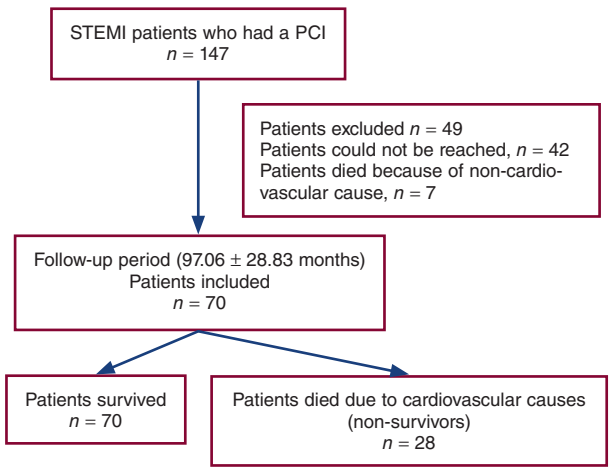

Fig. 1. Flow diagram of the patients included in the study.

The laboratory results and echocardiographic data are shown in Table 3. The peak creatine kinase MB level, triglyceride and initial glucose levels, platelet count, adiponectin levels (survivors: 5996.69 ± 3746.46, non-survivors: 15764.85 ± 19609.06, $p = 0.0001$) and copeptin levels (survivors: 0.6 ± 0.47, non-survivors: 1.25 ± 0.72, $p = 0.0001$) were significantly higher in the non-survivor group ($p < 0.05$). Only the LVEF was significantly lower in the non-survivor group ($p = 0.005$). There were no significant differences observed for the other data.

When the multivariate logistic regression analyses were performed for the factors that were found to be statistically

Table 1. Baseline demographics and findings of the patients

Demographics	*Survivors (n = 70)*	*Non-survivors (n = 28)*	p-*value*
Age (years), mean ± SD	54.69 ± 11.49	65.88 ± 12.29	0.0001
Gender, *n* (%)			
Male	60 (85.71)	18 (64.29)	0.026
Female	10 (14.29)	10 (35.71)	
DM, *n* (%)	13 (18.57)	12 (42.86)	0.018
Hypertension, *n* (%)	24 (34.29)	13 (46.43)	0.295
Family history of cardiac disease, *n* (%)	31 (44.29)	9 (32.14)	0.199
Hyperlipidaemia, *n* (%)	19 (27.14)	9 (32.14)	0.793
Smoking, *n* (%)			
No	22 (31.43)	13 (46.43)	0.086
Yes	44 (62.86)	10 (35.71)	
Quit	4 (5.71)	5 (17.86)	
Previous MI, *n* (%)	6 (8.57)	9 (32.14)	0.015
Previous PCI, *n* (%)	3 (4.29)	7 (25.00)	0.015
Previous CABG, *n* (%)	1 (1.43)	3 (10.71)	0.107
Previous PAD, *n* (%)	0 (0.00)	6 (21.43)	0.001
Previous CVA, *n* (%)	2 (2.86)	5 (17.86)	0.023
Previous congestive heart disease, *n* (%)	2 (2.86)	3 (10.71)	0.436
Angina, *n* (%)	21 (30)	9 (32.14)	0.272
Waist circumference (cm), mean ± SD	100.49 ± 13.4	103.14 ± 14.74	0.541
BMI, mean ± SD	27.99 ± 3.79	26.37 ± 3.29	0.111
Systolic blood pressure (mm/Hg), mean ± SD	124.43 ± 23.57	123.96 ± 26.25	0.935
Diastolic blood pressure (mm/Hg), mean ± SD	77.49 ± 16.47	72.61 ± 14.27	0.208
Heart rate, mean ± SD	81.41 ± 19.48	92.2 ± 25.61	0.034
Pulse pressure, mean ± SD	47.35 ± 15.93	51.35 ± 20.44	0.354
Median (IQR)	43.5 (40–54.75)	50 (35–64)	
Anterior MI, *n* (%)	28 (40.00)	14 (50.00)	0.487
LBBB, *n* (%)	1 (1.43)	3 (10.71)	0.117
Third-degree AV block, *n* (%)	8 (10.43)	4 (12.28)	0.844
Cardiogenic shock, *n* (%)	2 (2.86)	6 (21.43)	0.006
Anaemia, *n* (%)	15 (21.43)	8 (28.57)	0.504
Killip classification, *n* (%)			0.035
Score 1	66 (94.29)	20 (71.43)	
Score 2	1 (1.43)	3 (10.71)	
Score 3	1 (1.43)	0 (0.00)	
Score 4	2 (2.86)	5 (17.86)	
CADILLAC score			
Mean ± SD	2.17 ± 2.34	5.4 ± 3.15	0.0001
Median (IQR)	2 (0–4)	4.5 (2–8)	
Symptom-to-balloon time (h)			
Mean ± SD	4.26 ± 8.69	8.92 ± 16.07	0.018
Median (IQR)	3 (2–4)	4 (2.5–5.75)	
Follow up (m), mean ± SD	108.27 ± 1.77	52.15 ± 41.12	0.0001

DM: diabetes mellitus, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, PAD: peripheral artery disease, CVA: cerebrovascular accident, BMI: body mass index, LBBB: left bundle branch block, AV block: atrioventricular block.

Table 2. Angiographic findings and in-hospital follow-up data of the patients

Findings	*Survivors (n = 70)*	*Non-survivors (n = 28)*	p-*value*
Hospitalisation period (day)			
Mean ± SD	8.56 ± 4.19	9.01 ± 5.759	0.444
Median (IQR)	7 (6–10)	9 (7–14)	
CIN, *n* (%)	1 (1.43)	1 (3.57)	0.361
Inotropic period, *n* (%)	2 (2.86)	8 (28.57)	0.0001
In-hospital shock, *n* (%)	2 (2.86)	8 (28.57)	0.001
IABP, *n* (%)	1 (1.43)	4 (14.29)	0.028
In hospital AF, *n* (%)	3 (4.29)	5 (17.86)	0.063
Pre-PCI ST-elevation			0.675
Mean ± SD	10.14 ± 7.23	10.71 ± 6.35	
Median (IQR)	7.25 (5–16.875)	10(5–16.25)	
Post-PCI ST-elevation			0.375
Mean ± SD	3.34 ± 3.02	4.91 ± 4.88	
Median (IQR)	2.25(1–4.875)	3.5(1–7.875)	
DELTA ST-elevation			
Mean ± SD	6.75 ± 5.33	6.34 ± 4.47	0.971
Median (IQR)	5.5(3–10)	6.25(2.5–10)	
No-reflow, *n* (%)			0.006
No	64 (91.43)	17 (60.71)	
Yes	6 (8.57)	9 (39.29)	
Intervened artery, *n* (%)			0.167
LMCA	1 (1.45)	1 (4.17)	
LAD	28 (40.58)	10 (41.67)	
Cx	10 (14.49)	3 (12.50)	
RCA	29 (42.03)	7 (29.17)	
SVG	0 (0.00)	1 (4.17)	
LIMA	0 (0.00	1 (4.17)	
Dia	1 (1.45)	0 (0.00)	
OM	0 (0.00)	1 (4.17)	
Pre-PCI TIMI, *n* (%),			0.692
Grade 0	49 (70.00)	20 (71.43)	
Grade 1	8 (11.43)	4 (14.29)	
Grade 2	8 (11.43)	2 (7.14)	
Grade 3	5 (7.14)	2 (7.14)	
Post-PCI TIMI, *n* (%)			0.018
Grade 0	1 (1.43)	5 (17.86)	
Grade 1	2 (2.86)	3 (10.71)	
Grade 2	1 (1.43)	0 (0.00)	
Grade 3	66 (94.29)	20 (71.43)	
Number of intervened arteries, *n* (%)			
1 artery	36 (51.43)	7 (25.00)	
2 arteries	26 (37.14)	14 (50.00)	
3 arteries	7 (10.00)	7 (25.00)	
4 arteries	1 (1.43)	0 (0.00)	

CIN: contrast-induced nephropathy, IABP: intra-aortic balloon pump, AF: atrial fibrillation, PCI: percutaneous coronary intervention, TIMI: thrombolysis in myocardial infarction, LMCA: left main coronary artery, LAD: left anterior descending artery, Cx: circumflex artery, RCA: right coronary artery, SVG: saphenous vein graft, LIMA: left internal mammary artery, Dia: diagonal artery, OM: obtuse marginal artery.

Table 3. Laboratory findings and echocardiographic data of the patients

Findings	*Survivors (n = 70)*	*Non-survivors (n = 28)*	p-*value*
GFR (ml/min/1.73 m²), mean ± SD	117.02 ± 35.13	96.73 ± 51.35	0.06
Initial creatinine (mg/dl)			0.182
Mean ± SD	0.86 ± 0.2	0.99 ± 0.41	
Median (IQR)	0.83 (0.7075–1.03)	0.89 (0.735–1.16)	
Maximum creatinine (mg/dl)			0.372
Mean ± SD	1.11 ± 0.56	1.36 ± 1.18	
Median (IQR)	1.04 (0.9275–1.1825)	1.065 (0.885–1.42)	
Peak CK-MB (U/l)			0.028
Mean ± SD	167.64 ± 158.99	277.61 ± 230.37	
Median (IQR)	126 (62.5–211)	186 (91–459)	
Total cholesterol (mg/dl), mean ± SD	192.69 ± 41.07	193.86 ± 37.43	0.908
(mmol/l)	4.99 ± 1.06	5.02 ± 0.97	
LDL-C (mg/dl), mean ± SD	119.08 ± 35.29	121.67 ± 44.9	0.786
(mmol/l)	3.08 ± 0.91	3.15 ± 1.16	
HDL-C (mg/dl), mean ± SD	37.85 ± 9.58	40.52 ± 8.64	0.258
(mmol/l)	0.98 ± 0.25	1.05 ± 0.22	
Triglycerides (mg/dl), mean ± SD	178.2 ± 88.81	134.9 ± 53.52	0.038
(mmol/l)	2.01 ± 1.00	1.52 ± 0.60	
Glucose (mg/dl), Mean ± SD	148.73 ± 62.16	210.8 ± 99.32	0.0001
(mmol/l)	8.25 ± 3.45	11.70 ± 5.51	
Platelets (× 10³ cells/µl), mean ± SD	244.12 ± 56.69	276.44 ± 79.75	0.032
WBC (× 10³ cells/µl), mean ± SD	11.75 ± 2.81	18.04 ± 29.69	0.081
Haemoglobin (g/dl), mean ± SD	14.07 ± 1.92	13.39 ± 1.98	0.134
Haematocrit (%), mean ± SD	40.37 ± 5.45	38.5 ± 5.29	0.142
Mean platelet value, mean ± SD	8.43 ± 0.91	8.46 ± 1.2	0.912
K (mEq/l), mean ± SD	4.13 ± 0.5	4.23 ± 0.54	0.394
Mg (mg/dl), mean ± SD	2.2 ± 0.22	2.11 ± 0.25	0.129
Adiponectin (ng/ml)			0.0001
Mean ± SD	5996.69 ± 3746.46	15764.85 ± 19609.06	
Median (IQR)	5467.5 (2662.5–9032.5)	11925 (6310–16981.25)	
Copeptin (ng/ml)			0.0001
Mean ± SD	0.6 ± 0.47	1.25±0.72	
Median (IQR)	4.85 (3.15–8.0575)	11.22 (7.5–17.13)	
LVEF, mean ± SD	49.93 ± 10.43	41.9 ± 10.66	0.005

GFR: glomerular filtration rate, peak CK-MB: peak creatinine kinase myoglobin, LDL-C: low-density cholesterol, HDL-C: high-density cholesterol, WBC: white blood cells, K: potassium, Mg: magnesium, LVEF: left ventricular ejection fraction.

Table 4. Multivariate logistic regression analyses of the variables

					95% CI	
Variables	*B*	*SE*	p-*value*	*OR*	*Lower*	*Upper*
Age	0.03	0.07	0.716	1.03	0.90	1.17
Gender	–0.85	1.70	0.616	0.43	0.02	1.90
DM	4.30	1.59	0.007	0.01	0.00	0.31
Previous MI	–1.78	1.95	0.362	0.17	0.00	7.74
Killip	0.35	0.98	0.723	1.42	0.21	4.67
CADILLAC	0.38	0.16	0.02	1.46	1.06	2.01
Peak CK-MB	0.01	0.01	0.335	1.01	1.00	1.01
Triglycerides	0.01	0.01	0.332	0.99	0.96	1.01
Glucose	0.00	0.02	0.861	1.00	0.97	1.03
Symptom to balloon	0.02	0.08	0.849	1.02	0.86	1.20
Adiponectin	0.01	0.001	0.004	1.00	1.00	1.00
Copeptin	1.45	1.61	0.367	4.26	0.18	9.39
LVEF	–0.17	0.06	0.008	0.84	0.74	0.96

DM: diabetes mellitus, MI: myocardial infarction, peak CK-MB: peak creatinine kinase myoglobin, LVEF: left ventricular ejection fraction.

significant in the univariate tests, DM, higher CADILLAC scores, higher adiponectin levels and lower LVEF were found to be factors affecting long-term mortality (Table 4). The results of the goodness-of-fit test showed a good fit for the model of variables (chi-square: 2.97, $p = 0.887$).

According to CvsM, the subjects were divided into two groups. The AUC of adiponectin (0.785, 95% CI: 0.686−0.864), with the optimal cut-off level of 8 950 ng/ml, revealed 73.08% sensitivity and 75.71% specificity in the prediction of patients with increased mortality rates. The AUC of copeptin (0.789, 95% CI: 0.691−0.868), with the optimal cut-off level of 7.41 ng/ml, revealed 80.95% sensitivity and 71.43% specificity

Table 5. Receiver operating characteristics analyses for adiponectin and copeptin

	AUC	*SE*	*95% CI*	*Criterion*	*Sensitivity*	*Specificity*	*PPV*	*NPV*	*LR (+)*
Adiponectin	0.785	0.063	0.686–0.864	≥ 8950	73.08	75.71	52.8	88.3	3.01
Copeptin	0.789	0.062	0.691–0.868	≥ 07.41	80.95	71.43	45.9	92.6	2.83

AUC: area under the curve, SE: standard error, CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value, LR: likelihood ratio.

in the prediction of patients with increased mortality rates. The PPV, NPV and LR are shown in Table 5.

The risk of mortality of a patient with an adiponectin level of ≥ 8 950 ng/ml was 3.01 times higher than for a patient with an adiponectin level of < 8 950 ng/ml. Additionally, the mortality risk of a patient with a copeptin level of ≥ 7.41 ng/ml was 2.83 times higher than a patient with a copeptin level of < 7.41 ng/ml (Table 5, Fig. 2).

Fig. 3 demonstrates the Kaplan–Meier survival curve for the adiponectin and copeptin cut-off values. As shown in Fig. 3 and Table 6, an adiponectin level of ≥ 8 950 ng/ml and a copeptin level of ≥ 7.41 ng/ml were associated with a decreased survival time (log-rank statistic = 18.02 and 18.94, $p = 0.0001$ and $p = 0.0001$, respectively). The mortality rate was significantly higher in patients who had an adiponectin level of ≥ 8 950 ng/ml than in patients who had an adiponectin level of < 8 950 ng/ml ($p = 0.0001$). Similarly, patients who had a copeptin level of ≥ 7.41 ng/ml showed a significantly higher mortality rate than patients who had a level of < 7.41 ng/ml ($p = 0.0001$).

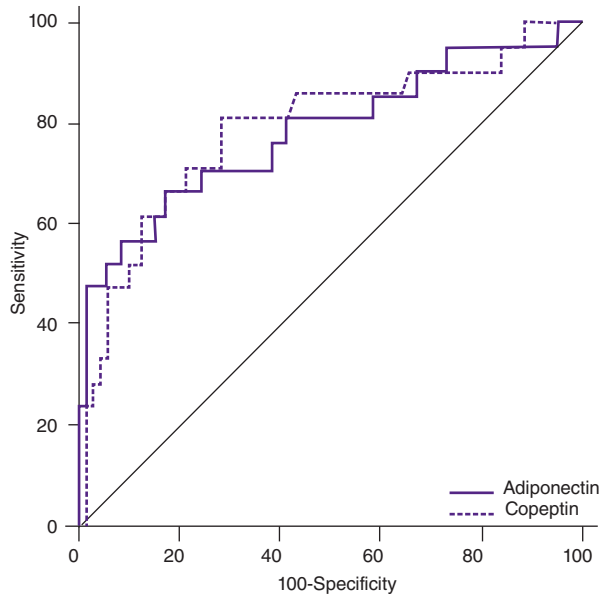

Fig. 2. ROC curve of adiponectin and copeptin levels and mortality rate.

Discussion

A CvsM rate of 26.66% was observed in this cohort of unselected patients, who were all diagnosed with STEMI and had had PCI. Second, the multivariate tests showed adiponectin level to be a significant predictor for CvsM. Third, adiponectin and copeptin showed significant cut-off levels regarding CvsM in the long term. To the best of our knowledge this is the first study showing such relationships for adiponectin and copeptin in STEMI patients at a long-term follow up of 112 months.

The pattern of long-term mortality after STEMI in the presence of PCI has been described in previous studies. All-cause mortality rates were reported between 8.05 and 28.9% in those

Table 6. Kaplan–Meier survival analyses for adiponectin and copeptin

Follow up	*Adiponectin < 8 950 ng/ml*	*Adiponectin ≥ 8 950 ng/ml*	*Copeptin < 7.41 ng/ml*	*Copeptin ≥ 7.41 ng/ml*
1 year	0.983	0.811	9.81	8.46
2 years	0.983	0.811	9.81	8.46
3 years	0.966	0.784	9.81	8.21
5 years	0.949	0.757	9.62	7.44
10 years	0.881	0.541	9.05	6.15
Survival, median ± SD	104.69 ± 2.57	79.76 ± 7.35	108.43 ± 1.40	82.51 ± 6.86
95% CI	99.66–109.72	65.35–94.17	105.67–111.17	69.06–95.96
	log rank: 18.02, $p = 0.0001$		log rank: 18.94, $p = 0.0001$	

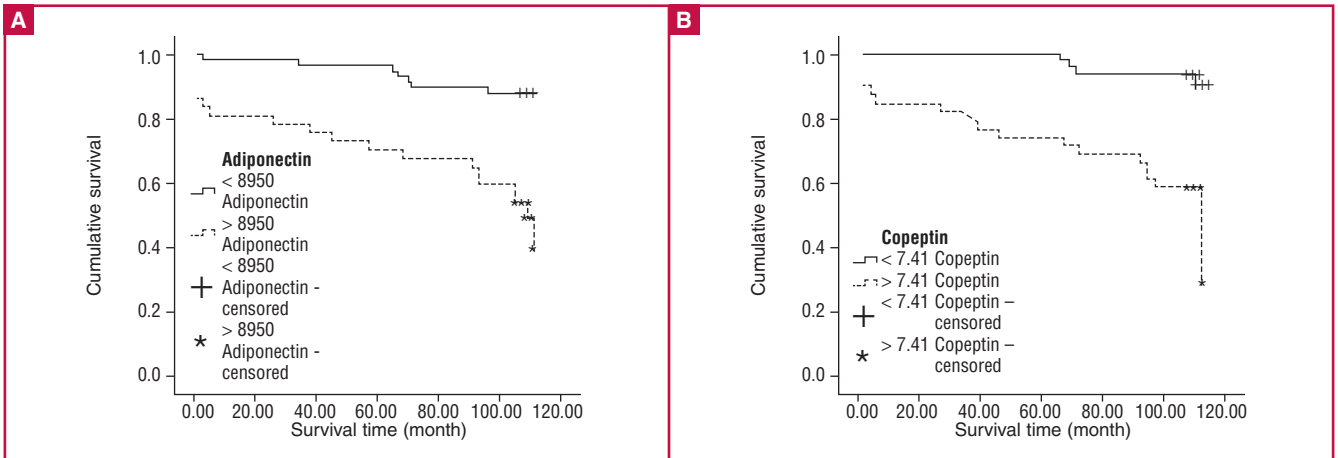

Fig. 3. Kaplan–Meier cumulative survival curve according to adiponectin (A) and copeptin (B) cut-off levels.

studies, at different follow-up periods, from one to eight years.[22-26] Our study focused on the CvsM in a cohort of unselected STEMI patients after PCI.

A literature search revealed the CvsM rate between 2.3 and 25.4% at different follow ups between 18.6 months and 4.7 years.[25,27-29] The CvsM rate observed in this study was 26.66%, which was found to be higher than previous reports. The greater prevalence of co-morbidities among patients might have caused those different CvsM rates. However, this study was the longest to date for the long-term CvsM outcome of PCI in STEMI patients, which might support the findings that longer follow-up periods might be associated with higher CvsM rates.

Furthermore, studies showed that CvsM was relatively high in the first month, and it fell considerably after the first month to < 1.5% per year.[28] This supports that, once unselected patients had survived from the acute phase of STEMI with PCI, they had a better late cardiac prognosis, even similar to that of selected patients of other trials.[28] This finding was similar in our study, where 21.4% of the mortality was observed within the first month, and 30.8% was within six months. These results suggest that, for prevention and treatment of cardiac death, resources should be directed to the early phase of STEMI.[28]

The prognostic value of adiponectin has been investigated intensely in the last decade. Although early reports indicated a protective association with the outcome,[10,30] recent reports associated higher adiponectin levels with a worse prognosis in healthy subjects and patients with MI or HF.[31]

Rathmann and Herder proposed that adiponectin may be upregulated in a counter-regulatory pattern to prevent the progression of cardiovascular dysfunction and atherosclerosis.[32] Conversely, Wannamethee *et al.* showed that a high adiponectin level was independently associated with CvsM. However, with the inclusion of NT-proBNP, the association disappeared.[33] Similarly, Lindberg *et al*. extended these findings to STEMI patients, reporting the importance of considering the levels of natriuretic peptide while evaluating the adiponectin levels for risk stratification.[34]

On the contrary, Reinstadler *et al*. showed that increased aortic stiffness was associated with high plasma adiponectin concentrations, which is a potential promoter of ischaemic heart disease in patients after acute STEMI, independent of gender, age, total cholesterol level, smoking status or NT-proBNP level.[35] Adiponectin was not related to LVEF or NT-proBNP in other reports on coronary artery disease and STEMI patients.[13,36]

It was reported that, even in younger adults without any prevalent cardiometabolic disease, adiponectin level had an independent positive association with CvsM at a follow up of 10.4 years.[37] However, there are only a few studies that investigated the long-term prognostic value of adiponectin level in STEMI patients undergoing PCI.[38]

Although Delhaye *et al.* observed preprocedural adiponectin as an independent predictor of mortality in patients with symptomatic stable coronary artery disease and non-ST elevation acute coronary syndrome in patients undergoing PCI at 3.7 years of follow up,[38] Lindberg *et al*. showed adiponectin to be an independent predictor of CvsM in STEMI patients treated with primary PCI.[13] In this study, the multivariate tests showed that higher levels of adiponectin were an independent predictor of CvsM. Moreover, we calculated a cut-off value using ROC curve analysis and found that a preprocedural adiponectin level of 8 950 ng/ml could predict increased CvsM rates with 73.08% sensitivity and 75.71% specificity. The mortality risk was 3.01 times higher for a patient with an adiponectin level higher than 8 950 ng/ml than a patient with a level below this cut-off value.

Early studies showed that higher copeptin levels were an independent prognostic factor for both poor functional outcome and mortality in cardio-cerebrovascular disease.[39,40] Several studies confirmed strong associations of all-cause mortality with copeptin in patients presenting to emergency departments due to stable angina pectoris or MI, in patients with acute HF and in haemodialysis patients with DM.[41,42]

Tasevska *et al*. reported that fasting copeptin levels predicted both CvsM and total mortality in a cohort of unselected healthy patients with or without DM at a follow-up period of 6.5 years. Additionally, it was reported as a predictor of coronary artery disease.[43] The authors suggested that subjects belonging to the top quartile of copeptin had a > 70% increased risk of dying from cardiovascular disease than those in the lowest quartile.[43] Engelbertz *et al*. suggested that patients who had elevated copeptin levels had an increased rate of mortality within 180 days, and copeptin level was a sole independent predictor of mortality.[44]

In a recent meta-analysis conducted by Zhang *et al*., the authors showed that the risk of death increased by 3% per unit increase in baseline level and by more than 200% for a 10-fold copeptin level increase.[8] Furthermore, in comparison to the group with a lower level, the patients with HF who had higher levels were at 1.69 times higher risk from all-cause mortality.[8] These multiple reports stated that circulating copeptin levels were necessary for risk stratification,[8,44,45] and defining uniform values will be helpful to use copeptin as a valuable predictor in everyday practice.[44]

Doğanay *et al*. reported that a higher copeptin level of 6.8 ng/ml was a predictor of occluded infarct-related arteries. Further copeptin levels were significantly related to TIMI flow grade in infarct-related arteries in STEMI patients who presented to the emergency departments within the first three hours of chest pain.[46] Although the results of this study showed a significant relationship between copeptin values and CvsM, it was not an independent predictor according to logistic regression analysis. Nevertheless, it was found that a cut-off preprocedural copeptin value of 7.41 ng/ml was strongly and significantly predictive for CvsM, and a value higher than this cut-off value was related to a 2.83-times higher CvsM risk in STEMI patients who underwent PCI procedure.

Limitations

One limitation was that this study specifically focused on CvsM. However, analyses of causes of cardiac death might be limited, because they might have been influenced by other diseases, particularly in patients with multiple organ dysfunction and patients who were found dead, especially for studies with these long follow-up periods. What is more, this was a single-centre study with a limited number of patients. Additionally, the data were observational data, therefore we cannot prove causality.

Adiponectin and copeptin levels were only determined at baseline and not at follow up. It would have been interesting to know whether adiponectin and copeptin levels had changed after successful PCI. Nevertheless, the blood samples were collected within the first 12 hours. Therefore, the detected values

of copeptin and adiponectin were not strongly corresponding with the real raised values within the window of the first hour. Additionally, the population of the study in terms of admission causes was strongly heterogeneous. Therefore, we believe that the population reflected a typical, critically ill population that physicians face on an everyday basis, which represents the major strength of these data.

Conclusions

The result of this study showed that, although some factors were significantly related to CvsM, adiponectin levels were an independent predictor of CvsM. Besides, the results showed that an adiponectin level of ≥ 8 950 ng/ml and a copeptin level of ≥ 7.41 ng/ml could predict CvsM with a high sensitivity and specificity in STEMI patients who had had PCI. Therefore, these markers might be helpful to provide information, not only in decision making for treatment, but also in the prediction of clinical outcomes. However, these findings should be further investigated in future studies.

The authors thank Fatih Cabbar for his contributions in the preparation of this article.

References

1. Bulluck H, Hoole SP. Management of ST segment elevation myocardial infarction. *Medicine* 2018; **46**(9): 540–546.
2. Steg G, James SK, Atar D, Badano LP, Lundqvist CB, Borger MA, *et al*. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Revista Española de Cardiología* (English edn) 2013; **66**(1): 53.
3. Anderson JL, Morrow DA. Acute myocardial infarction. *N Engl J Med* 2017; **376**(21): 2053–2064.
4. Kristensen SD, Laut KG, Fajadet J, Kaifoszova Z, Kala P, Di Mario C, *et al*. Reperfusion therapy for ST elevation acute myocardial infarction 2010/2011: current status in 37 ESC countries. *Eur Heart J* 2014; **35**(29): 1957–1970.
5. Le May M, Wells G, So D, Chong AY, Dick A, Froeschl M, *et al.* Safety and efficacy of femoral access vs radial access in ST-segment elevation myocardial infarction: the SAFARI-STEMI randomized clinical trial. *J Am Med Assoc Cardiol* 2020; **5**(2): 126–134.
6. Tobbia P, Brodie BR, Witzenbichler B, Metzger C, Guagliumi G, Yu J, e*t al.* Adverse event rates following primary PCI for STEMI at US and non-US hospitals: three-year analysis from the HORIZONS-AMI trial. *EuroIntervention* 2013; **8**(10): 1134–1142.
7. Raskovalova T, Twerenbold R, Collinson PO, Keller T, Bouvaist H, Folli C, *et al.* Diagnostic accuracy of combined cardiac troponin and copeptin assessment for early rule-out of myocardial infarction: a systematic review and meta-analysis. E*ur Heart J Acute Cardiovasc Care* 2014; **3**(1): 18–27.
8. Zhang P, Wu X, Li G, Sun H, Shi J. Prognostic role of copeptin with all-cause mortality after heart failure: a systematic review and meta-analysis. *Ther Clin Risk Manag* 2017; **13**: 49–58.
9. Vaiopoulos AG, Marinou K, Christodoulides C, Koutsilieris M. The role of adiponectin in human vascular physiology. *Int J Cardiol* 2012; **155**(2): 188–193.
10. Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB. Plasma adiponectin levels and risk of myocardial infarction in men. *J Am Med Assoc* 2004; **291**(14): 1730–1737.
11. Frystyk J, Berne C, Berglund L, Jensevik K, Flyvbjerg A, Zethelius B. Serum adiponectin is a predictor of coronary heart disease: a population-based 10-year follow-up study in elderly men. *J Clin Endocrinol Metab* 2007; **92**(2): 571–576.
12. Maiolino G, Cesari M, Sticchi D, Zanchetta M, Pedon L, Antezza K, *et al*. Plasma adiponectin for prediction of cardiovascular events and mortality in high-risk patients. *J Clin Endocrinol Metab* 2008; **93**(9): 3333–3340.
13. Lindberg S, Pedersen SH, Mogelvang R, Bjerre M, Frystyk J, Flyvbjerg A, *et al*. Usefulness of adiponectin as a predictor of all cause mortality in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. *Am J Cardiol* 2012; **109**(4): 492–496.
14. Kistorp C, Galatius S, Gustafsson F, Faber J, Corell P, Hildebrandt P. Prevalence and characteristics of diabetic patients in a chronic heart failure population. *Int J Cardiol* 2005; **100**(2): 281–287.
15. Hochman JS, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, *et al*. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should we emergently revascularize occluded coronaries for cardiogenic shock. *N Engl J Med* 1999; **341**(9): 625–634.
16. Killip T, 3rd, Kimball JT. Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. *Am J Cardiol* 1967; **20**(4): 457–464.
17. Kellum JA, Lameire N, Aspelin P, Barsoum RS, Burdmann EA, Goldstein SL, *et al*. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2012; **2**(1): 1–138.
18. Schroder R. Prognostic impact of early ST-segment resolution in acute ST-elevation myocardial infarction. *Circulation* 2004; **110**(21): e506–e510.
19. Teruel JLG, Catalán SB. Valoración de afección renal, disfunción renal aguda e hiperpotasemia por fármacos usados en cardiología y nefrotoxicidad por contrastes. *Revista Española de Cardiología* 2011; **64**(12): 1182–1192.
20. Gu YL, Voors AA, Zijlstra F, Hillege HL, Struck J, Masson S, *et al.* Comparison of the temporal release pattern of copeptin with conventional biomarkers in acute myocardial infarction. *Clin Res Cardiol* 2011; **100**(12): 1069–1076.
21. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, *et al*. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989; **2**(5): 358–367.
22. Gnavi R, Rusciani R, Dalmasso M, Giammaria M, Anselmino M, Roggeri DP, *et al*. Gender, socioeconomic position, revascularization procedures and mortality in patients presenting with STEMI and NSTEMI in the era of primary PCI. Differences or inequities? *Int J Cardiol* 2014; **176**(3): 724–730.
23. Shiyovich A, Bental T, Plakht Y, Vaknin-Assa H, Greenberg G, Lev EI, *et al*. Prediction of mortality in hospital survivors of STEMI: External validation of a novel acute myocardial infarction prognostic score. *Cardiovasc Revasc Med* 2019; **20**(2): 96–100.
24. Chan MY, Sun JL, Newby LK, Shaw LK, Lin M, Peterson ED, *et al.* Long-term mortality of patients undergoing cardiac catheterization for ST-elevation and non-ST-elevation myocardial infarction. *Circulation* 2009; **119**(24): 3110–3117.
25. Weintraub WS, Grau-Sepulveda MV, Weiss JM, Delong ER, Peterson ED, O'Brien SM, *et al*. Prediction of long-term mortality after percuta-

neous coronary intervention in older adults: results from the National Cardiovascular Data Registry. *Circulation* 2012; **125**(12): 1501–1510.
26. Piackova E, Jager B, Farhan S, Christ G, Schreiber W, Weidinger F, *et al.* Gender differences in short- and long-term mortality in the Vienna STEMI registry. *Int J Cardiol* 2017; **244**: 303–308.
27. Samanta R, Narayan A, Kovoor P, Thiagalingam A. Influence of BMI on short and long-term outcomes in patients with STEMI and LV dysfunction. *Heart Lung Circ* 2020; **29**(3): 361–367.
28. Pedersen F, Butrymovich V, Kelbaek H, Wachtell K, Helqvist S, Kastrup J, *et al*. Short- and long-term cause of death in patients treated with primary PCI for STEMI. *J Am Coll Cardiol* 2014; **64**(20): 2101–2108.
29. Samanta R, Narayan A, Kovoor P, Thiagalingam A. Long-term survival in patients presenting with STEMI complicated by out of hospital cardiac arrest. *Int J Cardiol Heart Vasc* 2019; **22**: 50–54.
30. Wolk R, Berger P, Lennon RJ, Brilakis ES, Davison DE, Somers VK. Association between plasma adiponectin levels and unstable coronary syndromes. *Eur Heart J* 2007; **28**(3): 292–298.
31. Lindberg S, Mogelvang R, Pedersen SH, Bjerre M, Frystyk J, Flyvbjerg A, *et al.* Relation of serum adiponectin levels to number of traditional atherosclerotic risk factors and all-cause mortality and major adverse cardiovascular events (from the Copenhagen City Heart Study). *Am J Cardiol* 2013; **111**(8): 1139–1145.
32. Rathmann W, Herder C. Adiponectin and cardiovascular mortality: evidence for 'reverse epidemiology'. *Horm Metab Res* 2007; **39**(1): 1–2.
33. Wannamethee SG, Welsh P, Whincup PH, Sawar N, Thomas MC, Gudnarsson V, *et al.* High adiponectin and increased risk of cardiovascular disease and mortality in asymptomatic older men: does NT-proBNP help to explain this association? E*ur J Cardiovasc Prev Rehabil* 2011; **18**(1): 65–71.
34. Lindberg S, Jensen JS, Hoffmann S, Pedersen SH, Iversen AZ, Galatius S, *et al*. Interplay Between adiponectin and pro-atrial natriuretic peptide and prognosis in patients with ST-segment elevation myocardial infarction. *Am J Cardiol* 2015; **116**(9): 1340–1345.
35. Reinstadler SJ, Klug G, Feistritzer HJ, Mayr A, Bader K, Mair J, *et al*. Relation of plasma adiponectin levels and aortic stiffness after acute ST-segment elevation myocardial infarction. *Eur Heart J Acute Cardiovasc Care* 2014; **3**(1): 10–17.
36. Schnabel R, Messow CM, Lubos E, Espinola-Klein C, Rupprecht HJ, Bickel C, *et al*. Association of adiponectin with adverse outcome in coronary artery disease patients: results from the AtheroGene study. *Eur Heart J* 2008; **29**(5): 649–657.
37. Witberg G, Ayers CR, Turer AT, Lev E, Kornowski R, de Lemos J, *et al*. Relation of Adiponectin to all-cause mortality, cardiovascular mortality, and major adverse cardiovascular events (from the Dallas Heart Study). *Am J Cardiol* 2016; **117**(4): 574–579.
38. Delhaye C, Kpogbemabou N, Modine T, Lemesle G, Staels B, Mahmoudi M, *et al*. Long-term prognostic value of preprocedural adiponectin levels in patients undergoing percutaneous coronary intervention. *Int J Cardiol* 2013; **168**(5): 4921–4924.
39. Sun H, Sun T, Ma B, Yang BW, Zhang Y, Huang DH, *et al*. Prediction of all-cause mortality with copeptin in cardio-cerebrovascular patients: A meta-analysis of prospective studies. *Peptides* 2015; **69**: 9–18.
40. Masson S, Latini R, Carbonieri E, Moretti L, Rossi MG, Ciricugno S, *et al*. The predictive value of stable precursor fragments of vasoactive peptides in patients with chronic heart failure: data from the GISSI-heart failure (GISSI-HF) trial. *Eur J Heart Fail* 2010; **12**(4): 338–347.
41. Von Haehling S, Papassotiriou J, Morgenthaler NG, Hartmann O, Doehner W, Stellos K, *et al*. Copeptin as a prognostic factor for major adverse cardiovascular events in patients with coronary artery disease. *Int J Cardiol* 2012; **162**(1): 27–32.
42. Pozsonyi Z, Forhecz Z, Gombos T, Karadi I, Janoskuti L, Prohaszka Z. Copeptin (C-terminal pro arginine-vasopressin) is an independent long-term prognostic marker in heart failure with reduced ejection fraction. *Heart Lung Circ* 2015; **24**(4): 359–367.
43. Tasevska I, Enhorning S, Persson M, Nilsson PM, Melander O. Copeptin predicts coronary artery disease cardiovascular and total mortality. *Heart* 2016; **102**(2): 127–132.
44. Engelbertz C, Brand E, Fobker M, Fischer D, Pavenstadt H, Reinecke H. Elevated copeptin is a prognostic factor for mortality even in patients with renal dysfunction. *Int J Cardiol* 2016; **221**: 327–332.
45. Miller WL, Grill DE, Struck J, Jaffe AS. Association of hyponatremia and elevated copeptin with death and need for transplantation in ambulatory patients with chronic heart failure. *Am J Cardiol* 2013; **111**(6): 880–885.
46. Doganay B, Okutucu S, Cetin M, Kiziltunc E, Karayigit O, Ozkan C, *et al.* Association of serum copeptin levels with patency of infarct-related arteries in patients with ST-segment elevation myocardial infarction. *Acta Cardiol Sin* 2019; **35**(4): 360–368.