

Correlation of Copeptin with N-terminal pro-brain natriuretic peptide in predicting the severity and prognosis of acute pulmonary embolism

Copeptin in acute pulmonary embolism

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Abstract

Aim: In this study, we aimed to compare copeptin with N-terminal pro-brain natriuretic peptide (NT-proBNP) and cardiac troponin I for predicting severity and 3-month mortality in acute PE in the emergency department (ED).

Material and Methods: All ED patients older than 18 years who were confirmed to have acute PE within six hours of diagnostic work-up were enrolled and prospectively screened. Risk stratification was made according to the 2014 European Society of Cardiology guideline on PE. The study endpoints were defined as 3-month mortality, presence of non-low risk PE, and presence of right ventricular (RV) dysfunction. The Mann-Whitney U test was used for the comparison of medians. Receiver operating characteristic curves were generated and the area under the curve (AUC) was calculated to determine the best cut-off values of copeptin and NT-proBNP. A P value < 0.05 was considered statistically significant.

Results: The study enrolled 82 patients. Twelve patients who died during 3 months had higher concentrations of NT-proBNP and copeptin, but not troponin I. The AUCs of NT-proBNP and copeptin to accurately predict the 3-month mortality were 0.73 ± 0.09 (95% CI, 0.62 - 0.82; $p = 0.013$) and 0.78 ± 0.09 (95% CI, 0.68 - 0.86; $p = 0.003$), respectively. Low-risk patients, according to Pulmonary Embolism Severity Index, had lower concentrations of copeptin and NT-proBNP compared to intermediate-high risk patients. All three markers discriminated the presence of RV dysfunction truly.

Discussion: Copeptin correlates with NT-proBNP and appears beneficial for early risk stratification of acute pulmonary embolism in the ED.

Keywords

Acute Pulmonary Embolism; Copeptin; Emergency Department; N-Terminal Probrain Natriuretic Peptide; Troponin I

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Introduction

Acute pulmonary embolism (PE) is a catastrophic cardiovascular diagnosis in emergency departments (EDs) with high mortality and morbidity rates. The aim of the emergency physician (EP) is to diagnose the disease as soon as possible, as well as to assess the risk stratification to guide the management and make treatment decisions, including the appropriate type and site of treatment. The European Society of Cardiology (ESC) classifies hemodynamically unstable patients with shock or hypotension as patients with a high risk of 30-day mortality. In these unstable patients, normal right ventricular (RV) function excludes PE as the cause of hemodynamic instability [1,2]. Therefore, after the diagnosis of PE, in hemodynamically stable, non-high risk patients, RV function is assessed by echocardiography or computed tomography angiography. Then cardiac biomarkers, such as N-terminal probrain natriuretic peptide (NT-proBNP) and cardiac troponins, are measured and a Pulmonary Embolism Severity Index (PESI) was calculated for further risk stratification [1-5]. When at least one of these factors is positive, the patient is classified as intermediate risk. If all these are negative, then the patient is classified as low risk [1,2]. Intermediate and high-risk PE patients have increased 30-day mortality compared to low-risk patients. Low-risk patients are considered for outpatient treatment.

All medical patients are under stress. The body responds to stress via activation of the hypothalamo-hypophyseal-adrenal axis. Arginine-vasopressin (AVP) is a component of this axis. Thus, copeptin, a C-terminal fragment of provasopressin, is an emerging marker and reflects the individual stress level [6]. It is used not only for diagnostic purposes but also for risk stratification of emergent cardiovascular conditions, including acute coronary syndromes and pulmonary embolism [7-13]. Copeptin levels have been shown to increase during 0-4 hours of acute myocardial infarction, when troponin T still remained undetectable [9]. This early increase appears to be an advantage of copeptin over other biomarkers.

In this study, we aimed to compare copeptin with NT-proBNP and cardiac troponin I for predicting the severity and 3-month mortality in acute PE in the ED.

Material and Methods

This prospective cohort study was conducted from June 2014 to May 2016. The local institutional ethics committee approved the study protocol (2014/99) and written informed consent was obtained from the participants prior to enrollment. The study complied with the international guidelines, the "Regulations on Pharmaceutical Research," enforced by the Ministry of Health of Turkey published in the 27089 numbered Official Journal dated 23 December 2008 and also with other regulations published at a later date. All patients older than 18 years who were admitted to the ED and were confirmed to have acute PE within six hours of diagnostic work-up, regardless of symptom duration, were enrolled and prospectively screened. The exclusion criteria included delayed diagnosis of more than six hours, lack of echocardiography, inability to provide consent, or patients with one of the following clinical states: pregnancy, renal insufficiency or dialysis, hypophysial tumor, steroid treatment, decompensated heart failure, acute coronary

syndrome, or known chronic pulmonary hypertension.

The diagnosis of acute PE was confirmed via computed tomography (CT) angiography performed with a 16-slice multidetector-row scanner (Toshiba Alexion™/ Advance, Toshiba Medical Systems Corporation, Nashu, Japan) following the intravenous administration of 100 mL non-ionic iodinated contrast reagent. Clinical data regarding age, sex, comorbid diseases, vital signs and routine blood count, blood chemistry, and arterial blood gases were recorded on every patient chart. When the diagnosis was confirmed within six hours, two tubes, each containing 3 milliliters (mL) of blood samples, were collected. One tube was for cardiac troponin I and was investigated in a routine laboratory during an emergency room visit. The other tube was centrifuged within 1 hour at 1000 g for 15 minutes, and the serum was isolated and stored at -80 °C until analysis.

Serum levels of human NT-proBNP and human copeptin were quantified via an enzyme-linked immunosorbent assay (ELISA) using commercially available matched antibodies (Eastbiopharm, Hangzhou, China). The intra-assay and inter-assay coefficients of variation were <10% and <12%, respectively. The sensitivity was calculated as 2.49 ng/L for NT-proBNP and 0.024 ng/mL for copeptin.

Within one hour after the diagnosis, all patients underwent transthoracic echocardiography in the ED to assess RV function by a cardiologist (VingMed Vivid 5S, GE Healthcare, Waukesha, USA). Unstable high-risk patients were hospitalized in the intensive care unit for thrombolysis, and the remaining intermediate and low-risk patients were treated in the clinic of chest diseases with low-molecular-weight heparin and warfarin. The study endpoints were defined as 3-month mortality, presence of non-low risk PE and presence of RV dysfunction. Two emergency residents, who were blinded to the laboratory measurements, assessed outcomes of the measurements of the discharged patients via telephone interview.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences version 17.0 (IBM Corp. Armonk, NY, USA) and MedCalc Statistical Software version 16.1 (MedCalc Software bvba, Ostend, Belgium). Categorical data are presented as frequencies and percentages. Normality analysis was done using the Kolmogorov-Smirnov test. Continuous data were non-normally distributed; thus, they are presented as medians with interquartile ranges (IQRs). The Mann-Whitney U test was used to compare the medians of the two groups.

Receiver operating characteristic (ROC) curves were generated, and the area under the curve (AUC) and Youden's Index were calculated to determine the effectiveness of copeptin and NT-proBNP in determining the best cut-off values with the highest sensitivity and specificity to predict mortality, severity and RV dysfunction. A p-value < 0.05 was considered statistically significant.

Results

Ninety-eight consecutive patients were diagnosed with acute PE during the study period. Sixteen of the patients were excluded. Finally, 82 patients were enrolled. The most

Table 1. Clinical Characteristics of the Patients

	All patients N = 82	3-month mortality	
		Survivors N = 70	Non-Survivors N = 12
Age, Median (IQR)	79 (68.5-84)	78,5 (66,5-83,25)	79,5 (75,75-85)
Gender (M/F)	27/55	24/46	3/9
Vital Signs			
Systolic BP	120 (95,75-140)	120 (100-140)	93,50 (80,50-119,75)
Diastolic BP	70 (60-80)	70 (60-80)	60 (49,25-70)
Heart rate	106,50 (85,75-118,50)	100,50 (82,75-111,25)	120 (109,75-129,25)
Respiratory rate	25 (22-31)	24 (21,75-29,25)	33,50 (22,75-40)
Saturation	90 (85-93)	90 (87-93,25)	74,50 (70-82)
Proportion of RVD	48 (58.54%)	38 (79.16%)	10 (20.83%)
Thrombolysis	17 (20.73%)	11 (64.70%)	6 (35.29%)
Risk categories			
ESC 2014			
High risk	20 (24.39%)	14 (70%)	6 (30%)
Intermediate risk	48 (58.53%)	42 (87.50%)	6 (12.50%)
Low risk	14 (17.07%)	14 (100%)	-
PESI			
Class I-II	18 (21.95%)	18 (100%)	-
Class III-V	64 (78.04%)	52 (81.25%)	12 (18.75%)

M/F; Male/Female, BP; Blood Pressure, ESC; European Society of Cardiology, PESI; Pulmonary Embolism Severity Index, RVD; Right ventricular dysfunction

Table 2. Association of the biomarkers with the study endpoints

a) Association of biomarkers with PESI			
PESI	Low Risk (Class I-II) n = 18	High-Intermediate Risk (Class III-V) n = 64	p Value
Troponin I	0.06 (0.03-0.15)	0.07 (0.03-0.17)	0.955
NT-proBNP	337.37 (279.99-488.41)	442.33 (358.68-609.04)	0.046
Copeptin	4.78 (3.86-5.63)	5.94 (4.27-8.27)	0.030
b) Association of biomarkers with RVD			
RVD	RVD (-) n = 34	RVD (+) n = 48	p Value
Troponin I	0.04 (0.02-0.10)	0.08 (0.04-0.24)	0.020
NT-proBNP	355.76 (284.59-425.16)	480.04 (396.04-789.42)	< 0.001
Copeptin	4.78 (3.42-5.93)	6.77 (4.68-11.03)	< 0.001
c) Association of biomarkers with 3-month mortality			
3-MONTH	Survivors n = 70	Non-Survivors n = 12	p Value
Troponin I	0.065 (0.022-0.163)	0.074 (0.060-0.200)	0.316
NT-proBNP	406.02 (333.64-487.18)	783.51 (427.87-1466.42)	0.005
Copeptin	5.12 (4.09-6.82)	11.20 (7.72-16.83)	0.002

Continuous data are presented as median (interquartile range, IQR). NT-proBNP; N-terminal probrain natriuretic peptide, PESI; Pulmonary Embolism Severity Index, and RVD; right ventricular dysfunction

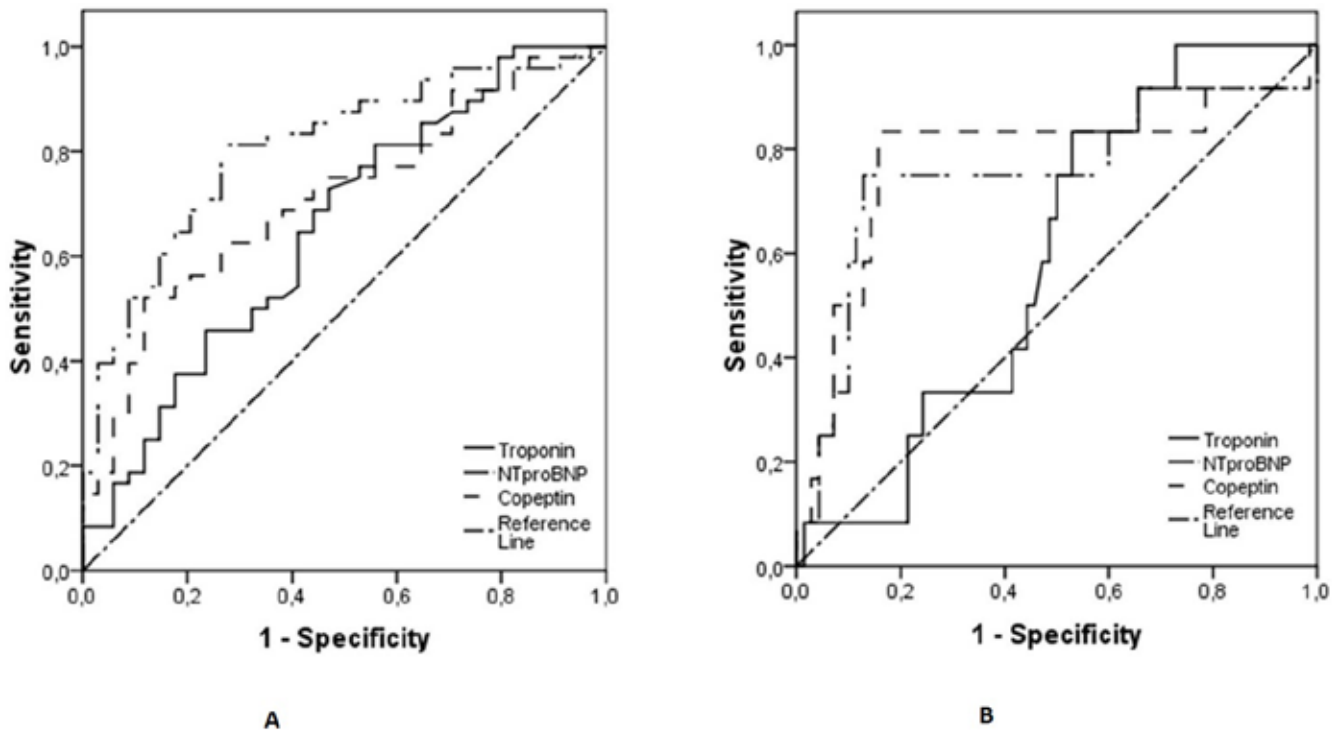


Figure 1. A) Receiver operating characteristic curves for Troponin I, NT-proBNP and copeptin for predicting right ventricular dysfunction
B) Receiver operating characteristic curves for Troponin I, NT-proBNP and copeptin for 3-month mortality

common presenting symptoms were dyspnea (67.07%), syncope (17.07%) and chest pain (9.75%) and others (6.09%), respectively. Twenty (24.39%) patients were candidates for thrombolysis; however, only 11 of these could receive. During hospitalization, six of the intermediate-risk patients developed hemodynamic decompensation and received thrombolysis, too. Twelve patients died within the 3-month follow-up period due to PE and related complications (all-cause mortality: four in the first week, five in the first month, one in the second month, and two in the third month). Clinical characteristics of the patients are presented in Table 1.

According to the PESI, there were 64 patients in the high-intermediate risk group (49 in high and 15 in intermediate risk groups) and 18 patients in the low-risk group. Patients in the high-intermediate risk group had higher plasma concentrations of NT-proBNP and copeptin, but not troponin I (Table 2).

Among the 82 patients, 48 patients had RV dysfunction during the echocardiographic examination. Patients with RV dysfunction had higher concentrations of troponin I, NT-proBNP and copeptin (Table 2). ROC curves and related AUCs of three markers for predicting RV dysfunction are shown in Figure 1A. The AUC of troponin I was 0.66 ± 0.06 (95% CI, 0.55 – 0.77; $p = 0.006$) with a sensitivity of 75% and a specificity of 53%. The AUC of NT-proBNP was 0.79 ± 0.05 (95% CI, 0.69 – 0.87; $p < 0.001$) with a sensitivity of 81% and a specificity of 73%. The AUC of copeptin was 0.71 ± 0.06 (95% CI, 0.60 – 0.81; $p < 0.001$) with a sensitivity of 52% and a specificity of 88%. The optimal cut-off values for troponin I, NT-proBNP and copeptin were 0.04 ng/mL, 376.21 ng/L and 6.63 ng/mL for the presence of RV dysfunction, respectively.

The patients who died at the end of the 3-month had higher concentrations of NT-proBNP and copeptin but not troponin I (Table 2). The AUCs of NT-proBNP and copeptin to accurately predict the 3-month mortality were 0.73 ± 0.09 (95% CI, 0.62 – 0.82; $p = 0.013$) with a sensitivity of 75% and a specificity of 84% and 0.78 ± 0.09 (95% CI, 0.68 – 0.86; $p = 0.003$) with a sensitivity of 83% and a specificity of 84%, respectively. There was no statistical difference between the ROC curves of NT-proBNP and copeptin ($p = 0.632$). The optimal cut-off values for NT-proBNP and copeptin were 609.64 ng/L and 7.34 ng/mL, respectively. ROC curves and related AUCs of three markers for predicting 3-month mortality are shown in Figure 1B. There was a moderate correlation between copeptin and NT-proBNP ($r = 0.478$, $p < 0.001$).

Discussion

The main findings of the present study are that higher copeptin levels have prognostic significance for the prediction of 3-month mortality, as well as the severity of acute PE and the presence of RV dysfunction. Copeptin, obtained within six hours following presentation to the ED, shows better performance than troponin, regardless of symptom duration. Copeptin and NT-proBNP exhibit a moderate correlation to predict the severity of acute PE in the ED.

Biomarkers that identify the RV dysfunction and contribute to risk stratification are crucial, especially when echocardiographic assessment is not available. In these circumstances, biomarkers appear to be the only marker of risk stratification. As for many

other biomarkers, there is an inevitable diagnostic gap in the initial hours after the onset of symptoms of acute PE. Several hours are required for the cardiac troponins and BNP levels to increase in the blood following the onset of acute myocardial stretch. Newer biomarkers that minimize or narrow this gap or require shorter time periods for testing are of clinical importance.

Cardiac troponins (I and T) comprise widely used markers of myocardial damage; however, they require 6-12 hours to rule out myocardial necrosis. Highly sensitive troponins have been developed to increase their diagnostic performance that identifies myocardial necrosis in 1-3 hours [14]. Cardiac troponins have also been well-studied for the risk stratification of acute PE, and increased levels have been associated with the RV strain, a complicated clinical course, and mortality [5,15]. In our study, patients with RV dysfunction had higher levels of troponin, although median troponin level was below the laboratory cut-off level of 0.1 ng/mL. Troponin levels did not differ between 3-month survivors and non-survivors. This discrepancy may be explained by the fact that in the previously described studies, the blood samples for troponins were collected at any time within 24 hours of symptom onset, which is sufficient for troponins to increase in blood; however, in our study, blood samples were acquired within six hours of diagnostic confirmation, regardless of symptom onset.

BNP and NT-proBNP are released from cardiac ventricles in response to ventricular strain. Both BNP and NT-proBNP have been suggested as reliable markers for identifying RV dysfunction and predicting mortality and serious adverse events [5,15]. For this purpose, the ROC curve analysis indicated a cut-off value of 600 or 1000 pg/mL for NT-proBNP [5,15,16]. This value was higher than our cut-off value (1 pg/mL = 1 ng/L). The exact times of blood sample collection regarding the symptom onset were not provided in these studies. An early collection of samples may be the reason for lower cutoff values in our study. Copeptin, the C-terminal part of AVP prohormone, is a promising marker. AVP is co-secreted with copeptin and neurophysin II from neurohypophysis in response to hemodynamic or osmotic stimuli, as well as endocrine stress [17]. It is not a disease or a single organ specific marker. It reflects an individual's overall stress level rather than only cardiovascular stress because it has a more central role in the stress response. This role enables it to be a more generalized marker for disease severity rather than for diagnosis. Copeptin results are available within one hour, which makes it an attractive biomarker in the ED [4,17]. It is also stable in both serum and plasma at room temperature for one to two weeks, making it suitable for retrospective analysis [17].

Because RV dysfunction indicates a poor prognostic factor, early detection with a simple blood test in acute stages, especially when echocardiography is not available, is essential. PE patients with RV dysfunction were found to have increased serum copeptin levels [10,11,13]. The result of the present study is similar with the literature in this aspect.

Liebetrau et al. demonstrated that copeptin concentrations began to increase at 30 minutes and peaked at 90 minutes following the induction of myocardial infarction in patients with hypertrophic obstructive cardiomyopathy undergoing

transcoronary ablation of septal hypertrophy. The concentration returned to baseline after 24 hours [18]. In a similar model, the authors also examined NT-proBNP and demonstrated that it began to increase at 45 minutes after the induction of myocardial infarction and decreased after 76 minutes. The concentration returned to baseline after 8 hours [19].

Previously, it has been demonstrated that the copeptin levels decreased following the initiation of proper therapy for pulmonary hypertension. Thus, increased levels of copeptin suggest that the AVP system is also activated due to RV strain in acute PE [8]. Normotensive PE patients with a 30-day unfavorable outcome had increased copeptin levels compared with patients with a favorable course [10]. However, the increased copeptin levels were not associated with 30-day mortality. This finding may be explained by the exclusion of high-risk patients in their study in contrast to our study. Usul et al. also did not find any relation between copeptin levels and 30-day mortality, but in their study, copeptin had an AUC of 0.82 with a sensitivity of 69% a specificity of 83% in patients with RV dysfunction [13].

Deveci et al. found that high-risk PE patients according to a simplified PESI score had higher copeptin levels compared to low-risk patients and controls [12]. This is similar with the result of the present study. In a multicenter validation study, Hellenkamp et al. showed that copeptin might enable identifying normotensive PE patients at high risk [20].

A recent study conducted with 107 acute PE patients and 64 controls demonstrated that the copeptin levels were increased in the diseased patients compared with the controls [21]. The authors also stated that the low-risk patients' plasma copeptin concentrations were lower than the intermediate/high-risk patients. The non-survivors within 30 days had higher copeptin levels than survivors. However, there were only four non-survivors in their study. Their study reported that the patients with a complicated clinical course had higher copeptin levels than the patients with a benign clinical course. However, they did not state the accurate time for blood sample collection. Most of our results are similar to this study; however, we have more patients who reached the study endpoints despite a lower number of included patients.

Limitations

First, because of institutional reasons, more patients were included in the intermediate-high risk group. The geriatric patients in these groups had more comorbidities that may influence the copeptin levels to some degree. Second, as a result of the limited number of patients who reached the primary endpoint, we did not perform regression analysis because reliable results would not be attained. Third, copeptin and NT-proBNP were studied using ELISA. The use of commercially available automated assays with fast turnaround time may give faster results.

Conclusion

When time is crucial, in patients with acute PE, copeptin, obtained within six hours following presentation to the ED, regardless of symptom duration, shows better performance than troponin, possibly due to delayed increase of troponin in the serum. It moderately correlates with NT-proBNP and appears beneficial for early risk stratification of acute PE in

the ED. It also precisely discriminates low-risk patients with the same accuracy as NT-proBNP who are candidates for outpatient treatment.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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