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The diagnostic value of serum copeptin levels in an acute pulmonary embolism

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Abstract

Background: *Acute pulmonary embolism (APE) is a common disease which is associated with high mortality and morbidity. Circulating level of copeptin, which was demonstrated to be elevated in heart failure, acute myocardial infarction and pulmonary arterial hypertension, were reported to be independent predictors of poor outcome in recent studies. The aim of the present study was to investigate the clinical utility of copeptin in the diagnosis of APE.*

Methods: *A total of 90 consecutive patients, admitted to emergency service due to acute chest pain and/or dyspnea and who underwent pulmonary computerized tomography angiography (CTA) due to suspicion of APE, were included in this prospective study. The patients diagnosed with APE were defined as APE (+) group and the remaining individuals with normal pulmonary CTA result were defined as APE (–) group.*

Results: *Copeptin levels (7.76 ± 4.4 vs. 3.81 ± 1.34 ng/dL; $p < 0.001$) were higher in the APE (+) group as compared to the APE (–) group. Copeptin was significantly positively correlated with B-type natriuretic peptide ($r = 0.434$, $p < 0.001$), D-dimer ($r = 0.315$, $p = 0.003$) and troponin I ($r = 0.300$, $p = 0.004$) and inversely correlated with arterial oxygen saturations ($r = –0.533$, $p < 0001$). When the correlation of copeptin with right ventricular dysfunction parameters was investigated, it was significantly inversely correlated with the tricuspid annular plane systolic excursion ($r = –0.521$, $p < 0.001$) and positively correlated with right to left ventricle ratio ($r = 0.329$, $p = 0.024$). Copeptin (OR 1.836, 95% CI 1.171–2.878, $p = 0.008$) was found as a significant independent predictor of APE in a multivariate analysis, after adjusting for other risk parameters.*

Conclusions: *Copeptin is a promising new biomarker, which may be used to support the need for further investigations and to improve the diagnosis of patients with APE.* (Cardiol J 2016; 23, 1: 42–50)

Key words: copeptin, acute pulmonary embolism, diagnosis

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Introduction

Acute pulmonary embolism (APE) is a common disease which, if not properly diagnosed and treated, is associated with significant morbidity and mortality rates that can reach 17.4% [1, 2]. As the presenting symptoms and signs are nonspecific, diagnostic tests are necessary to establish the presence or absence of PE in order to avoid the risks of unnecessary anticoagulation or fatal thromboembolic recurrence that can occur if APE is left untreated [3, 4]. Early diagnosis and risk stratification and improved inpatient management may yield better short- and long-term prognoses. Approximately 30–40% of all APEs are submissive, which makes fast and accurate diagnosis of right ventricular dysfunction (RVD) crucial for correct identification of patients in this high-risk group [5]. In addition to evaluation of RVD by 2-dimensional (2D) transthoracic echocardiography (TTE), the use of inexpensive, easy-to-use and readily available measurements of biomarkers may be beneficial. Some proven efficacy biomarkers such as D-dimer, B-type natriuretic peptide (BNP), and troponin I are used in the diagnosis and risk stratification of APE [6–9].

Copeptin, the C-terminal portion of pro-vasopressin, is a glycosylated polypeptide comprised of 39 amino acids and harboring a leucine-rich core segment. Since it is part of the uncleaved pro-arginine vasopressin (AVP) and emerges equimolar to AVP, it can be used as an indirect marker for AVP [10]. Copeptin is also co-secreted with AVP from the hypothalamus. The diagnostic and prognostic utility of copeptin was reported in some acute illnesses such as sepsis, pneumonia, lower respiratory tract infections, and stroke [11]. In addition, the usefulness and accuracy of copeptin for diagnosis and risk stratification of cardiovascular diseases were investigated in recent studies and it was found that copeptin combined with troponin T enhanced the accuracy in the diagnosis of acute myocardial infarction (AMI) and in the prognosis of heart failure [12–14]. Furthermore, high copeptin levels were reported to be associated with worse outcomes in patients who were admitted to the Emergency Department with dyspnea [15]. Copeptin levels were also demonstrated to be elevated in patients with pulmonary arterial hypertension, and circulating levels of copeptin were found to be an independent predictor of poor patient outcome in a recent study [16]. In APE, anatomical obstruction and vasoconstriction of pulmonary artery lead to an increase in pulmonary vascular resistance and results in right ventricular (RV) dilation, while neurohumoral activation leads to inotropic and chronotropic stimulation [17] and it is likely that the AVP system is also activated. As a result, left ventricular (LV) filling is impeded in early diastole, and this may lead to a reduction of the cardiac output and contribute to systemic hypotension and hemodynamic instability [18]. According to this information, we hypothesized that copeptin, as an indirect marker for AVP system, may facilitate the diagnosis of APE.

Since there is no data in the literature concerning the clinical utility of copeptin in the diagnosis of APE, we aimed at investigating this association in the present study.

Methods

A total of 90 consecutive patients, who were admitted to emergency service for acute chest pain and/or dyspnea and underwent pulmonary computerized tomography angiography (CTA) due to suspicion of APE between January 2014 and February 2015, were included in this prospective study. The indications of pulmonary CTA were as follows: high clinical probability indicated by ≥ 7 Wells Score, or low/intermediate clinical probability indicated by < 7 Wells Score and D-dimer level was positive. Exclusion criteria of the present study were as follows: sepsis, lung neoplasms, end-stage renal failure requiring hemodialysis treatment, acute coronary syndromes, acute cerebrovascular disease, acute or chronic aortic dissection, decompensated heart failure, surgery or bed rest within the past 30 days, prior PE or deep venous thrombosis, severe chronic obstructive lung disease (FEV1 < 50%), pulmonary hypertension, acute or chronic infectious diseases, acute or chronic inflammatory diseases such as acute myocarditis and/or pericarditis, chronic constrictive pericarditis, rheumatoid arthritis, systemic lupus erythematosus, and vasculitis. The patients diagnosed with APE were defined as APE (+) group (n = 47) and the remaining individuals with normal pulmonary angiography result defined as APE (–) group (n = 43).

The demographic, clinical, and laboratory characteristics of the study groups were taken from the patients' histories and results of physical examinations, which were collected by cardiologists on admission.

N-terminal B-type natriuretic peptide (NT-proBNP), troponin I, D-Dimer, and copeptin serum levels were quantified from a venous blood sample,

which was drawn early after admission to the Emergency Department. Plasma BNP and troponin I concentrations were determined with a chemiluminescent microparticle immunoassay using an ADVIA Centaur kit (Henkestrasse 127 D-91052 Erlangen Germany). D-dimer was measured with an enzyme-linked immunosorbent assay (ELISA). Hematological parameters were obtained using the Coulter LH 780 Hematology Analyzer (Beckman Coulter Ireland, Inc., Mervue, and Galway, Ireland).

Serum copeptin levels were measured with a commercially available kit using an ELISA (Human copeptin ELISA kit, Catalogue No: CK-E90208 Hangzhou East Biopharm CO, Hangzhou, China) with a lower sensitivity limit of 0.024 ng/mL. Samples were measured in duplicate in a single experiment. The intra- and inter-assay coefficients of variance of this kit are < 10% and < 12%, respectively. The detection range of copeptin was 0.05–20 ng/mL.

All of the study patients underwent echocardiographic examinations. These examinations were performed by 2 expert cardiologists, who were fully independent from the study and diagnosis of patients, within 24 h after the onset of symptoms.

TTE 2D was performed using a Vivid S6 device with a 3.5 MHz phased array transducer (GE Medical Systems, Horten, Norway) to evaluate RV dimensions and function. 2D studies were performed with the patient in the left lateral decubitus position and using conventional (parasternal long- and short-axis, apical 4-chamber) views [19].

The tricuspid annular plane systolic excursion (TAPSE) was measured as the distance of systolic movement of the RV tricuspid annular segment along its longitudinal plane. The RV fractional area change (RVFAC) was calculated from the apical 4-chamber view using the percentage change in areas of the end-diastolic and end-systolic areas of the RV. McConnell's sign was defined as hypokinesia of the infundibular RV region with normal contraction of the RV apex. RV dimensions were measured from an RV-focused apical 4-chamber view [13]. Specifically, the RV was evaluated for the presence or absence of the following signs: RV diameter > 35 mm or RV/LV end-diastolic ratio > 1 from the apical 4-chamber view; RVFAC < 35%; and TAPSE < 15 mm. A diagnosis of RVD was established in the presence of 2 or more of these criteria.

Pulmonary CTA was carried out using a dual-source CT system (Definition Flash, Siemens Medical Solution, Forchheim, Germany) with 280 ms of rotation time, 2 × 128 slices, a pitch of 3.4 and 60% of the R-R interval. The tube current for the protocol was set at 180–300 mAs and 0.6 mm slice collimation was used. Non-ionic contrast reagent (Iomeron 400 mgI/mL; Bracco, Milan, Italy) was administered at a rate of 5 mL/s (80–100 mL total) through an 18-gauge needle positioned in the antecubital vein using a dual-head power injector. Images were obtained during a single interval of 6 s in which the patient held his or her breath using the bolus tracking technique.

The study protocol was approved by the local Ethics Committee and all patients provided their informed consent. The study was conducted in accordance with the ethical principles described by the Declaration of Helsinki.

Statistical analysis

Continuous, normally distributed variables were presented as mean ± standard deviation. Categorical variables were presented as frequencies and/or percentages. The Kolmogorov-Smirnov test was used to evaluate whether the continuous variables were normally distributed. The Student's t-test was used for the comparison of normally distributed continuous numerical variables, the Mann-Whitney U-test was used for non-normally distributed numerical variables, and the χ^2-test was used to compare categorical variables between the two groups. Any correlation between data was tested by a Spearman or Pearson correlation analysis. A receiver operating characteristic analysis was performed to investigate the diagnostic value of serum copeptin, D-dimer, troponin, and NT-proBNP levels in differentiating patients with APE from those with other causes of acute dyspnea. A univariate and backward stepwise multivariate logistic regression analysis, which included variables with a p-value of less than 0.1 and the respective odds ratios (OR) with 95% confidence intervals (CI) were performed to identify independent predictors of APE. A p value < 0.05 was considered statistically significant. Analysis was performed using SPSS version 17.0.0 (SPSS Inc., Chicago, IL).

Results

The study population available for analysis consisted of 90 patients with a mean age of 57 ± 16 years. Forty-seven (52.2%) patients were diagnosed with APE and 43 (47.7%) patients had normal pulmonary angiography. Fourteen (29.7%) patients in the APE group were taking thrombolytic treatment, 33 (70.3%) patients were treated with

Table 1. Demographic, clinical, laboratory and echocardiographic characteristics of the study patients.

	APE (+) (n = 47)	APE (–) (n = 43)	P
Age [years]	57 ± 16	58 ± 16	0.710
Male gender [n, %]	25 (53%)	20 (46%)	0.527
Systolic blood pressure [mm Hg]	129 ± 19	132 ± 22	0.807
Diastolic blood pressure [mm Hg]	76 ± 13	77 ± 12	0.688
Oxygen saturation in room air [%]	89.6 ± 4.51	91.8 ± 13	**< 0.001**
Heart rate [bpm]	97 ± 24	89 ± 19	**0.022**
Surgery within 30 days [n, %]	13 (28%)	16 (37%)	0.330
Bed rest for > 3 days within 30 days [n, %]	16 (34%)	14 (32%)	0.881
Prior thromboembolism [n, %]	14 (30%)	8 (18%)	0.218
Diabetes mellitus [n, %]	10 (21%)	11 (26%)	0.631
Chronic obstructive lung disease [n, %]	11 (23%)	8 (18%)	0.577
Smoking [n, %]	18 (38%)	18 (42%)	0.730
Body mass index [kg/m^2]	30 ± 4	29 ± 6	0.186
Glucose [mg/mL]	128.2 ± 38.2	116.3 ± 34.3	0.056
Creatinine [mg/mL]	0.9 ± 0.3	0.9 ± 0.4	0.624
Hematocrit [%]	38.8 ± 5.4	38.0 ± 4.4	0.451
C-reactive protein [mg/L]	43.2 ± 44.4	43.4 ± 53.3	0.328
Copeptin [ng/mL]	7.76 ± 4.4	3.81 ± 1.34	**< 0.001**
Troponin I [ng/mL]	0.36 ± 0.48	0.13 ± 0.28	**< 0.008**
D-dimer [ng/mL]	4239 ± 3048	1773 ± 2545	**< 0.001**
B-type natriuretic peptide [pg/mL]	494 ± 357	173 ± 258	**< 0.001**
Right ventricular diameter [cm]	3.5 ± 0.7	3.0 ± 0.7	**0.002**
RVFAC [%]	42 ± 12	48 ± 10	**0.031**
Left ventricular ejection fraction [%]	55 ± 10	58 ± 10	0.055
RV/LV ratio	0.78 ± 0.15	0.73 ± 0.13	0.082
TAPSE [mm]	1.76 ± 0.48	2.23 ± 0.48	**< 0.001**
Right ventricular hypokinesis [n, %]	9 (19%)	2 (5%)	**0.036**

Values are presented as means ± standard deviation or number (%), as appropriate; APE — acute pulmonary embolism; RVFAC — right ventricular fractional area change; RV/LV ratio — right ventricular to left ventricular diameter ratio; TAPSE — tricuspid annular plane systolic excursion

heparin according to the current guideline [20]. The demographic, clinical, laboratory and echocardiographic characteristics of the study groups are presented in Table 1. There was no difference between the two groups in terms of demographic and clinical parameters except heart rate and oxygen saturation. Heart rates were significantly higher in the APE (+) group compared to the APE (–) group ($p = 0.02$). However, oxygen saturations (SaO_2) were found to be significantly lower in the APE (+) group than in the APE (–) group ($p < 0.001$).

When the echocardiographic parameters of the APE (+) and APE (–) groups were compared, the RV diameter was significantly larger (3.5 ± 0.7 vs. 3.0 ± 0.7 cm; $p = 0.002$, respectively) and McConnell's sign was more frequently observed in the patients with APE compared to those without (19.1% vs. 4.7%; $p = 0.036$). The APE (+) group has worse RV systolic function compared to the APE (–) group.

RVFAC and TAPSE were detected as being lower in the APE (+) group than in the APE (–) group (42 ± 12 vs. 48 ± 10; $p = 0.031$ and 1.76 ± 0.48 vs. 2.23 ± 0.48; $p < 0.001$, respectively). Moreover, the rate of RV hypertrophy was significantly higher in the APE (+) group than the APE (–) group (19% vs. 5%, $p = 0.036$).

The serum levels of copeptin (7.76 ± 4.4 vs. 3.81 ± 1.34 ng/dL; $p < 0.001$), troponin I (0.36 ± ± 0.48 vs. 0.13 ± 0.28 ng/mL; $p < 0.008$), BNP (494 ± 357 vs. 173 ± 258 pg/mL; $p < 0.001$), and D-dimer (4,239 ± 3,048 vs. 1,773 ± 2,545 ng/mL; $p < 0.001$) were demonstrated to be higher in the APE (+) group as compared to the APE (–) group.

Table 2. The receiver operating characteristic curve for copeptin, troponin I, D-dimer and B-type natriuretic peptide (BNP) for predicting acute pulmonary embolism.

Variable	AUC	P	SE	95% CI	Sensitivity	Specificity	PPD	NPD
Copeptin	0.836	**< 0.001**	0.041	0.755-0.917	68.1%	83.7%	82.1%	70.6%
Troponin I	0.733	**< 0.001**	0.053	0.629-0.837	63.8 %	76.7%	75.0%	66.0%
D-dimer	0,794	**< 0.001**	0.050	0,697-0.892	85.1 %	60.5%	70.2%	78.8%
BNP	0.827	**< 0.001**	0.047	0.734-0.919	74.5 %	81.4%	81.4%	74.5%

AUC — area under the curve; SE — standard error; CI — confidence interval; PPD — positive predictive diameter; NPD — negative predictive diameter

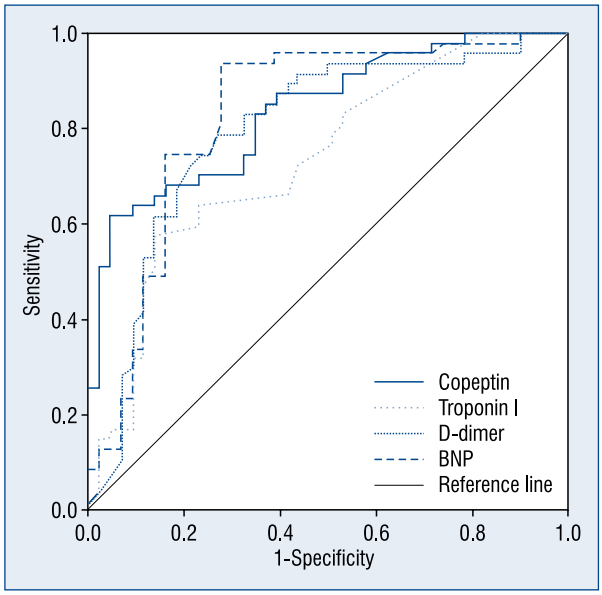

Figure 1. The receiver operating characteristic curve for copeptin, troponin I, D-dimer and B-type natriuretic peptide (BNP) for predicting acute pulmonary embolism.

A receiver operating characteristic curve was generated for sensitivity and specificity, and the respective areas under the curve (AUCs) were used to investigate the diagnostic value of serum copeptin, D-dimer, troponin, and BNP levels in differentiating patients with APE from those with other causes of acute dyspnea (Table 2, Fig. 1). The analysis indicated that copeptin levels > 4.84 had a 68.1% sensitivity and 83.7% specificity for predicting APE (AUC 0.836, 95% CI 0.755–0.917; $p < 0.001$). Their negative and positive predictive values were 82.1% and 70.6%, respectively. D-dimer levels > 1,041.5 had an 85.1% sensitivity and 60.5% specificity (AUC 0.794, 95% CI 0.697–0.892; $p < 0.001$). Their negative and positive predictive values were 70.2% and 78.8%, respectively. BNP levels > 247.4 had a 74.5% sensitivity and 81.4% specificity (AUC 0.827, 95% CI 0.734–0.919; $p < 0.001$). Their negative and positive predictive values were 81.4% and 74.5, respectively. Finally, troponin I levels > 0.065 had a 63.8% sensitivity and 76.7% specificity for prediction of APE (AUC 0.733, 95% CI 0.629–0.837; $p < 0.001$) with 75% and 66% positive and negative predictive values, respectively.

When the correlations of study biomarkers with RV parameters were investigated, copeptin was significantly inversely correlated with TAPSE ($r = -0.521$, $p < 0.001$) and positively correlated with RV/LV ratio ($r = 0.329$, $p = 0.024$). Moreover, copeptin was significantly positively correlated with BNP ($r = 0.434$, $p < 0.001$), D-dimer ($r = 0.315$, $p = 0.003$) and troponin I ($r = 0.300$, $p = 0.004$) (Figs. 2A–C, Table 3). Furthermore, there was a significant negative correlation between SaO_2 and copeptin ($r = -0.533$, $p < 0001$).

In a univariate regression analysis, copeptin, troponin I, D-dimer, BNP, TAPSE, RV diameter, SaO_2 and heart rate were significantly associated with APE. Copeptin (OR 1.836, 95% CI 1.171–2.878, $p = 0.008$) and D-dimer (OR 1.000, 95% CI 1.000–1.001, $p = 0.003$) were found to be significant independent predictors of APE in a multivariate analysis, after adjusting for other risk parameters (Table 4).

The APE (+) group was divided into two subgroups according to the presence or absence of acute RV failure. Fifteen out of the 47 patients (31%) with APE had acute RV failure. Levels of copeptin ($p = 0.02$), troponin I ($p = 0.02$), D-dimer ($p = 0.01$), and BNP ($p = 0.001$) were higher in the patients with RV failure compared to the patients with normal RV function (Table 5).

Discussion

The main findings of the present study were as follows: 1) copeptin levels were demonstrated to be higher in the APE (+) group compared to the APE (–) group; 2) copeptin was significantly inversely

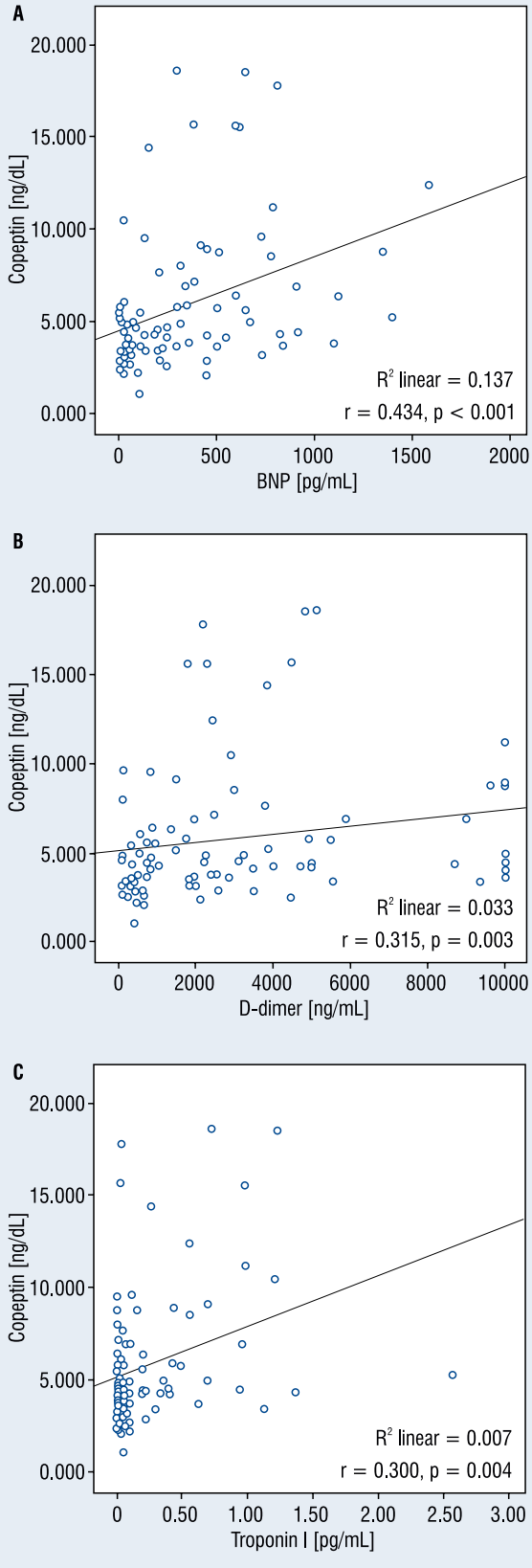

Figure 2. The correlations of copeptin with B-type natriuretic peptide (BNP) (**A**); with D-dimer (**B**); with troponin-I (**C**).

correlated with TAPSE and positively correlated with RV/LV ratio, BNP, D-dimer and troponin I; 3) copeptin and D-dimer were found to be significant independent predictors of APE, after adjusting for other risk parameters; 4) copeptin is a potential biomarker, which may be used to support the need for further investigations, with moderate sensitivity and specificity and 5) copeptin, troponin I, D-dimer, and BNP levels were significantly higher in the patients with acute RV failure due to APE as compared to patients with normal RV function.

Effective strategies for risk stratification and diagnosis in patients with APE are crucial and biomarkers such as D-dimer and troponin I could be used to diagnose APE, especially in patients who are in the low/intermediate risk group [6].

Copeptin, the C-terminal part of the vasopressin prohormone, has emerged as a promising surrogate target for measurement of vasopressin concentration and also seems useful in cardiovascular disease [12–15]. In previous studies, the prognostic and diagnostic accuracy of copeptin were analyzed in acute coronary syndrome, heart failure, and pulmonary hypertension [12–16]. A strong relationship between copeptin levels and short- and long-term mortality in patients who were referred to the Emergency Department was also reported in a recent study [21].

The present study is the first to investigate the clinical utility of copeptin in the diagnosis of APE. In this study, copeptin was found to be a significant independent predictor of APE, after adjusting for other risk parameters. In addition, biomarkers related to APE such as BNP, D-dimer, and troponin I had been evaluated previously and were found to be higher in patients with APE, which is consistent with the results of our study.

When the diagnostic value of study biomarkers were compared, copeptin was the most specific marker for APE, with 83.7% specificity and 82.1% positive predictive value. Moreover, D-dimer was the most sensitive biomarker for APE, with 85.1% sensitivity and 78.8% negative predictive value. Although D-dimer values may be used to exclude PE in patients with either a low or a moderate probability of PE, measurement of D-dimer is not useful for confirming PE [22–25]. Copeptin may be used to support the need for further investigations with moderate specificity and positive predictive value. However, it will not be replacing pulmonary CTA or spiral thorax CT as a diagnostic tool of APE.

In previous studies, increased BNP levels were demonstrated to be associated with adverse outcomes and RVD in patients with APE [26–27].

Table 3. Correlation analysis between study biomarkers and right ventricular parameters.

		RV diameter	RVFAC	TAPSE	RV/LV ratio
Copeptin	r	0.275	–0.262	–0.521	0.329
	p	0.061	0.076	< 0.0001	**0.024**
Troponin I	r	0.042	–0.246	–0.155	0.178
	p	0.780	0.096	0.298	0.233
D-dimer	r	0.164	–0,350	–0.223	0.272
	p	0.271	**0.016**	0.132	0.065
BNP	r	0.423	–0.483	–0.416	0.278
	p	**0.003**	**0.001**	0.004	0.059

RV — right ventricular; RVFAC — RV fractional area change; TAPSE — tricuspid annular plane systolic excursion, RV/LV ratio — RV to left ventricular diameter ratio; BNP — B-type natriuretic peptide

Table 4. Univariate and multivariate regression analyses of predictors of acute pulmonary embolism.

	Univariate			Multivariate		
	P	OR	95% CI	P	OR	95% CI
Copeptin	**0.008**	1.836	1.171–2.878	**0.008**	1.836	1.171–2.878
Troponin I	**0.017**	6.985	1.423–3.4303	0.658	0.648	0.095–4.424
D-dimer	**< 0.001**	1.000	1.000–1.001	**0.003**	1.000	1.000–1.001
BNP	**< 0.001**	1.004	1.002–1.006	0.088	1.002	1.000–1.005
SaO_2	**0.005**	0.853	0.764-0.953	0.780	1.026	0.859-1.225
TAPSE	**< 0.001**	0.117	0.038–0.360	0.175	0.304	0.054–1.700
Age	0.769	0.996	0.970–1.023			
RV diameter	**0.003**	2.602	1.382–4.901	0.724	1.193	0.448–3.180
Heart rate	**0.02**	1.026	1.004–1.048	0.078	1.028	0.997–1.059
SBP	0.390	0.991	0.971–1.011			

CI — confidence interval; OR — odds ratio; BNP — B-type natriuretic peptide; SaO_2 — oxygen saturation, TAPSE — tricuspid annular plane systolic excursion; RV — right ventricular, SBP — systolic blood pressure

Table 5. Comparison of the study biomarkers levels between with and without right ventricular dysfunction (RVD) in patients with acute pulmonary embolism (APE).

	APE with RVD (n = 15)	APE without RVD (n = 32)	P
Copeptin [ng/dL]	9.36 ± 4.61	6.94 ± 4.14	**0.020**
Troponin I [ng/dL]	0.48 ± 0.40	0.30 ± 0.51	**0.029**
D-dimer [ng/dL]	6,032 ± 3,313	3,398 ± 2,557	**0.010**
B-type natriuretic peptide [ng/dL]	684 ± 299	405 ± 351	**0.001**

Ohigashi et al. [26] investigated the role of BNP, D-dimer, troponin I, and C-reactive protein in predicting adverse outcomes and RVD in patients with APE and they demonstrated that only high plasma BNP level was found to be a predictor of RVD and short- and long-term prognosis of APE. In the present study, all of the parameters were found to be higher in the patients with acute RVD. However, only plasma BNP levels were found to be significantly correlated with all the echocardiographic parameters that are used for diagnosis of acute RVD. While D-dimer was only correlated with RVFAC, copeptin was found to be correlated with TAPSE and RV/LV ratio.

Vasopressin is an antidiuretic and vasoconstrictive hormone, whose levels of circulating form underlie a complex feedforward and feedback regulation. Among the stimuli that lead to vasopressin release are increased plasma osmolality, decreased arterial pressure, reduced cardiac filling, and neurohumoral peptides such as angiotensin [28]. Levels of vasopressin have been shown to be elevated in heart failure [29]. Copeptin is secreted stoichiometrically with vasopressin from the neurohypophysis and is much more stable, thus overcoming the limitations and difficulties of assessing the arginine-vasopressin system [30]. It is reported that copeptin is strongly associated with severity and long-term prognosis of left ventricular heart failure [29]. Nickel et al. [16] reported increased levels of copeptin in patients with pulmonary hypertension and RV failure. Increased copeptin levels were linked to increased neurohumoral activation due to RV failure in patients with pulmonary artery hypertension. In our study, copeptin was higher in the patients with APE and it was also found in increased amounts in the patients with RVD compared to those without RVD. Elevated levels of copeptin in the patients with APE might be due to acute right heart overload and failure and raised neurohumoral activation. Since it is known that RVD is a poor prognostic factor in patients with APE, assessing copeptin levels on admission might be useful for performing a risk stratification of the patients with APE.

Limitations of the study

The present study has some limitations. First, the study population was relatively small; however, we were still able to demonstrate a strong relationship between increased copeptin levels and the presence of APE and RVD. Second, a lack of short- and long-term follow-up of patients was another limitation to this study. Third, because of a single measurement on admission, the changes in copeptin in response to treatment could not be evaluated. Fourth, there are some issues in terms of cost and timeliness of copeptin assays. The cost-effectiveness of copeptin assays is controversial in the literature. Furthermore, it may take more than 24 h to come back or it will have to be sent elsewhere to study this assay. These disadvantages of copeptin assays may reduce the clinical utility of this new biomarker routinely in APE [31, 32]. The last limitation of the present study was having many exclusion criteria limiting generalizability. The patients who are a challenge to diagnose are often the ones who might have congestive heart failure or chronic obstructive lung disease or an inflammatory disorder. Because of many exclusion criteria, our results cannot be extrapolated to all patients with APE.

Conclusions

This study is the first to demonstrate a diagnostic value of copeptin in patients with APE. Copeptin was found an independent significant predictor of APE, even after adjustments for various risk parameters. Copeptin is a promising new biomarker, which may be used to support the need for further investigations and to improve the diagnosis of patients with APE, with moderate sensitivity and specificity. Since it is not specific to a certain disease, copeptin could be used as an adjunct with more specific biomarkers where it may increase diagnostic accuracy and aid clinicians in making better diagnostic judgements. Moreover, a larger study is warranted in a more general emergency department population being considered for PE without as many exclusions to see if copeptin is truly useful or if the early positive results will get masked by other diagnoses leading to similar elevations in copeptin.

Conflict of interest: None declared

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