

## PAPER DETAILS

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# Copeptin As A Diagnostic PH Marker in Acute Pulmonary Embolism

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## ABSTRACT

**Objective:** The present study aimed to investigate the effectiveness of copeptin levels in detecting increased pulmonary artery pressure and right ventricular dysfunction in patients with acute pulmonary embolism.

**Methods:** A total of 116 patients who presented to the emergency department with chest pain or dyspnea and were diagnosed with acute pulmonary embolism and 30 healthy controls were included in the study. Plasma copeptin levels of patients and healthy control group were measured. Right ventricular functions and pulmonary artery pressures were evaluated in echocardiography of patients diagnosed with acute pulmonary embolism.

**Results:** Copeptin levels were significantly higher in patients with right ventricular dysfunction than in those without right ventricular dysfunction [median 1.06(0.03–7.14) vs. 0.59(0.31–2.50),  $p=0.01$ ].

**Conclusion:** Copeptin can be used as a new biomarker in the diagnosis of acute pulmonary embolism and in predicting right ventricular dysfunction and increased pulmonary artery pressure in patients with acute pulmonary embolism.

**Keywords:** Pulmonary embolism, mortality, pulmonary wedge pressure, right ventricular dysfunction

## 1. INTRODUCTION

Acute pulmonary embolism (PE) is a common condition that can lead to high mortality and morbidity rates unless treated properly (1). As such, diagnostic tests with radiological and laboratory data are necessary for the detection and differential diagnosis of PE due to its nonspecific symptomatology, which can be mimicked by other conditions (2). Notably, 30%–40% of all PEs are submassive, making the rapid and accurate diagnosis of right ventricular dysfunction (RVD) crucial for the correct risk stratification of these patients (3). However, to the best of our knowledge, there has been no biochemical marker or other available means that are definitely useful in early diagnosis (2).

Under different stress levels, vasopressin, a hypothalamic hormone, is stimulated to enhance the activity of corticotropin-releasing hormone, leading to adrenocorticotrophic hormone secretion and cortisol production (4). Copeptin, which is a stable peptide of the vasopressin precursor, constitutes the C-terminal portion of provasopressin and is a new

neurohormone of the arginine vasopressin (AVP) system (5). Similar to arginine vasopressin, it is synthesized in the hypothalamus and released into the portal circulation of the neurohypophysis. Moreover, copeptin is secreted in molar proportions equal and reflective to those of arginine vasopressin (6). Thus, it can reflect individual stress responses at the hypothalamic level (7). Furthermore, copeptin has been reported to have prognostic value in various diseases, including acute coronary syndrome, cerebral hemorrhage, congestive heart failure, lung diseases, and sepsis (8).

Despite this, only a limited number of studies have demonstrated the relationship between copeptin and right-sided heart failure. A recent study reported that copeptin levels were increased and prognostic in pulmonary hypertension and right-sided heart failure (9). This study also reported that increased neurohumoral activity due to right ventricular failure led to increased copeptin levels in patients with pulmonary hypertension (9).

Therefore, the aim of this study was to investigate the utility of copeptin levels in detecting increased pulmonary artery pressure (PAP) and RVD in patients with acute PE.

## 2. METHODS

This study was conducted in accordance with the principles of the Declaration of Helsinki and the principles of research after obtaining approval from the Ethics Board of Erciyes University (dated 10.02.2012 and no. 2012/136).

Patients older than 18 years with a diagnosis of acute PE at the emergency department were included in the study and divided into three groups. The first group comprised patients with PE and RVD, the second group comprised patients with PE but without RVD, and the third group comprised healthy controls.

In contrast, patients with severe chronic obstructive pulmonary disease, congestive heart failure, right-sided heart failure, sepsis, chronic renal failure, acute cerebrovascular disease, pneumonia, aortic dissection, pulmonary hypertension, and a history of PE were excluded from the study.

Demographics, computed tomography and transthoracic echocardiography (TTE) findings, laboratory data, and administered treatments were all recorded in the computer software. Wells scores were calculated for all the patients, and the PE severity index (PESI) and simplified PESI (sPESI) were calculated for prognostication based on their clinical characteristics and medical history on admission.

RVD was determined by TTE.

### 2.1. Copeptin Measurement

Exactly 3 ml of venous blood was extracted from the antecubital region into ethylenediaminetetraacetic acid-containing tubes for the measurement of serum copeptin levels. After shaking the specimen, the collected blood was transferred and centrifuged for 10 minutes at 3,500 rpm to separate the serum. Samples were then stored at  $-70^{\circ}\text{C}$  until further analysis. Sandwich enzyme-linked immunosorbent assay was manually conducted, and blood levels were quantitatively measured using the EK-065-32 Human Copeptin enzyme immunoassay test kit from Phoenix Pharmaceuticals Inc.

### 2.2. Statistical Analysis

The Statistical Package for the Social Sciences version 24.0 software was used for statistical analyses, and P values of  $<0.05$  were considered statistically significant. The Kolmogorov–Smirnov test was used to analyze the normality of the data, and the Shapiro–Wilk test was used for normality analysis in groups with  $<30$  patients. The Mann–Whitney U test was used to compare two groups that did not exhibit normal distribution, whereas the Kruskal–Wallis test was used to compare three groups that did not exhibit normal

distribution. Bonferroni correction was also performed in the post-hoc analysis, wherein p values of  $<0.017$  was considered statistically significant. Furthermore, receiver operating characteristic (ROC) analysis was performed to determine the utility of copeptin levels in PE diagnosis.

## 3. RESULTS

A total of 116 patients with acute PE were included in the study. The mean age was  $66.77 \pm 14.22$  years, and dyspnea (41.4%) was the most common presenting symptom. Deep vein thrombosis (12.9%), history of surgery (19%), and immobilization (19.8%) were the most common risk factors. According to the PESI scores, 31% of patients were in the low-risk group, and 69% were in the high-risk group. Based on TTE, 51.7% of the patients had RVD. The mean PAP was  $44.8 \pm 18.6$  mmHg, of which 68 patients (58.6%) had a PAP of  $>40$  mmHg. Five patients (4.3%) received thrombolytic therapy, and 28 patients (24.1%) died within 30 days of admission (Table 1). Furthermore, copeptin levels were higher in patients who were considered suitable for thrombolytic therapy than in patients who were not. Patients with a mortal course were notably found in the high-risk group.

Plasma copeptin levels were significantly higher in patients with acute PE than in the healthy controls [median: 0.65 (0.03–7.14) vs. 0.41 (0.09–0.97),  $p = 0.002$ ] (Figure 1). Assuming a cut-off value of 0.42 for the ROC analysis of copeptin in detecting PE, the area under the curve (AUC) was 0.7, sensitivity was 84.5%, specificity was 46.7%, positive predictive value (PPD) was 87.5%, and negative predictive value (NPD) was 47.1% (Figure 2A, Table 2).

Comparison of plasma copeptin levels among patients with and without RVD, as revealed by TTE, and healthy controls showed that there was a significant difference between these groups ( $p = 0.001$ ). Specifically, plasma copeptin levels were significantly higher in patients with RVD than in those without RVD [median: 1.06 (0.03–7.14) vs. 0.59 (0.31–2.50),  $p = 0.01$ ] (Figure 3). Similarly, plasma copeptin levels were significantly higher in patients with PE but without RVD than in the healthy controls [median: 0.59 (0.31–2.50) vs. 0.41 (0.09–0.97),  $p = 0.016$ ]. Assuming a cut-off value of 1.01 for the ROC analysis of copeptin in predicting RVD, the AUC was 0.638, sensitivity was 51.7%, specificity was 89.3%, PPD was 83.8%, and NPD was 63.3% (Figure 2B, Table 2).

Significant differences in the plasma copeptin levels of patients with a PAP of  $>40$  mmHg, PAP of  $<40$  mmHg, and healthy controls were also observed ( $p < 0.001$ ). In patients with a PAP of  $>40$  mmHg, plasma copeptin levels were significantly higher than those of patients with a PAP of  $<40$  mmHg [median: 0.77 (0.03–7.14) vs. 0.59 (0.21–4.03),  $p = 0.046$ ] (Figure 4). Likewise, plasma copeptin levels were significantly higher in patients with a PAP of  $>40$  mmHg than in the healthy controls ( $p = 0.012$ ). According to the ROC analysis to determine the power of copeptin in predicting increased PAP, the AUC was 0.609, sensitivity was 54.4%,

specificity was 75.0%, PPD was 75.5%, and NPD was 53.7% (Figure 2C, Table 2).

On the other hand, there was no significant difference in the plasma copeptin levels of patients who died and survived within 30 days of admission [median: 0.68 (0.19–5.64) vs. 0.64 (0.03–7.14),  $p = 0.91$ ]. Assuming a cut-off value of 0.32 for the ROC analysis of copeptin in determining the 30-day mortality risk, the AUC was 0.551, sensitivity was 96.0%, specificity was 16.9%, PPD was 25.2%, and NPD was 89.9% ( $p = 0.339$ ) (Table 2).

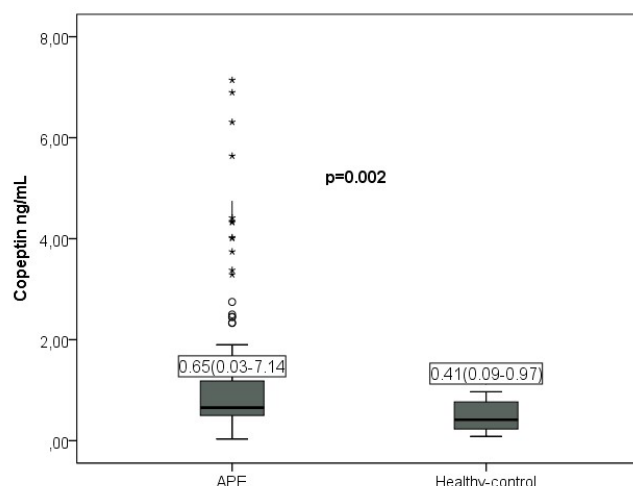
**Table 1.** Demographic, clinical, laboratory, and echocardiography findings of patients

<b>Age years (mean ± SD)</b>	66.77 ± 14.22
<b>Symptoms n (%)</b>	
Dyspnea	48 (41.4)
Chest pain	12 (10.3)
Hemoptysis	1 (0.9)
Syncope	2 (1.7)
Palpitations	4 (3.4)
Cough	13 (11.2)
<b>Risk factors n (%)</b>	
Symptoms of DVT	15 (12.9)
Previous surgery	22 (19.0)
Malignancy	11 (9.5)
Coagulation disorder factor deficiency	2 (1.7)
Immobilization	23 (19.8)
CBVD	1 (0.9)
<b>Vital signs</b>	
Age years (mean ± SD)	66.77 ± 14.22
Systolic blood pressure (mean ± SD)	134 ± 24 (87–190)
Diastolic blood pressure (mean ± SD)	78 ± 13 (42–120)
Pulse/min (mean ± SD)	101 ± 20 (10–147)
Respiratory rate/min (mean ± SD)	21 ± 2 (14–32)
O <sub>2</sub> saturation (mean ± SD)	90 ± 7 (60–99)
Tachycardia n (%)	46 (39.7)
<b>Wells score (mean ± SD)</b>	4.03 ± 2.14
Low Risk n (%)	12 (10.3)
Medium Risk n (%)	88 (75.9)
High Risk n (%)	16 (13.8)
<b>median PESI score (range)</b>	3 (1–5)
Class 1 n (%)	6 (5.2)
Class 2 n (%)	30 (25.9)
Class 3 n (%)	34 (29.3)
Class 4 n (%)	25 (21.6)
Class 5 n (%)	21 (18.1)
<b>sPESI</b>	
Low risk n (%)	36 (31.0)
High risk n (%)	80 (69.0)
<b>Right ventricular dysfunction in echo n (%)</b>	60 (51.7)
<b>PAP (mean ± SD)</b>	44.8 ± 18.6
<b>PAP≥40 mmHg n (%)</b>	68 (58.6)
<b>Thrombolytic therapy n (%)</b>	5 (4.3)
<b>30-day mortality n (%)</b>	28 (24.1)

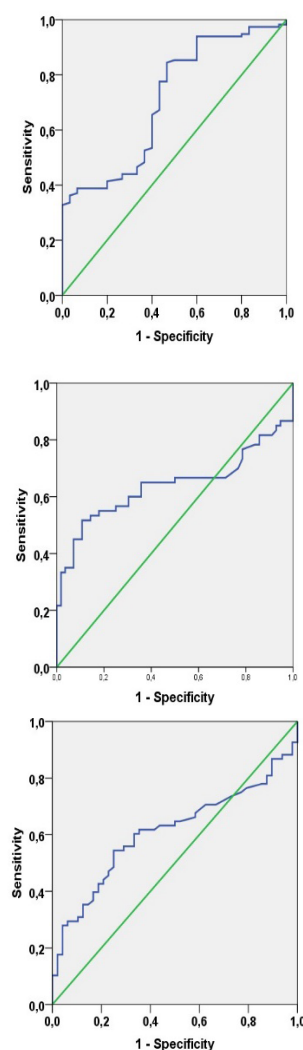
DVT: Deep Vein Thrombosis

CBVD: Cerebrovascular Disease

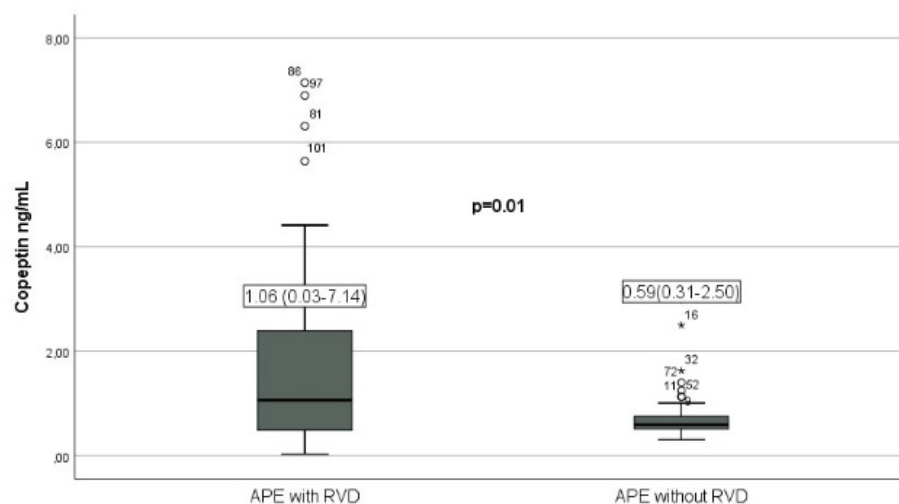
PAP: Pulmonary Artery Pressure



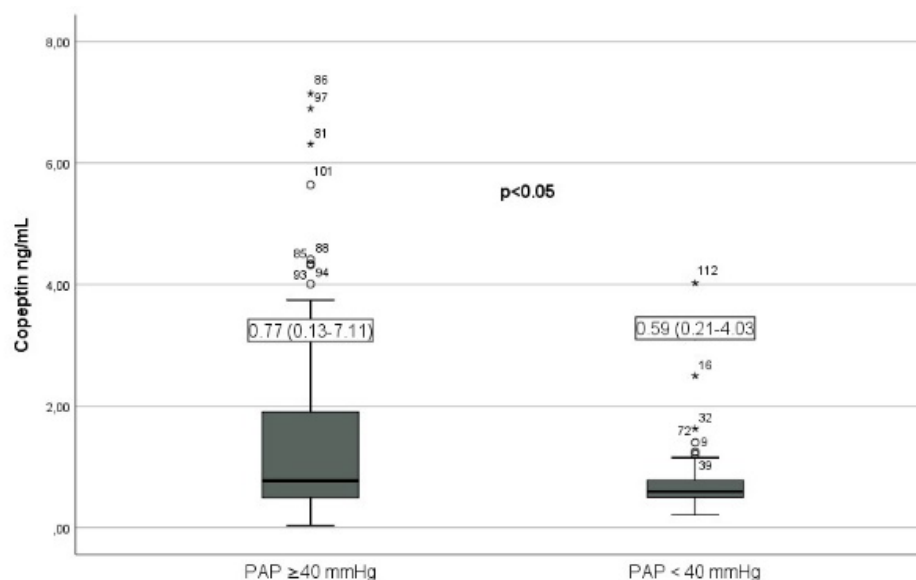
**Figure 1.** Comparison of plasma copeptin levels between patients with pulmonary embolism and healthy controls. Mann–Whitney U test:  $p < 0.05$  statistically significant



**Figure 2** a-c. Receiver operating characteristic (ROC) curve for copeptin levels in terms of detecting pulmonary embolism (a). ROC curve for copeptin levels in terms of detecting right ventricular dysfunction (b). ROC curve for copeptin levels in terms of detecting the increase in pulmonary artery pressure (c).



**Figure 3.** Comparison of copeptin levels according to the state of right ventricular dysfunction.



**Figure 4.** Comparison of copeptin levels according to pulmonary artery pressure.

**Table 2.** Receiver operating characteristic (ROC) analysis results of copeptin levels for detecting PE, RVD, increased PAP, and mortality risk

	Copeptin cut-off value	AUC	P	SE	95%CI	Sensitivity %	Specificity %	PPD %	NPD %
PE	>0.42	0.709	<0.001	0.052	0.607–0.812	84.7	46.7	87.5	47.1
RVD	>1.01	0.638	0.010	0.055	0.532–0.745	51.7	89.3	83.8	63.3
PAP increase	>0.73	0.609	0.046	0.052	0.507–0.712	54.4	75.0	75.5	53.7
Mortality	>0.32	0.551	0.399	0.058	0.437–0.665	96.0	16.9	25.2	59.9

PE: Pulmonary Embolism

RVD: Right Ventricular Dysfunction

PAP: Pulmonary Artery Pressure

#### 4. DISCUSSION

Several biomarkers have been used in acute PE diagnosis and risk classification in previous studies (3,10). Contributing to these findings, the results of the present study showed that plasma copeptin levels were higher in patients with acute PE than in healthy controls. Furthermore, these levels were higher in patients with PE and RVD than in those who had normal right ventricular function.

Copeptin levels have been associated with prognosis and mortality in various cardiovascular diseases, where increasing levels reflect increasing disease severity (11). In the present study, the median plasma copeptin levels were 0.65 (0.03–7.14) in patients with PE and 0.41 (0.09–0.97) in healthy controls, showing a statistically significant difference. In a similar study conducted by Öztürk et al., plasma copeptin levels were reported to be significantly higher in patients with acute PE ( $n = 32$ ) than in healthy controls ( $n = 24$ ) (2). Kalkan et al. similarly found that among patients who presented to the emergency department with chest pain or dyspnea, plasma copeptin levels were significantly higher in patients diagnosed with acute PE than in those without acute PE. A previous study also reported that although troponin, D-dimer, and pro-BNP levels were elevated in patients with acute PE, copeptin was a more specific biomarker in PE diagnosis by comparison (AUC: 0.836, sensitivity: 68%, selectivity: 83.7%, PPD: 82.1%, and NPD: 70.6%) (3). Vasopressin is an antidiuretic and vasoconstrictive hypothalamic hormone that is released after stimulation by different levels of stress. Specifically, systemic vasoconstriction and renal fluid retention caused by increased plasma osmolality, decreased arterial pressure, decreased cardiac filling, or activated neurohumoral peptides (e.g., angiotensin) and baroreceptors in the carotid sinus stimulate the release of vasopressin (12). As part of the AVP system, copeptin is much more stable than vasopressin, allowing it to reflect individual stress responses at the hypothalamic level (13). As such, we believed that increased neurohumoral activity due to pathophysiological changes and individual stress responses from hemodynamic changes, chest pain, and dyspnea would lead to elevated copeptin levels in patients with PE.

In acute PE, pulmonary vasoconstriction and high PAP result in increased right ventricular afterload and dilatation, thereby leading to RVD (14). Among patients with PE, RVD is an important indicator of poor prognosis and has been demonstrated to be the most important cause of death (15). Echocardiography and certain cardiac biomarkers have been used in determining RVD (16). Excessive neurohumoral activation occurring due to thrombosis from PE leads to bronchoconstriction, hypoxia, vascular resistance, and changes in blood volume and heart contraction, all of which contribute to the development of heart failure (9). Interestingly, elevated plasma levels of vasopressin have been reported in patients with heart failure (17). Elevated plasma copeptin levels were also shown to be associated with disease severity and long-term prognosis in patients with left ventricular failure (17). In the present study, plasma

copeptin levels were elevated in patients with acute PE, which was especially higher in patients with acute PE and RVD. Assuming a cut-off value of 1.01 on ROC analysis, the sensitivity, specificity, PPD, and NPD of plasma copeptin levels in detecting RVD was 51.7%, 89.3%, 83.8%, and 63.3%, respectively. According to Kalkan et al., the copeptin levels of patients with acute PE and RVD were significantly higher than in patients with acute PE but without RVD, which was consistent with our findings (3). Given the findings from our study and from previous studies, we believe that the increased neurohumoral activity due to the hemodynamic stimulus in acute PE with RVD is responsible for the significant increase in plasma copeptin levels. Therefore, serum copeptin levels can be used as a novel biomarker for detecting RVD.

Nickel et al. compared copeptin levels in patients with and without pulmonary arterial hypertension, finding that copeptin levels were markedly higher in patients with pulmonary arterial hypertension. Furthermore, they reported that patients with pulmonary arterial hypertension and high copeptin levels had poor prognosis and were at higher risk for mortality (9). Although the present study did not include patients with chronic pulmonary hypertension, the plasma copeptin levels of patients with and without acute pulmonary arterial hypertension secondary to acute PE were compared, showing that patients with increased PAP had significantly higher plasma copeptin levels. According to the present study, the 30-day mortality rate in patients with acute PE was 24.1%; however, there was no significant difference between the copeptin levels of patients who died and survived within 30 days of admission. Similarly, according to the PESI score, there was no significant difference in the copeptin levels between patients in the low-risk and high-risk groups. In a study conducted by Vuilleumier et al., the specificity and sensitivity of copeptin levels in determining the 1-month mortality risk was reported to be 20% and 83.3%, respectively (10). According to another study by Deveci et al., there were significant differences in the plasma copeptin levels between patients with acute PE who died and survived during hospitalization, as well as between patients who died and survived within 1 month of admission. Contrarily, there was no significant difference in the 3-month mortality. In the same study, a significant difference in the copeptin levels between patients in the low-risk and high-risk groups was also observed, as revealed by the sPESI scores (18). Other studies have shown that acute PE remains a major cause of mortality (19,20). Likewise, the results of the present study showed that PE was a major cause of mortality, although we failed to demonstrate the relationship between mortality and copeptin levels.

#### 5. CONCLUSION

The present study showed that copeptin levels were significantly elevated in patients with acute PE, especially those who developed RVD. Although copeptin is nonspecific and does not have high sensitivity, it can be used as an alternative biomarker for determining RVD in patients with



acute PE. Extensive studies are warranted in the future to determine the cut-off values associated with the diagnosis, prognosis, and mortality rate, as well as to reveal the sensitivity and specificity of copeptin levels in patients with acute PE.

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**Conflicts of interest:** The author declare no conflict of interest

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