

# The Value of Cardiotrophin-1 in the Diagnosis, Severity, and Prognosis of Pulmonary Embolism

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## Abstract

**Aim:** Pulmonary embolism (PE) is a life-threatening condition that requires early diagnosis and treatment. There is still a need for precise and non-invasive biomarkers that can be used to diagnose PE. This study aimed to determine the diagnostic value of Cardiotrophin-1 (CT-1) in patients with acute PE and ascertain the relationship between serum CT-1 level and disease prognosis and severity.

**Materials and Methods:** In this prospective study, the serum CT-1 levels of 165 patients with suspected acute PE were measured. The patients were divided into two groups, PE (+) and PE (-), based on their computed tomography angiography results. Their serum CT-1 levels were compared.

**Results:** The CT-1 levels of the PE (+) group (median=4.18 pg/mL, range=3.57-9.55 pg/mL) was non-significantly ( $p=0.08$ ) different from those of the PE (-) group (median=4.38 pg/mL, range=3.57-51.64 pg/mL). Based on the severity of the condition, there were significant differences ( $p=0.001$ ) in the CT-1 levels of the patients in the intermediate-low risk group (median=4.19 pg/mL, range=3.62-5.32 pg/mL), intermediate-high risk group (median=4.06 pg/mL, range=3.57-9.31 pg/mL) and high risk group (median=5.01 pg/mL, range=3.89-9.55 pg/mL). Based on the clinical course, the CT-1 levels of the patients in the good clinical course group (median=4.15 pg/mL, range=3.57-9.31 pg/mL) were significantly different ( $p=0.004$ ) from those in the poor clinical course group (median=4.53 pg/mL, range=3.66-9.55 pg/mL).

**Conclusion:** CT-1 level was not observed to be a precise biomarker for the diagnosis of acute PE. However, our study demonstrated that the serum CT-1 levels can be used as a biomarker for ascertaining the severity and prognosis of patients with PE.

**Keywords:** Pulmonary embolism, diagnosis, severity, prognosis, Cardiotrophin-1

## Introduction

Pulmonary embolism (PE) is a common and potentially life-threatening clinical condition that may cause obstruction of the pulmonary vascular bed and concomitant right heart failure (1,2). Early diagnosis and treatment can be life-saving. Currently, there are still various difficulties in the diagnosis of PE in emergency

departments due to nonspecific symptoms and signs. D-dimer is a marker with high negative and low positive predictive value that can be used non-invasively in the diagnosis of PE. Definitive diagnosis is made by expensive techniques such as pulmonary scintigraphy and spiral computed tomography (CT) or invasive methods such as pulmonary angiography (3). However, these invasive and expensive methods may not always be available.



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There is still a need for easy and non-invasive alternative biomarkers that can be used to diagnose PE and determine its severity and prognosis. Several guidelines recommend modified Well's Score (mWS) for assessing PE risk levels for patients without clinically shock findings. According to mWS, D-Dimer, CT angiography (CTA) and bedside echocardiography are the choices of diagnostic tools. There are advantages and disadvantages of both CTA and echocardiography. The latter is non-invasive and can be performed at the bedside, while its major disadvantages are that it is user-dependent and is not as sensitive and specific as CTA (3).

PE may follow an asymptomatic course, or may also result in severe right ventricular failure, hypotension, shock, and arrest. It is known that there is a strong relationship between the severity of PE and prognosis. The use of thrombolytic therapy in haemodynamically stable patients with PE causing RVD is still controversial. Studies in which thrombolytic therapy administered to the patients with moderate-risk PE, defined as patients with RVD findings and with high biochemical parameters such as Troponin (Tn) or B-type Natriuretic Peptide (BNP), proBNP, heart type fatty acid-binding protein (H-FABP) despite not being hypotensive, have shown that such treatment has positive effects on preventing the development of haemodynamic decompensation (4). Biochemical parameters therefore also play a role, in addition to echocardiography and CT, in determining the severity and prognosis of PE (1). There are prognostic models such as the PE Severity index (PESI) or simplified PESI (sPESI), established using the clinical features of the patients at presentation (5,6). These models are used to determine the risk of early mortality in patients with confirmed diagnosis of acute PE by evaluating imaging results together with other clinical findings (1). In addition, they can also assist clinicians in the decision whether to admit patients with acute PE or observe them on an outpatient basis (7).

CT-1, a novel biochemical marker, is a 21.5 kDa protein from the interleukin-6 family, containing 201 amino acids and found in human heart, lung, and skeletal muscle. This cytokine performs transmembrane signaling through the glycoprotein 130 receptor. It has been shown to exhibit a powerful protective and hypertrophic effect on cardiac myocytes (8,9). CT-1 has also been shown to be of prognostic and diagnostic value in several cardiovascular diseases, such as hypertension, congestive heart failure, acute myocardial infarction, and valvular heart disease (10). It is probable that CT-1 levels may play a role in the diagnosis of PE and also it may be useful to determine the prognosis and the severity.

## Materials and Methods

Approval for this prospective, randomized clinical study was granted by the Karadeniz Technical University Scientific

Researches Ethical Committee (no: 2016/7). The study was performed in the Karadeniz Technical University School of Medicine Department of Emergency Medicine, a tertiary centre serving approximately 100,000 patients a year.

## Selection of Participants

In the one-year period following receipt of ethical committee approval, patients aged over 18, consenting to take part and presenting to the emergency department with suspected acute PE and undergoing CTA were included in the study. Patients with kidney failure or advanced liver failure at time of presentation, pregnant women, and patients with deficient records were excluded.

## Study Design and Setting

The diagnostic algorithm specified in the 2014 European Society of Cardiology (ESC) guidelines on the diagnosis and management of PE was used to evaluate the patients presenting to the emergency department on suspicion of acute PE. Consistent with that algorithm, patients undergoing spiral CTA (Siemens Somatom Sensation, Germany) and identified as having PE were included in the PE (+), and those without PE were enrolled in the PE (-) group. The diagnostic value of CT-1 was then investigated. In addition, patients diagnosed with acute PE were classified as low risk, intermediate-low risk, intermediate-high risk, and high risk based on early mortality classification as described in the 2014 ESC guidelines on the diagnosis and management of PE. Analysis of CT-1 and other biochemical parameters was then performed among these groups. Finally, all patients in the PE (+) group was followed-up for 90 days and prognostic analysis was performed according to defined clinical endpoints: intensive care requirements, intubation and mechanical ventilation requirements, vasopressor requirements, cardiopulmonary resuscitation and mortality. Patients developing one of these clinical endpoints were classified as the poor clinical course group, while those not developing any of the clinical endpoints were classified as the good clinical course group, and the prognostic value of CT-1 measured at time of presentation in acute PE patients was investigated. Informed consent was obtained from all patients included in the study.

## Biochemical Measurements

Blood specimens were placed into gel separator blood tubes and allowed to clot for 20 min at room temperature. The tubes were then centrifuged at 1800xg for 10 min. Following centrifugation, the serum was carefully transferred to small, closed tubes and stored at -80 °C until the day of study.

Serum specimen CT-1 levels were measured using an enzyme-linked immunosorbent assay (ELISA) kit (BioVendor, Cat

No: RD192026200CS, Brno, Czech Republic) in line with the manufacturer's instructions. The results were expressed as pg/mL. The intra-assay repeatability of this method was 4.4% (CV%).

### Statistical Analysis

Statistical analysis was performed on SPSS 23.0 (IBM SPSS, Armonk, NY, USA) and MedCalc 12.3 (MedCalc Software, Mariakerke, Belgium) statistical software. Compatibility with normal distribution was assessed using the Shapiro-Wilk test. The Mann-Whitney U test was applied to compare the PE (+) and PE (-) groups. p values <0.05 were regarded as statistically significant. To determine the accuracy and respective best cut-off values of CT-1 for predicting APE, the receiver operating characteristic (ROC) curves and their corresponding areas under the curve were used. A p value of <0.05 was considered statistically significant.

### Outcomes

The primary aim of this study was to investigate the value of CT-1 in the diagnosis of PE. Our secondary aim was to determine the value of CT-1 in determining the severity of PE using CT and echocardiography findings and Tn levels. We also investigated whether CT-1 is of any value in showing prognosis in PE patients.

### Results

During the study period 221 patients presenting with suspected acute PE to emergency department were evaluated. Twenty-seven patients were excluded for not meeting the inclusion criteria. CTA was not performed on seven patients due to findings of right ventricular dysfunction (RVD) at echocardiography, and these were also excluded. Another four patients were excluded since CTA could not be performed due to instability. CTA was also not performed on 18 patients in the low risk group based on clinical probability analysis and with negative D-dimer results. Information about the patients included in and excluded from the study is shown in Figure 1. CTA was finally performed on 165 patients, 67 were in acute PE group, and 98 in the non-acute PE group. A comparison of the two groups' basic clinical and demographic characteristics is shown in Table 1. No statistically significant difference was determined between the two groups' demographic and clinical characteristics ( $p>0.05$  for all).

Since the primary aim of this study was to determine the diagnostic value of CT-1 in PE, acute PE and non-PE groups were compared in terms of CT-1 and other biochemical parameters. Median CT-1 values were 4.38 pg/mL (3.57-51.64) in the non-PE group and 4.18 pg/mL (3.57-9.55) in the acute PE group. These results revealed no statistically significant difference between the two groups in terms of CT-1 values at time of presentation ( $p=0.08$ ). Comparisons of other biochemical markers between

the two groups revealed significant differences in terms of TnT-hs, D-dimer, WBC and pCO<sub>2</sub> levels ( $p=0.004$ ,  $p<0.0001$ ,  $p=0.022$ , and  $p=0.002$ , respectively). Biochemical parameters between the acute PE and non-PE groups are shown in Table 2. ROC curve analysis was performed for CT-1 in patients diagnosed with APE and the area under the curve was found to be 0.581 ( $p=0.071$ ; 95% CI 54,6 to 74,4 Figure 2). The best cut-off values for CT-1 when predicting APE in patients with clinically suspected APE presenting at the ED were 4.2 pg/mL (sensitivity 54.5%; specificity 64.9%).

The secondary aim of this study was to determine the value of CT-1 in determining the severity of PE in patients diagnosed with the condition. For that purpose, we compared CT-1 and other biochemical parameters between the intermediate-low, intermediate-high and high-risk groups previously established. Since there were no patients in the low-risk group, this could not be included in the analysis. Median CT-1 values were 4.19 pg/mL (3.62-5.32) in the intermediate-low risk group, 4.06 pg/mL (3.57-9.31) in the intermediate-high risk group, and 5.01 pg/mL (266.5-1435.1) in the high-risk group. Analysis revealed significant differences in terms of CT-1 values among the three

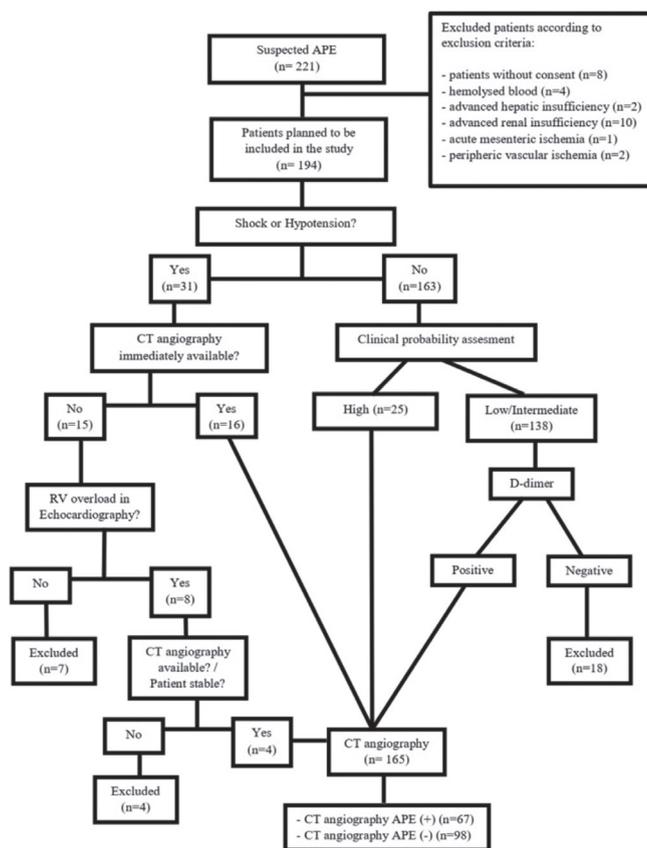


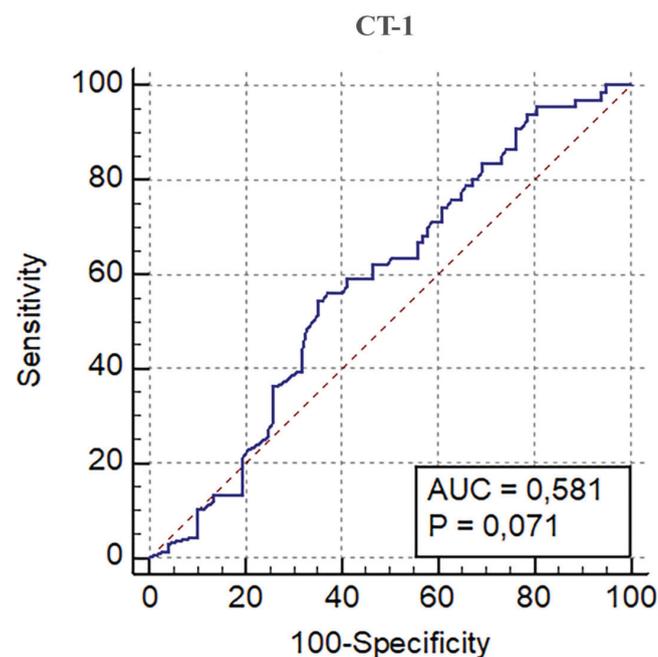
Figure 1. Study flow chart

CT: Computed tomography, APE: Acute pulmonary embolism, n: Number

	<b>APE Negative, n (%)</b>	<b>APE Positive, n (%)</b>	<b>p</b>
<b>Age, med (min-max)</b>	72.5 (18-96)	78 (38-95)	0.69
<b>Gender</b>			
Female	55 (33.3%)	43 (27.3%)	0.194
Male	45 (26.1%)	22 (13.3%)	
<b>Symptom</b>			
Dyspnea	82 (49.7%)	55 (33.3%)	0.834
Chest pain	24 (14.5%)	17 (10.3%)	1.0
Hemoptysis	4 (2.4%)	3 (1.8%)	1.0
Syncope	16 (9.7%)	16 (9.7%)	0.237
DVT symptoms	3 (1.8%)	6 (3.6%)	0.161
Other symptoms	27 (16.4)	23 (13.9%)	0.391
<b>Vitals</b>			
SBP mmHg, mean ± SD	118.57±23.9	117.08±24.4	0.649
DBP mmHg, med (min-max)	71.5 (40-140)	72 (40-120)	0.831
Pulse/min, mean ± SD	101.94±23.3	98.65±21.9	0.320
Respiratory rate/min, med (min-max)	22 (10-45)	24 (10-42)	0.257
Body temperature °C, med (min-max)	36.7 (35.9-39.5)	36.8 (36-39.2)	0.697
<b>ECG findings</b>			
S1Q3T3	4 (2.4%)	4 (2.4%)	0.716
Sinus tachycardia	28 (17.0%)	24 (14.5%)	0.394
Atrial fibrillation	24 (14.5%)	16 (9.7%)	1.0
Negative T waves	13 (7.9%)	17 (10.3%)	0.64
RBBB	0 (0.0%)	3 (1.8%)	0.65
<b>X-ray findings</b>			
Pleural effusion	20 (12.1%)	9 (5.5%)	0.301
Atelectasia	23 (13.9%)	13 (7.9%)	0.57
Diaphragm elevation	2 (1.2%)	5 (3.0%)	0.121
Hampton hump	1 (0.6%)	0 (0.0%)	1.0
Pulmonary artery dilatation	9 (5.5%)	4 (2.4%)	0.453
<b>VTE risk factors</b>			
Previous PE	6 (3.6%)	10 (6.1%)	0.105
Previous DVT	4 (2.4%)	4 (2.4%)	0.716
Varicose veins	3 (1.8%)	4 (2.4%)	0.443
Chronic venous insufficiency	1 (0.6%)	0 (0.0%)	1.0
Previous stroke	14 (8.5%)	11 (6.7%)	0.826

Pregnancy	0 (0.0%)	0 (0.0%)	1.0
Malignancy	29 (17.6%)	25 (15.2%)	0.315
Obesity	12 (7.3%)	13 (7.9%)	0.269
Smoking history	12 (7.3%)	11 (6.7%)	0.496
Immobilisation	38 (23.0%)	35 (21.2%)	0.111
Surgery in 4 weeks	6 (3.6%)	7 (4.2%)	0.362
Trauma in 4 weeks	4 (2.4%)	5 (3.0%)	0.488
<b>Coagulopathy</b>	1 (0.6%)	1 (0.6%)	0.406
<b>Oral contraceptive use</b>	0 (0.0%)	0 (0.0%)	1.0
<b>Postpartum period</b>	0 (0.0%)	1 (0.6%)	0.406

APE: Acute pulmonary embolism; DVT: Deep vein thrombosis; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; RBBB: Right bundle branch block, VTE: Venous thromboembolism; PE: Pulmonary embolism, SD: Standard deviation, med: Median, n: Number, ECG: Electrocardiogram



**Figure 2.** Roc curve analysis

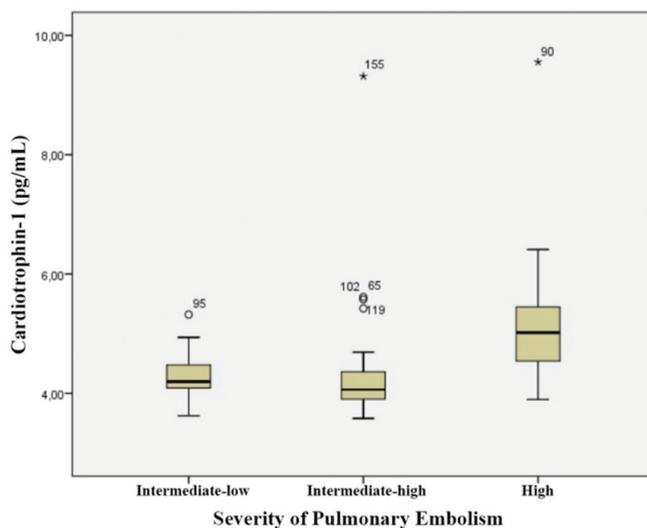
AUC: Area under the curve, CT-1: Cardiotrophin-1 groups (p=0.001). Bonferroni correction was used in two-way comparisons between groups and showed a significant difference between the high-risk group and the intermediate-low and intermediate-high risk groups (Bonferroni test p=0.002 and p=0.001, respectively). CT-1 level in these three groups are shown in Figure 3.

Comparisons among these three groups in terms of other biochemical parameters revealed statistically significant differences in Tn-T and proBNP values (p=0.044, and p=0.016, respectively), but none in terms of the other biochemical

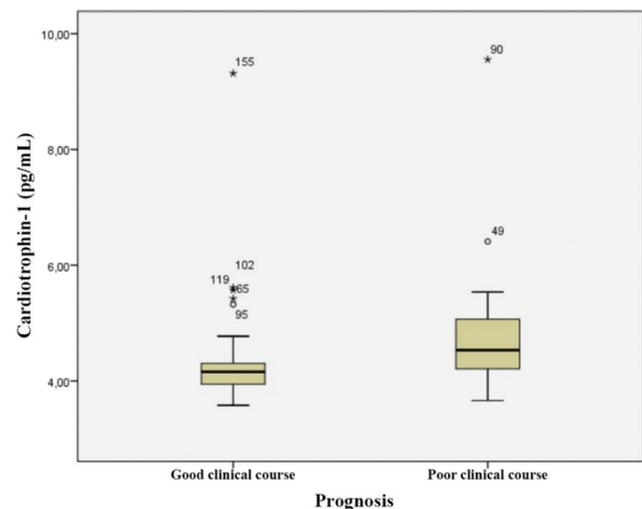
parameters. Comparisons using Bonferroni correction revealed a significant difference in pro-BNP between the intermediate-low risk group and the intermediate-high risk group ( $p=0.005$ ). A comparison of biochemical parameters among the three groups constituted to determine the severity of PE is shown in Table 3.

For the third aim of this study, to evaluate the prognostic value of CT-1 in patients with PE, comparison of biochemical values in the good and poor clinical course groups that established according

to previously mentioned was performed. Median CT-1 values were 4.15 pg/mL (3.57-9.31) in the good clinical course group and 4.53 pg/mL (3.66-9.55) in the poor clinical course group and a statistically significant difference was found between the two groups ( $p=0.004$ ). CT-1 values between the groups evaluated in terms of prognosis are shown in Figure 4. The analysis of other biochemical parameters between two groups showed a significant difference only in terms of Tn-T ( $p=0.008$ ). The



**Figure 3.** Distribution of Cardiotrophin-1 levels in the PE severity groups  
PE: Pulmonary embolism



**Figure 4.** Comparison of biochemical parameters among the acute PE clinical course groups  
PE: Pulmonary embolism

Marker	PE negative (n=98) (59.4%)	PE positive (n=67) (40.6%)	p
CT-1 (pg/mL), med (min-max)	4.38 (3.57-51.64)	4.18 (3.57-9.55)	0.080
TnT-hs (ng/L), med (min-max)	27.14 (3.18-6676.0)	38.64 (3.0-315.8)	0.004
CK-MB (ng/L), med (min-max)	1.905 (0.3-38.62)	2.29 (0.32-13.69)	0.302
Ph, med (min-max)	7.45 (6.82-7.67)	7.45 (7.05-7.57)	0.414
pCO <sub>2</sub> (mmHg), med (min-max)	34.85 (17.0-74.3)	31.3 (15.2-61.0)	0.002
pO <sub>2</sub> (mmHg), med (min-max)	71.3 (38.9-177.0)	71.3 (44.5-166.0)	0.758
sO <sub>2</sub> (%), med (min-max)	93.45 (56.3-99.0)	92.8 (72.9-99.3)	0.459
Glucose (mg/dL), med (min-max)	131 (78-393)	129 (90-498)	0.897
BUN (mg/dL), med (min-max)	21.5 (6.0-87.0)	23.0 (6.0-92.0)	0.386
Creatinine (mg/dL), med (min-max)	0.9 (0.23-2.39)	0.9 (0.43-1.74)	0.470
ALT (U/L), med (min-max)	19.5 (3.0-396.0)	15.0 (3.0-199.0)	0.128
AST (U/L), med (min-max)	30.0 (9.0-285.0)	25.0 (10.0-531.0)	0.124
D-dimer (µg/mL), med (min-max)	2.71 (0.57-40.0)	7.54 (1.11-42.92)	<0.0001
CRP (mg/dL), med (min-max)	4.97 (0.13-37.28)	7.0 (0.2-36.29)	0.448
WBC (/µL), med (min-max)	7860 (180-168000)	10630 (1120-38340)	0.022

PE: Pulmonary embolism, CT-1: Cardiotrophin-1, TnT-hs: High sensitive cardiac troponin T, CK-MB: Creatine kinase myocardial band, BUN: Blood urea nitrogen, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C reactive protein, WBC: White blood cell, SD: Standard deviation, med: Median, min: Minimum, max: Maximum, n: Number

comparison of biochemical markers between the two groups is shown in Table 3.

## Discussion

Acute PE is a common acute cardiovascular disease. However, diagnosis of patients presenting with acute PE can be difficult (11). Since mortality decreases significantly in cases that are treated early, rapid diagnosis is particularly important in this clinical condition with high mortality and morbidity.

Several biochemical markers and parameters have been investigated in the diagnosis of PE but to the best of our knowledge, this is the first study to evaluate the prognostic value of Cardiotrophin-1 (CT-1) in the diagnosis of PE. In this study, we also evaluated the relationship between the serum CT-1 levels with the prognosis and the risk levels of the disease.

CT-1 is a survival promoting cytokine detected in cardiomyocytes and cardiac fibroblasts in response to mechanical, humoral, metabolic and hypoxic stress. In acute stress conditions, CT-1 increases cell survival, whereas in increased stress states, the chronic effect of CT-1 is cardiomyocyte hypertrophy and consequently left ventricular failure (12). CT-1 is also released from vascular endothelial cells and produces direct vascular effects in the form of atherogenesis, vascular dysfunction, arterial stiffness and increased blood pressure (13,14). Overall, CT-1 is an effective profibrotic agent for the heart and vessels (12,14). In a review Calabrò et al. (15) evaluated the role of CT-1 in cardiovascular diseases and said that, plasma CT-1 levels are higher in patients with hypertension (with left ventricular hypertrophy), significant mitral regurgitation (with left ventricular function), aortic stenosis, unstable angina, acute myocardial infarction, and heart failure than healthy subjects.

Although it may be a biochemical marker that can be used as a diagnostic tool in cardiovascular diseases, because of the low specificity and the sensitivity rates, we concluded that CT-1 alone will not be useful in the diagnosis of acute PE. And we found that among other biochemical parameters, TnT-hs and D-dimer levels were higher in the PE group, consistent with the literature. It is well known that elevated plasma troponin levels are associated with worse prognosis in PE (1). But the use of plasma troponin levels alone in the diagnosis of PE is not appropriate because plasma troponin levels are elevated in many different cardiovascular diseases and may cause errors in diagnosis. Also, D-Dimer has a high negative and low positive predictive value, and it is used in the primary evaluation of the PE in suspected patients.

The use of cardiac troponin levels to assess the severity of PE is recommended by the 2019 ESC guideline. In addition to this, increased Heart-type fatty acid-binding protein (H-FABP), BNP, N-terminal (NT) proBNP and lactate levels were reported to be associated with poor prognosis in PE (1). Hellenkamp et al. (16) investigated the effect of copeptin on the prognosis of PE and found that patients with high levels of copeptin had more adverse outcomes. It was said that copeptin levels could improve risk stratification in normotensive patients if it was integrated in the risk assessment algorithm in the 2014 ESC algorithm. In our study we found that CT-1 levels were higher in the high-risk group compared to intermediate-high risk and intermediate-low risk groups. According to these findings we can say that CT-1 levels can be used to identify high risk PE patients. We also found that CT-1 levels are higher in the previously defined poor clinical course group and higher CT-1 levels are associated with poor prognosis.

Marker	PE severity groups				Acute PE clinical course groups		
	Intermediate-low risk (n=23) (%34.3)	Intermediate-high risk (n=32) (%47.8)	High risk (n=12) (%17.9)	p	Good clinical course (n=44) (%65.7)	Poor clinical course (n=23) (%34.3)	p
CT-1 (pg/mL), med (min-max)	4.19 (3.62-5.32)	4.06 (3.57-9.31)	5.01 (3.89-9.55)	0.001	4.15 (3.57-9.31)	4.53 (3.66-9.55)	0.004
D-dimer (µg/mL), med (min-max)	7.54 (1.11-30.0)	9.54 (1.25-39.41)	5.72 (1.59-42.93)	0.821	8.22 (1.11-30.0)	7.49 (1.59-42.93)	0.235
TnT-hs (ng/L), med (min-max)	34.16 (3.00-197.00)	37.46 (15.39-226.50)	65.22 (14.80-315.80)	0.044	35.0 (3.0-208.20)	67.0 (12.92-315.80)	0.008
Nt-proBNP (pg/mL), med (min-max)	789.0 (71.0-12172.0)	2686.5 (80.0-18691.0)	3861.0 (178.0-17647.0)	0.016	1833.50 (71.0-18691.0)	1849.20 (147.0-17647.0)	0.607

PE: Pulmonary embolism, CT-1: Cardiotrophin-1, TnT-hs: High sensitive cardiac troponin T, Nt-proBNP: N terminal prohormone of B-type natriuretic peptide, min: Minimum, max: Maximum, med: Median, n: Number

## Study Limitations

When our study was conducted, since the 2019 ESC guideline has not yet been published and the valid guideline for PE was the 2014 ESC guideline, we used the 2014 ESC guideline to determine the patient inclusion criteria and PE severity classification and algorithm.

The major limitation of this study is that the time of onset of PE was unclear, and that since time of presentation to hospital differed for all patients, serum collection times could not be standardized for all individuals.

Another important limitation of this study is that blood was collected from patients presenting with suspected PE only at time of presentation, rather than periodically, and no analysis of time-dependent changes in CT-1 levels was possible.

## Conclusion

The results of this study do not support the use of CT-1 as a diagnostic marker in acute PE patients. However, they do suggest that serum CT-1 may be useful in determining clinical severity and prognosis in patients with acute PE.

## Ethics

**Ethics Committee Approval:** Approval for this prospective, randomized clinical study was granted by the local clinical research ethical committee (no: 2016/7).

**Informed Consent:** Informed consent was obtained from the patients.

**Peer-review:** Externally peer-reviewed.

## Authorship Contributions

Surgical and Medical Practices: S.P., O.A., M.İ., Concept: S.P., O.A., M.İ., A.M., M.Ş., Ö.T., Design: S.P., O.A., M.İ., A.M., M.Ş., Ö.T., Data Collection or Processing: S.P., O.A., M.Ç., M.Y., Analysis or Interpretation: M.Ç., M.Y., S.D., A.M., Ö.T., Literature Search: S.P., O.A., M.İ., Writing: S.P., O.A., M.İ.

**Conflict of Interest:** The authors declare that they have no significant competing financial, professional or personal interests that might have influenced the performance or presentation of the work described in this manuscript.

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