

ORIGINAL ARTICLE

Adropin as a Novel Biomarker in the Diagnosis of Acute Pulmonary Embolism: a Prospective Analysis

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ABSTRACT

Background: Pulmonary embolism (PE) is a potentially life-threatening condition requiring rapid diagnosis and management. While computed tomography pulmonary angiography (CTPA) is the gold standard for diagnosis, its overuse raises concerns about radiation exposure and healthcare costs. The objective of this study was to evaluate the diagnostic performance of serum adropin (ADR) levels in patients presenting to the emergency department with suspected acute PE.

Methods: This prospective, cross-sectional study included 120 patients who underwent CTPA due to suspected PE. Serum ADR levels were measured using ELISA. Patients were stratified by Wells score into low, moderate, and high-risk groups. Receiver operating characteristic (ROC) analysis was used to determine the diagnostic accuracy of ADR for predicting PE.

Results: Of the 120 patients, 40% had confirmed PE (n = 48) of patients. Median ADR levels were lower in patients with PE than in those without PTE (419, IQR: 270 - 512 vs. 481.6, IQR: 375 - 606, respectively; p = 0.03). This was also true for patients with chronic disease when compared to patients without chronic disease (413, IQR: 264 - 534 vs. 500, IQR: 433 - 685, respectively; p = 0.01). ROC analysis revealed an AUC value of 0.612 (95% CI: 0.510 - 0.714; p = 0.032) for ADR in diagnosing PE.

Conclusions: While ADR alone is insufficient as a primary diagnostic tool for PE, it may serve as a complementary biomarker particularly in D-dimer positive patients with low clinical probability at specific cutoff values. However, prospective studies are warranted to validate this approach.

(Clin. Lab. 2026;72:xx-xx. DOI: 10.7754/Clin.Lab.2025.251024)

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KEYWORDS

pulmonary embolism, adropin, biomarkers, emergency medicine, D-dimer, Wells score, diagnosis

INTRODUCTION

Pulmonary embolism (PE) is a serious clinical condition that requires prompt diagnosis and intervention due to its potentially life-threatening consequences. The clinical signs and symptoms of PE are often non-specific, which makes diagnosis challenging [1]. Traditionally, mortality rates following PE have been reported to range between 18% and 30%; however, recent studies indicate a significant decline, with current mortality estimates falling to approximately 1 - 3% [2]. This dra-

matic reduction in mortality is largely attributed to the widespread adoption of computed tomography pulmonary angiography (CTPA), which has improved early detection and timely management of the disease. This practice results in significant radiation exposure and contributes to increased healthcare costs.

Modeling studies indicate that, under current imaging patterns, CT-associated cancers could contribute up to 5% of new cancer diagnoses annually in the United States [3]. Consequently, there is a growing need for reliable, non-invasive, and radiation-free diagnostic tools that can safely rule out PE. Despite its high negative predictive value (~98%), the low specificity of D-dimer limits its ability to confirm the diagnosis of pulmonary embolism and confines its use to low- and intermediate-risk patients. Because of the test's low positive predictive value, high D-dimer levels are not a reliable indicator for confirming pulmonary embolism. D-dimer levels are frequently elevated in patients with malignancies, in hospitalized individuals, and in those with severe infections, inflammatory disorders, or physiological states such as pregnancy, reflecting increased activation of coagulation and fibrinolysis that is not necessarily indicative of thromboembolic disease. Accordingly, the search for novel biomarkers has become increasingly important to optimize diagnostic algorithms and reduce unnecessary imaging. Among emerging candidates, adropin (ADR) - a peptide hormone involved in energy homeostasis, endothelial integrity, and cardiovascular function - has drawn particular interest. Given its regulatory role in vascular health, ADR has been proposed as a potential biomarker for thromboembolic disorders, including PE [4-6].

Emerging evidence suggests that serum ADR levels are significantly lower in patients with acute PE compared to healthy individuals. At certain threshold values, ADR has demonstrated favorable sensitivity and specificity, indicating its potential as a supportive diagnostic tool in emergency settings. Nevertheless, larger-scale, prospective studies are warranted to validate these preliminary findings and to determine ADR's definitive role in the diagnostic algorithm for PE [7].

D-dimer is a well-established and widely used biomarker in the diagnosis of PE. However, the aim of this study is not to compare a well-known diagnostic marker with a novel one. Instead, we sought to evaluate the diagnostic performance of ADR using CTPA, the accepted gold standard, to definitively assess its accuracy compared to D-dimer. Furthermore, we investigated whether ADR could contribute to the diagnosis of PE in patient groups where D-dimer results are inconclusive or insufficient.

MATERIALS AND METHODS

Study design

This prospective cross-sectional study was performed in the emergency department of a tertiary hospital. The local ethical committee approved the study. Informed consent was obtained from each study patient.

Selection of Participants and Data Collection Process

This study enrolled patients presenting to the emergency department with clinically suspected acute PE – manifested by symptoms such as chest pain, dyspnea, palpitations, hemoptysis, or fever. Initial clinical probability was assessed using the Wells scoring system in accordance with current guidelines from the European Respiratory Society, the American College of Emergency Physicians, the American College of Physicians, and the American Society of Hematology [1,8,9].

Patients with a Wells score of 0 to 6, indicating low- to intermediate pretest probability, underwent D-dimer testing. A negative D-dimer result was used to exclude PE without further imaging. Patients with a positive D-dimer or a Wells score > 6 (high clinical probability) proceeded to CTPA for definitive diagnosis. All patients in whom CTPA confirmed pulmonary embolism were included in the study, regardless of the size or extent of the embolic lesion.

Patients without clinical suspicion of PE, pregnant individuals, those whose primary presentation was more plausibly attributable to an alternative diagnosis (e.g., cardiac tamponade, acute coronary syndrome, aortic dissection, pneumothorax, esophageal rupture, or myalgia), patients with contraindications to CTPA, including contrast allergy or acute renal failure, and hemodynamically unstable patients were excluded from the study.

A total of 120 patients who underwent CTPA based on this diagnostic algorithm were included in the study. Recruitment was terminated upon reaching the predetermined sample size.

Sample collection and measurement of adropin levels

Blood samples were collected in tubes containing heparin by cardiac puncture. Serum samples were removed by centrifugation for 10 minutes at 3,000 rpm. The samples were maintained at -80°C until analysis. Samples were thawed, and Adropin ELISA kit (Sunred Biotechnology Company, Shanghai) was used for the quantitative measurement of adropin in serum samples. Samples and standards were added to appropriate wells, which were precoated with anti-human monoclonal antibody before incubation. Biotin was added to all wells and combined with streptavidin-horseradish peroxidase to form the immune complex; incubation was carried out again, and then cells were washed to remove the uncombined enzyme. Chromogen solutions A and B were added and the color of the liquid changed to the blue. Finally, stop solution was added and color changed to

Table 1. Distributions of study results.

Measure		Median (IQR) or n (Percent) n = 120
Median (IQR) age, years		64.5 (21 - 90)
Female gender		62 (51.7%)
Final Diagnosis		
	PE	47 (39.2%)
	Pneumonia	26 (21.7%)
	Malignancy	4 (3.3%)
	Noncardiac chest pain	22 (18.3%)
	Pulmonary Edema	18 (15%)
	COLD	2 (1.7%)
	PTE+Pneumoni	1 (0.8%)
CTPA		48 (40%)
Wells Score		
	Low risk	65 (54.2%)
	Intermediate risk	50 (41.7%)
	High risk	5 (4.2%)
Mortality	Yes	21 (17.5%)
Chronic Disease		
	DM	8 (6.7%)
	HT	19 (15.8%)
	COLD	5 (4.2%)
	Malignancy	4 (3.3%)
	Stroke	1 (0.08%)
	DM+HT	19 (15.8%)
	HT+COLD	1 (0.8%)
	CAD	6 (5.0%)
	CHF	7 (5.8%)
	CRF	1 (0.8%)
	COLD+CRF+CAD	3 (2.5%)
	No	46 (38.3%)

DM: Diabetes mellitus, HT: Hypertension, COLD: Chronic obstructive lung disease, CAD: Chronic artery disease, CHF: Chronic heart failure, CRF: Chronic renal failure.

Table 2. Relationship between chronic disease and PE.

Variable	PE n (%)	Non-PE n (%)	p-value
Chronic disease			
No	28 (38.9)	18 (37.5)	1.00
Yes	44 (61.1)	30 (62.5)	

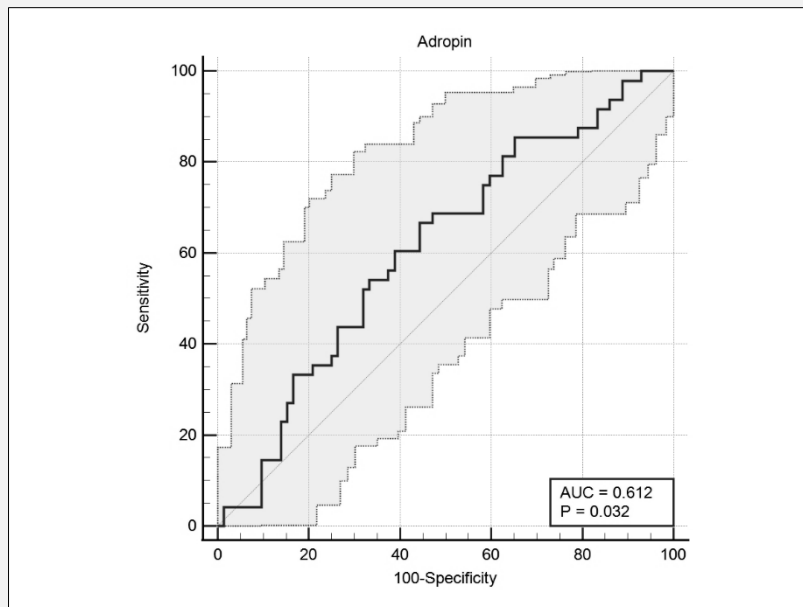
PE: pulmonary embolism.

Table 3. Relationship between PE and serum adropin level.

Variable	Adropin	Difference (95% CI)	p-value
PE			
Yes	419 (270 - 512)	77 (4 - 163)	0.03
No	481.6 (375 - 606)		
Chronic disease			
Yes	413 (264 - 534)	118 (47 - 216)	0.01
No	500 (433 - 685)		

CI: confidence interval, IQR: interquartile range.

All the data presented as median and interquartile range.

**Figure 1. ROC curve analyses of the adropin in predicting in PE patients.**

yellow. Optical density was read on a standard automated plate reader at 450 nm (ThermoScientific Microplate Reader). The detection range of the kit was between 5 and 1,000 pg/mL.

Statistical analysis

Study data were analyzed using MedCalc (Version 23.0.8). Numerical data were expressed as mean $\pm$ standard deviation and median [interquartile range (IQR)], while frequency data were expressed as percentages. For comparisons between two independent groups, Mann-Whitney U test was used for the numeric data

distributed not normally and Fischer's Exact test for categorical data. Normality was assessed using the Kolmogorov-Smirnov test.

The diagnostic validity of adropin in detecting PE was analyzed by using ROC (Receiver Operating Characteristics) analysis as well as using the sensitivity, specificity, positive likelihood ratio and negative likelihood ratio values.

All hypotheses were two-tailed, and a critical alpha value of 0.05 was considered statistically significant.

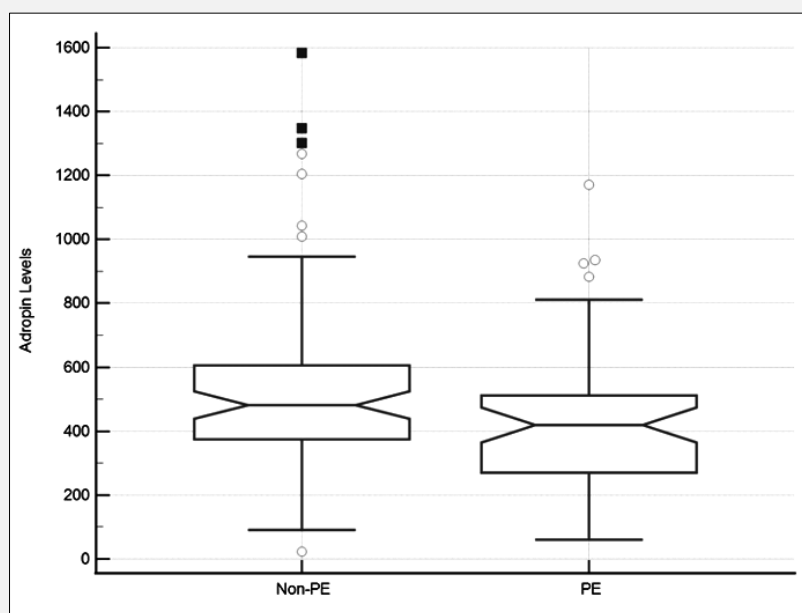


Figure 2. Serum adropin levels in PE and non-PE patients.

RESULTS

A total of 120 patients were included in the study. The median age of the participants was 64.5 years (IQR: 53 - 76 years), and 48.3% (n = 58) were male. According to the Wells scoring system, 54.2% (n = 65) of patients were categorized as low risk (score < 2), 41.7% (n = 50) as moderate risk (score 2 - 6), and 4.2% (n = 5) as high risk (score > 6) (Table 1). Among patients who underwent CTPA with a preliminary diagnosis of PE in the emergency department, 40% (n = 48) were ultimately diagnosed with PE, 21.7% (n = 26) with pneumonia, and 18.3% (n = 22) with atypical chest pain. Mortality was observed in 17.5% (n = 21) of patients during hospitalization.

Of the study patients, 61.7% (n = 74) of patients had chronic comorbidities. Among these patients, PE was detected in 61.1% (n = 44). No statistically significant difference was found in the presence of PE between patients with and without chronic comorbidities following CTPA (n = 44, 61.1% vs. n = 30, 62.5%, respectively; p = 1.000) (Table 2).

Median adropin levels were lower in patients with PE than in those without PE (419, IQR: 270 - 512 vs. 481.6, IQR: 375 - 606, respectively; p = 0.03). This was also true for patients with chronic disease when compared to patients without chronic disease (413, IQR: 264 - 534 vs. 500, IQR: 433 - 685, respectively; p = 0.01) (Table 3).

ROC analysis for the presence of PE in patients who underwent CTPA with suspected PE yielded an ADR cutoff value of 462.59 pg/mL, with an AUC of 0.612 (95% confidence interval [CI]: 0.519 to 0.700, p = 0.032). The sensitivity was 66.67% (95% CI: 51.6 - 79.6), specificity was 55.56% (95% CI: 43.4 - 67.3), positive likelihood ratio of 1.5 (95% CI: 1.08 - 2.08) and negative likelihood ratio of 0.6 (95% CI: 0.38 - 0.94) (Figure 1).

DISCUSSION

In this study, we investigated the diagnostic value of serum adropin (ADR) levels in patients presenting to the emergency department with suspected acute PE. Our findings indicate that ADR levels were significantly lower in patients diagnosed with PE, suggesting that this biomarker, particularly in low- and intermediate-risk clinical settings, may offer additional support in the diagnostic process.

Adropin is a multifunctional peptide hormone involved in energy homeostasis, endothelial regulation, and inflammatory modulation [9]. Emerging evidence supports its involvement in a wide range of pathological conditions, including cardiovascular diseases, metabolic syndrome, and chronic kidney disease [10,12]. In the context of PE, a condition characterized by acute endothelial dysfunction and systemic inflammation, lower

ADR levels may reflect the severity of vascular impairment. The significantly reduced ADR levels observed in our PE-positive cohort ($p = 0.04$) support this hypothesis and are consistent with studies associating low adropin concentrations with impaired endothelial function [12].

Nevertheless, the diagnostic performance of ADR as a standalone tool was limited. The area under the ROC curve (AUC) was 0.612, indicating only modest discriminatory power. At a cutoff value of 462.59 pg/mL, sensitivity and specificity were 66.67% and 55.56%, respectively. These figures suggest that ADR cannot replace established diagnostic tools but may provide complementary value, particularly when interpreted alongside clinical scoring systems.

When integrated with the Wells scoring system, ADR showed improved diagnostic balance. In the low-risk group, ADR demonstrated high specificity (86.96%), indicating its potential to reduce false-positive results in this subgroup. However, the sensitivity remained insufficient (47.37%) to reliably exclude PE. In the intermediate-risk group, sensitivity (76%) and specificity (64%) were more balanced, but not superior to the performance of existing diagnostic tests such as D-dimer.

Another important finding was the significant influence of chronic comorbidities on ADR levels. Patients with chronic conditions had significantly lower ADR values, even among those with confirmed PE ($p = 0.01$). This observation indicates that ADR levels may be affected not only by acute thromboembolic events but also by underlying systemic inflammation or metabolic dysfunction, thus limiting its disease-specific diagnostic value. Previous research has similarly demonstrated that comorbidities such as diabetes, hypertension, and kidney disease can influence ADR expression [10,11]. In this study, while the presence of chronic illness was not associated with a higher incidence of PE, it likely contributed to elevated D-dimer levels due to ongoing fibrinolytic activity. D-dimer is a fibrin degradation product that increases in the presence of active thrombus formation and fibrinolytic activity. In patients with chronic conditions, particularly those involving inflammation or malignancy, D-dimer levels are frequently elevated, which can reduce its specificity for venous thromboembolism diagnosis. For instance, elevated D-dimer may be observed in elderly patients or in the context of malignancy or severe infection, yet this does not necessarily indicate the presence of PE. In this context, high ADR values - although rare - could potentially help identify patients in whom D-dimer positivity is driven by comorbidities rather than acute embolism, thereby supporting more selective imaging decisions. In hemodynamically stable patients with elevated D-dimer levels and underlying chronic conditions, the combined assessment of ADR and D-dimer may potentially enhance the reliability and accuracy of CT-based decision-making for the diagnosis of PE. However, these findings are preliminary, and larger, more comprehensive studies are required to more definitively establish the clinical

utility of this approach. In our analyses, we observed that ADR levels in patients with chronic diseases and a diagnosis of PE were significantly different from those in PE patients without chronic diseases. However, including and comparing individuals with chronic diseases who have not experienced VTE/PE would be necessary to more clearly define the specific effects of ADR. This group was not included in the present study. We have noted this point as an important suggestion for consideration in future studies.

These findings are particularly relevant given the increasing recognition of the risks associated with overuse of imaging in PE diagnosis. CTPA, while the gold standard, exposes patients to radiation and contrast-related risks. Furthermore, recent estimates suggest that up to 5% of annual cancer cases in the United States may be attributable to diagnostic imaging radiation [3]. Thus, identifying additional tools that may safely reduce unnecessary CTPA use is of growing importance.

Our study has several limitations. It was conducted in a single center with a relatively small sample size, limiting the generalizability of the findings. Moreover, it was not possible to fully control for all confounding variables, such as subclinical inflammation, medication use, or unrecognized metabolic disturbances, which may have influenced ADR levels. Further multicenter studies with larger sample sizes and more rigorous control of confounding factors are needed to clarify ADR's role in diagnostic algorithms.

CONCLUSIONS

In conclusion, ADR shows potential as a supplementary biomarker in the diagnostic evaluation of suspected pulmonary thromboembolism, particularly when integrated with clinical scoring systems and D-dimer testing. Its diagnostic performance, however, is currently insufficient for standalone use. The observed influence of comorbidities on ADR levels underscores the need for careful interpretation within a broader clinical context. Further large-scale prospective studies are warranted to determine the utility of ADR in reducing unnecessary imaging and optimizing diagnostic strategies in emergency settings.

Data Availability Statement:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of Generative AI and AI-assisted Technologies in the Writing Process:

The authors declare that no generative AI or AI-assisted technologies were used in the preparation of this manuscript.

Source of Funds:

The authors have no funding to declare.

Declaration of Interest:

The authors declare that there are no known financial or personal relationships that could have appeared to influence the work reported in this paper.

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