

Diagnostic Value of D-dimer in Detecting Pulmonary Embolism in Patients with Acute COPD Exacerbation

Somayeh Sadeghi ¹, Mohammad Emami Ardestani ², Elham Raofi ², Akbar Jalaie Esfandabadi ²

¹ Acquired Immunodeficiency Research Center, Al-Zahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran, ² Department of Internal Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.

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Correspondence to: Jalaie Esfandabadi A

Address: Department of Internal Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.

Email address: tahmasb_jalaie@yahoo.com

Background: Signs and symptoms of chronic obstructive pulmonary disease (COPD) exacerbation may overlap with pulmonary embolism. Patients with acute COPD exacerbations have higher level of D-dimer which may D-dimer lead to false detection of pulmonary thromboembolism (PTE). In this study diagnostic value of D-dimer for diagnosis of pulmonary embolism during acute exacerbation in patients with COPD was investigated.

Materials and Methods: This study was performed on 112 patients with acute COPD exacerbations. In all patients, Wells criteria and D-dimer serum levels were evaluated. Then, all cases were subjected to CT angiography (CTA) and ultrasonography. The diagnostic value of serum D-dimer level and Wells criteria and also their combination for PTE was compared to the gold standard method.

Results: Of 112 patients, 17%, diagnosed with PTE using CTA. The D-dimer cut-off value in COPD patients was higher than 990 µg/L, which was higher than 3 for the Wells score while D-dimer alone showed no good diagnostic value for PTE diagnosis, but Wells score was acceptable (P-value = 0.019). Moreover, the combination of cut-off values, Wells score, and D-dimer level, as a new criterion, with a sensitivity and specificity rate of 47.37% and 88.17% respectively, had an acceptable diagnostic value in PTE diagnosis (AUC=0.678, P value=0.004).

Conclusion: It is suggested that D-dimer concentration alone could not make a good PTE diagnosis, but the simultaneous combination of this test with the Wells criterion can detect the PTE risk with better confidence. To obtain more accurate findings and to get the best criterion, further studies are needed in this field.

Key words: Exacerbation, D-dimer; Pulmonary Embolism; COPD

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a debilitating and progressive lung disease, caused due to abnormal lung inflammatory response to harmful stimuli and is a major global health problem, accounting for more than annual 3 million deaths (1). COPD is the fourth leading cause of death in the world and that is estimated to be known as the third leading cause of death by 2030 (2, 3).

The signs and symptoms of clinical exacerbations of COPD and pulmonary embolism (PE) can be the same; thus, PE diagnosis in patients with acute COPD exacerbation is a clinical challenge (4).

The risk of PE and other cases of venous thromboembolism in COPD patients is twice more than people without COPD (5-7). On the other hand, venous thromboembolism (VTE) (in particular deep vein

thrombosis (DVT) and PE) is an important cause of mortality and morbidity (8). Therefore, clinical suspicion is important in PE diagnosis.

Basic PE diagnosis is done using CT angiography (CTA) and the main technique of DVT diagnosis is Doppler; however, applying both methods in patients with suspected PE is neither possible nor cost-effective, and it was approved only in 25% of suspected pulmonary thromboembolism (PTE) patients who underwent diagnosis surveys (9).

Evidences indicated that using the Wells criterion based on the patients' condition is not an appropriate diagnostic tool for PTE and it is necessary to develop an appropriate criterion or a combination of multi-criteria for the accurate diagnosis of the disease (10, 11).

The current guidelines for the diagnosis of PTE are based on measuring the level of D-dimer combined with clinical suspicion (12). The D-dimer is a simple and noninvasive test that excludes PTE without further imaging procedures (13).

D-dimer is one of the endogen fibrinolytic activity demonstrations (14). It is the specific marker of fibrin production breakdown and endogenous fibrinolytic activity. Its concentration in plasma increases with any chronic inflammatory disease (12). D-dimer is an acute phase reactant that leads to the activation of monocytes and neutrophils, and ultimately leads to increased production of IL-6 and IL-1 (15).

COPD is associated with systemic inflammation which could be presented by an increased level of inflammatory markers, such as C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF- α). It is also characterized by hypercoagulation (16-18).

Pre-inflammatory cytokines, such as interleukin-6 have a key role in the liver production of CRP, fibrinogen, and other inflammatory phase proteins that may play a role in the coagulation cascade activation (19).

Many studies demonstrated that patients with COPD considered as a high-risk group for PTE due to its related

characteristics such as systemic inflammation, polycythemia, and immobility (20, 21).

There are controversies regarding the association of D-dimer with COPD. Some studies did not find a significant difference in D-dimer level of patients with and without COPD (22, 23), while some others have shown that D-dimer level in patients with COPD and also during its acute exacerbation phase was higher than the patients without COPD or healthy subjects (24-27). Therefore, there are still controversies regarding the effectiveness of D-dimer evaluation in PTE diagnosis in patients with acute exacerbation of COPD (23, 28).

With the development of chest computed tomography pulmonary angiography (CTPA), it is now possible to visualize the clot by an imaging technique and confirm the diagnosis of PTE in COPD cases. The limitations of CTPA are adverse reaction to the contrast agents, risk of contrast nephropathy in patients with renal dysfunction, radiation exposure and high cost of the procedure which emphasize the development of new methods with less adverse effects in this field (28, 29).

Therefore, considering the increased risk of PTE in patients with COPD and the high probability of increased level of D-dimer in these patients as well as the adverse effects and high cost of CTA, this study was done to evaluate the diagnostic value of D-dimer in combination with Wells criteria for accurate detection of diagnosis of PTE cases in COPD.

MATERIALS AND METHODS

This cross-sectional study was performed in Al-Zahra hospital in Isfahan, Iran. The study population included all patients with acute COPD exacerbation referring to the emergency room of Al-Zahra hospital with severe illness who needs hospitalization. After receiving the ethics code from the Ethics Committee of Isfahan University of Medical Sciences and written consent from these patients, they were included in the study.

COPD diagnosed based on the GOLD criteria and the findings of previous spirometry at the time of stable

condition. In addition, potential indications for hospitalization assessment included severe symptoms, such as sudden worsening of dyspnea, high respiratory rate, decreased oxygen saturation, confusion, drowsiness, acute respiratory failure, onset of new signs (e.g., cyanosis and peripheral edema), exacerbation not responsive to medical treatments, presence of serious comorbidities (e.g., heart failure, new arrhythmias, etc.), and insufficient home care.

Patients with hematologic disorders, such as hemostatic dysfunction, renal and gastrointestinal diseases, malignancies, collagen vascular disease, autoimmune disease, drug history of anticoagulants or glucocorticoids use, and also patients with a specific cause of acute COPD exacerbation (lobar pneumonia, etc.) were excluded from the study.

In all patients, the D-dimer level was measured by laboratory kits and enzyme-linked fluorescent immunoassay (ELFA) using VIDAS. Also, regardless of the D-dimer level in patients and in the absence of contraindication, CTA was done according to the PTE protocol in the first 48 h by a 64-slice CT scanner (Discovery CT750 HD, GE Healthcare).

Venous Doppler sonography was done on lower extremities to check the existence of DVT by a single radiologist in all patients using Philips Affinity 70G ultrasound system.

Characteristics of all admitted patients including demographic, sign and symptoms based on the Wells criteria scoring were recorded at baseline. Patients with filling defect in the CTA were assigned to the PTE group and those with negative CTA and Doppler sonography findings classified as control group.

Patients with no venous thrombosis evidenced by CTA and the diagnosis of thrombosis using Doppler Vein ultrasound were excluded from the study (Figure 1).

Finally, the collected data were analyzed by the SPSS software (version 24). Characteristics of patients with and without PTE were compared by using Fischer's exact test

and student t-test/or Mann-Whitney U test for categorical and continuous variables, respectively.

To evaluate the diagnostic value of the combination of D-dimer tests and Wells criteria, the Rock analysis was used and its results, including cut-off point, specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV) were reported. In all analyzes, a significance level of less than 0.05 was considered.

RESULTS

A total of 112 patients with acute COPD exacerbation were studied. The mean age of patients was 69.57 ± 6.35 years and 91 patients (81.3%) were males. In general, the mean level of D-dimer was 1697.36 ± 2077.45 $\mu\text{g/L}$. PTE was diagnosed by CTA in 17% of the patients. From COPD patients with PTE, 17 patients (89.5%) were male and 2 patients (10.5%) were female with a mean age of 70.39 ± 9.19 years and from COPD patients without PTE, 74 patients (79.6%) were male and 18 cases (20.4%) were female with the mean age of 69.41 ± 7.64 years ($P\text{-value} > 0.05$). DVT was diagnosed using sonography in 10.5% of patients with PTE ($P\text{-value} = 0.028$) (Table 1). In addition, the score of Wells criteria in COPD patients with PTE was significantly higher than COPD patients without PTE (of 3.66 ± 2.15 vs. 2.38 ± 1.81 ; $P\text{-value} = 0.010$). The mean value of D-dimer in COPD patients with PTE was slightly higher than COPD patients without PTE (1988.61 ± 2501.03 $\mu\text{g/L}$ vs. 1123.15 ± 891.88 $\mu\text{g/L}$; $P\text{-value} = 0.133$) (Table 1).

In general, 36 patients (32.1%) had a Wells score of > 4 , and 76 patients (67.9%) had a Wells score of ≤ 4 .

Level of D-dimer in 27 patients (24.1%) was ≤ 500 and in 85 ones (75.9%) was > 500 .

In COPD patients without PTE, (52) had Wells score of ≤ 4 and D-dimer level of > 500 . None of the COPD patients with PTE had Wells score of ≤ 4 and D-dimer of ≤ 500 .

The appropriate cut-off for D-dimer and the Wells score for diagnosis of PTE in COPD patients were > 990 $\mu\text{g/L}$ and 3, respectively. Sensitivity and specificity of D-dimer at this cut-off and based on area under the curve

(0.603 ± 0.066) were 68.42% and 61.18%, respectively. This criterion was not acceptable for PTE diagnosis in COPD patients (P-value = 0.121). Sensitivity and specificity of the Wells score were 9.12% and 75.27%, respectively, which was statistically at diagnostic power levels (AUC: 0.684, P-value = 0.019).

From patients with PTE diagnosis, 13 cases had the Wells scores higher than 3 and in 13 cases level of D-dimer

was higher than 990 µg/L. Nine patients with PTE had both Wells scores > 3 and D-dimer level of >990 µg/L. The sensitivity and specificity of these two criteria simultaneously were 47.37% and 88.17%, respectively. Combination of the two mentioned cut-offs was statistically acceptable for diagnosis of PTE in COPD patients (AUC = 0.678, P-value = 0.004) (Table 3 and 4 and Figure 2).

Table 1. Baseline and spirometric characteristics and Wells score and D-dimer levels of COPD patients with and without PE

Characteristics		COPD with PTE(n=19)	COPD without PTE(n=93)	P value
Sex	Male	17(89.5%)	74(79.6%)	0.519†
	Female	2(10.5%)	19(20.4%)	
Age; year		70.39±9.19	69.41±7.64	0.623††
Doppler ultrasound (+)		2(10.5%)	0(0%)	0.028†
Never smokers		8(42.1%)	26(28%)	0.275†
Chest Pain		7(36.8%)	24(25.8%)	0.400†
PAP; mmHg		42.64±17.05	44.29±17.12	0.745††
HR; bpm		94.63±18.59	89.58±17.58	0.261††
RR; bpm		20.58±4.363	22.41±6.170	0.222††
SPO₂; %		83.68±6.89	81.11±13.49	0.420††
Hemoptysis		2(10.5%)	14(15.1%)	0.607†
Malignancy w/ treatment within 6 months or palliative		0(0.0%)	0(0%)	-
Previous, objectively diagnosed PE or DVT		6(31.6%)	9(9.7%)	0.020†
Hospitalization 3 months ago		10(52.6%)	36(39.1%)	0.313†
Tachycardia*		7(36.8%)	25(26.9%)	0.410†
Clinical signs and symptoms of DVT**		11(57.9%)	34(36.6%)	0.122†
Wells score		3.66±2.15	2.38±1.81	0.010†††
D-dimer; µg/L		1988.61±2501.03	1123.15±891.88	0.133†††

COPD: Chronic Obstructive Pulmonary Disease, PTE: pulmonary thromboembolism, SPO₂: Saturation of Peripheral Oxygen, RR: Respiratory rate, HR: Heart rate, PAP: Pulmonary Artery Pressure

Data shown mean ± SD or n(%)

*: Heart rate > 100 bpm

** : There is a difference in the size of two feet based on ultrasound

†: Significant level of Fisher exact test

††: Significant level of independent t-test

†††: Significance level of the Mann-Whitney test

Table 2. Distribution of wells score and D-dimer level in patients with and without PTE

		No PTE		PTE	
		D-dimer ≤500	D-dimer >500	D-dimer ≤500	D-dimer >500
Wells score	≤4	18	52	0	6
	>4	7	16	2	11
Total		25	68	2	17

Table 3. Diagnostics performance of D-dimer and wells score

Value	Wells score	D-dimer	Wells score and D-dimer
Cut-off point	>3	>990 µg/l	>3 and >990 µg/l
Area Under the ROC Curve	0.684	0.603	0.678
Standard Error	0.079	0.066	0.062
Sensitivity	69.12%	68.42%	47.37%
Specificity	75.27%	61.18%	88.17%
Positive Predictive value	36.1%	28.3%	45.0%
Negative Predictive value	92.1%	89.7%	89.1%
P value	0.019	0.121	0.004

Table 4. Wells score and D-dimer in patients with (PTE) and without (Non PTE) pulmonary thromboembolism

Patients	Wells score; Point		D-dimer; µg/L		D-dimer (>990 µg/l)	
	WS≤3 (n=76)	WS>3 (n=36)	DD≤990 (n=58)	DD>990 (n=54)	WS≤3 (n=34)	WS>3 (n=20)
PTE	6	13	6	13	4	9
Non-PTE	70	23	52	41	30	11
P value	<0.001		0.053		0.009	

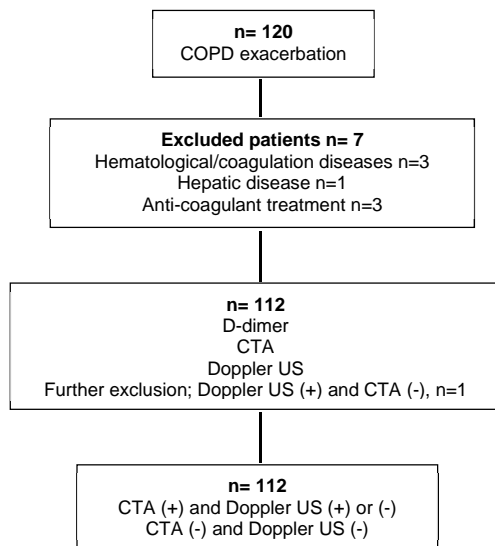


Figure 1. The design of the study

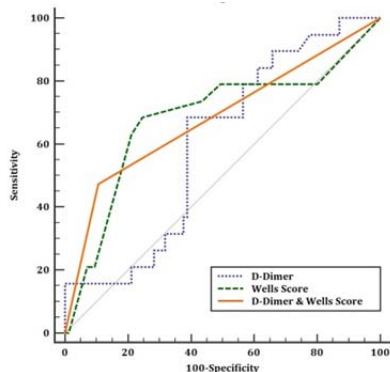


Figure 2. Receiver Operating Characteristics (ROC) curve for wells score, D-dimer and both of them.

DISCUSSION

Given that the exacerbated COPD clinical signs and PTE overlap with each other, it is essential to use non-aggressive techniques or methods with minimum aggression for PTE diagnosis in this group of patients (22). According to some studies, COPD may increase biologically thrombotic activities (3, 5, 6) and PTE is considered as one of the differential diagnosis of an acute exacerbation of COPD (5). It is well established that COPD is considered a risk factor for PTE due to disease immobility, polycythemia, and systemic inflammation (20). Systemic inflammation related to COPD (especially acute inflammatory response caused by COPD exacerbation) is the result of endothelial and coagulation systems activation and prothrombotic conditions that make changes in hemostatic pathway (30). In this study, 81.3% of the patients with COPD were male, with a mean age of ≥ 60 years. Level of D-dimer in most of the patients were higher than 1500 µg/l. PTE was diagnosed in 17% of the patients.

Though COPD patients with PTE were older than those without PTE but the difference was not significant statistically.

Many studies have reported that the occurrence rate of PTE in patients with acute COPD exacerbation has increased (3, 6). Gunen et al. have suggested that all hospitalized patients with acute COPD exacerbation

should be examined for the presence of VTE (6). They stated that the prevalence of VTE was three times higher in patients with an exacerbation of unknown origin than in patients with the known origin (6).

The results of the Wells criteria and D-dimer test in PTE identification of our patients indicated that the Wells criteria with a cut-off of higher than 3 with a sensitivity and specificity of 69.12% and 75.27%, respectively, had a significant effect on PTE diagnosis. Although the mean level of D-dimer in COPD patients with PTE was higher than in COPD patients without PTE, but the difference was not significant. The diagnostic value of D-dimer level had the best value in a cut-off point of higher than 990 µg/l for PTE diagnosis with a sensitivity of 68.42% and a specificity of 61.18%, but it was not considered statistically significant. It is suggested that in COPD patients, the low Wells score warns the risk of PTE, and in the case of using the D-dimer test, the use of cut-off point in this criterion cannot be trusted in the diagnosis of PTE.

Our findings were in line with the study of Hartmann et al. They showed that the D-dimer in COPD patients with and without PTE had the same precision (22). On the other hand, some other studies also reported a higher-than-normal level of D-dimer in COPD patients (even without PE), but in this study, the level of this test was normal (28, 31). Another study showed that D-dimer levels and the Wells criteria can be used to determine whether these patients should be assessed for a thromboembolic event (6).

Therefore, using the D-dimer test in patients with and without COPD is different. It seems that the presence of COPD affects the likelihood of obtaining reliable test results. Therefore, some cut-off points must be estimated in order to reduce the rate of CTE in this group of patients to decrease COPD related cost.

Akpınar et al. reported that the concentration of D-dimer in COPD patients with acute exacerbations may be higher than normal. They reported a 70% sensitivity and 71% specificity for a D-dimer cut-off level of 0.95 pg/ml (28). In other studies, they reported a sensitivity and

specificity of 70% and 71% for a D-dimer cut-off level of 0.95 pg/ml and sensitivity and specificity of 90.9% and 77.8% for a D-dimer cut-off level of 2348 µg/ml for diagnosis of PTE in patients with acute COPD (29).

Raviv et al. reported 94.4% sensitivity rate for the D-dimer cut-off level of 900 ng/ml (32). According to their findings, the obtained sensitivity in younger patients (under 40 years) was even higher (100%). In general, they showed that shifting up the D-dimer level in screening for PTE seems an important option, but for tailoring the cut-off value with patients' individual characteristics, such as age, more studies are required (32). Some previous studies have also confirmed higher levels of D-dimer in older COPD patients (33). In the present study, the mean age of patients with COPD in the two groups with and without PTE had no significant difference; therefore, age did not have a confounding effect on the outcomes.

Considering the results of previous studies as well as current study it is suggested that there are controversies regarding the best cut-off point of D-dimer for diagnosis of PTE in this group of patients. It seems that COPD could impair the accurate measurement of D-dimer. So, considering the controversies it is recommended to plan more studies in this field. Moreover, it seems that combination of different criteria and simultaneous use of the D-dimer test with other diagnostic methods may improve the proper diagnosis of PTE.

In this study we used combination of these two criteria with the obtained cut-off to increase the diagnostic accuracy of PTE in COPD patients. We indicated that by combination of the following criteria; D-dimer level >990 µg/l and Wells score >3, we had a specificity and sensitivity rate of 88.17% and 47.37%, respectively, which could be considered as a reliable diagnostic criteria for PTE.

Our findings regarding the simultaneous use of diagnostic criteria for PTE were similar to some previous studies. AbdelHalim and AboElNaga reported that the combination of a low D-dimer level and a low clinical

probability decline the diagnosis of PTE in patients with COPD exacerbation (29). Szturmowicz et al. concluded that a combination of the low/medium Wells' scores and negative D-dimer result (less than 500 ng/ml), could effectively decline the possibility of PTE in patients with acute or exacerbated pulmonary disease (34). Sohne and colleagues showed that the low clinical probability combined with a normal level of D-dimer offered similar safety for exclusion of PTE in COPD patients (35).

The results of another study also indicated that the concurrence of the D-dimer test results of 0.5 mg/l and the Wells score of 4 had diagnostic value for PTE. In addition, they showed that the D-dimer test alone had a higher negative predictive value than the Wells criteria, and the combination of these two tests improved the diagnostic algorithm (36).

It seems that the combination of different criteria and tests provides a more accurate diagnostic protocol for PTE in this group of patients. Although the combination of Wells criteria and D-dimer level was able to diagnose PTE precisely, due to the small samples of COPD patients with PTE, the results cannot be generalized and further studies in this field are required. It is suggested to conduct future studies on the combination of these two criteria in order to develop more accurate diagnostic method.

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