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D-Dimer Specificity for the Diagnosis of Acute Symptomatic Pulmonary Embolism

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Abstract

Introduction: D-dimer is present in elevated levels with different diseases. In this study we aimed to determine if a high D-dimer cut-off value might increase its specificity for the diagnosis of venous thromboembolism.

Materials and methods: Retrospective analysis was carried out on 136 patients with a D-dimer value ≥ 8000 ng/ml.

Results: 53 were diagnosed of VTE by objective methods (40%), and 65 were excluded from VTE diagnosis (49%). The final diagnoses for the patients excluded from VTE were: infections (n=23), cardiovascular diseases (n=14), fractures/traumas (n=12), disseminated malignancy (n=5), brain disease (n=5), and others (n=6). 30 patients died whilst hospitalized (23%). There were 6 deaths among the patients diagnosed with VTE (11%) and 20 among the patients excluded from VTE (31%) (p<0.01).

Conclusions: A D-dimer threshold >8000 ng/mL is not specific to diagnose VTE. Patients with a D-dimer value >8000 ng/mL have a significantly worse prognosis when VTE is excluded by objective methods.

Keywords: D-dimer; Diagnosis; Pulmonary embolism

Introduction

D-dimer is a small protein that appears in the blood as a product of fibrin clot lysis due to the action of plasmin, which begins at the same time the clot begins to form. The fibrin degrades into several protein fragments (fibrin monomers, fibrin dimers), of which D and E are the most well-known. The D fragment (or D-dimer) can be measured in the blood simply and non-invasively. The protein is initially detectable in the plasma 1 hour after the formation of the fibrin clot, remaining detectable for up to 7 days, after which the level starts to subside.

The measurement of the levels of fibrin degradation products in the plasma began to be used in clinical practice to support the diagnosis of disseminated intravascular coagulation [1,2]. The quantification of D-dimer now forms part of diagnostic algorithms for deep vein thrombosis (DVT) and pulmonary embolism (PE) [3]. A low level of high sensitivity D-dimer combined with a low or intermediate clinical probability is useful for excluding PE in symptomatic outpatients, due to its high negative predictive value. On the other hand, high D-dimer levels are associated with a higher probability of relapses of venous thromboembolism and a higher risk of mortality in the short term for PE patients [4-6]. In addition, the detection of lower D-dimer levels supports the possibility of suspending anticoagulant treatment in patients that have suffered a thromboembolic event, with continued high values suggesting the need to maintain the anticoagulant treatment indefinitely [7].

Also, with venous thromboembolism (VTE), the concentration of D-dimer can rise with different pro-thrombotic disorders [8-10], such recent major surgery [11], traumatism [12], pregnancy [13], cancer [14], sepsis [15,16], esophageal variceal bleeding [17], and acute arterial thrombosis [18]. D-dimer is, therefore, a sensitive marker, but not very specific for VTE, which means it is not useful to confirm the diagnosis. In addition, D-dimer concentration increases both with age [19,20] and when patients are hospitalized [21], meaning its determination has limited usefulness in those cases.

Extremely high concentrations of D-dimer can occasionally be detected during every day clinical practice. Given what has already been stated, it is doubtful whether this finding could be related to an increase in specificity when it comes to VTE diagnosis. The study objectives were: A) to analyze the specificity of a D-dimer >8000 ng/mL threshold; and B) to compare mortality rates of patients in function of the etiology causing the elevation.

Materials and Methods

Patients

This was descriptive observational study, which included patients with D-dimer levels equal or higher than 8000 ng/mL, between January 2009 and April 2011. This cut-off was the lower limit of the fourth quartile as calculated in our registry of consecutive patients with acute PE [22]. D-dimer concentration was measured using the VIDAS® D-Dimer technique (bioMérieux, Lyon, France).

Diagnostics

Two researchers (AP and VG) had access to the patients' clinical histories and agreed the final diagnosis of the event that led to a request for the D-dimer evaluation. The clinical probability of PE was calculated retrospectively for all patients using the Wells scale for dichotomous variables [23]. Objective tests were undertaken to exclude or confirm the presence of PE (Pulmonary ventilation/perfusion scan [VQ] or CT pulmonary angiogram [angio-TC]), or DVT (Doppler ultrasound of the lower extremities) as the causes of the elevation of D-dimer in patients with associated symptoms (dyspnea, chest pain and/or syncope for PE; unilateral edema and/or extremity pain for DVT). A PE diagnosis was accepted when the patient received a high probability for this diagnosis with a pulmonary ventilation/perfusion scan, or had a positive pulmonary angiogram. A positive Doppler ultrasound of the lower extremities was required to diagnose DVT. The consensus of the Prospective Investigation of Pulmonary Embolism Diagnosis [24] was followed to diagnose both diseases. Based on these tests, the patients were classified into three groups: A) Group 1, which included patients that had objective imaging tests that confirmed VTE; B) Group 2, which included patients that had objective tests that excluded the presence of VTE; and C) Group 3, which included patients that had not undergone objective tests to confirm or exclude the presence of VTE.

Evaluation parameter

Mortality by all causes was taken as the primary event during hospitalization.

Statistical analysis

The SPSS statistical package, version 18.0, was used for the statistical analysis. The level of adjustment of the sample to the normal distribution was checked using the Kolmogorov-Smirnov test. The quantitative data was expressed as the mean and standard deviation, or as the median and interquartile range, depending on whether or not the distribution adjusted to the norm. For the comparative analysis, the Mann-Whitney test was used on the quantitative variables, and the chi-squared test was used for comparing percentages. The Kappa range was used to measure the inter-observer agreement for the final diagnosis. A p=0.05 value was considered the significance threshold.

Ethical standards

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study.

Results

Patients

132 patients with a D-dimer value >8000 ng/mL were included, who were identified during the study period. The mean (standard deviation) age was 72 years old (20). The gender distribution was 56 men (42%) and 76 women (58%). Sixteen patients had a history of VTE (12%), 31 (23%) had an active malignancy when included in the study, 9 (6.8%) had a history of chronic obstructive pulmonary disease (COPD), and 7 (5.3%) had a history of congestive cardiac failure (Table 1).

	All patients	Probable PE	Improbable PE	P
	N=132	N=82	N=50	
Clinical characteristics, n (%)				
Age, years, median (25-75 percentiles)	(-)	(-)	(-)	0
Age >65 years old	98 (74%)	61 (74%)	37 (74%)	1
Gender male	56 (42%)	29 (35%)	27 (54%)	0.05
Risk factors for VTE, n (%)				
Prior VTE events	16 (12%)	14 (17%)	2 (4.0%)	0.03
Cancer	31 (23%)	12 (15%)	19 (38%)	< 0.01
Comorbidity, n (%)				
COPD	9 (6.8%)	3 (3.6%)	6 (12%)	0.08
CCF	7 (5.3%)	3 (3.6%)	4 (8.0%)	0.42
Symptoms, n (%)				
PE symptoms	77 (58%)	54 (66%)	23 (46%)	0.03
DVT symptoms	28 (21%)	22 (27%)	6 (12%)	< 0.001
Tests undertaken, n (%)				
Thoracic angio-TC	71 (54%)	50 (61%)	21 (42%)	0.05
V/Q scan	15 (11%)	10 (12%)	5 (10%)	0.78
Lower extremity ultrasound	55 (42%)	39 (48%)	16 (32%)	0.1
VTE diagnosis, n (%)				
PE diagnosis	33 (25%)	23 (28%)	10 (22%)	0.3
DVT diagnosis	20 (15%)	15 (18%)	5 (10%)	0.22

Table 1: Characteristics of the patients in the set [Abbreviations: PE: Pulmonary Embolism; VTE: Venous Thromboembolism; COPD: Chronic Obstructive Pulmonary Disease; CCF: Congestive Cardiac Failure; DVT: Deep Vein Thrombosis; CT: Computer Tomography; VQ: Ventilation Perfusion.

Diagnostics

Seventy seven patients (58%) presented PE symptoms, 28 (21%) presented DVT symptoms, and 6 patients (4.5%) presented both PE and DVT symptoms. According to the Wells scale for dichotomous variables, PE was considered probable in 82 patients (82/132, 62%). A pulmonary angio-TC was undertaken on 71 patients from the set, a VQ scan on 15 patients, and a Doppler ultrasound on the lower extremities on 55 patients. 9 patients had both a pulmonary angio-TC

and a VQ scan, and 14 patients had both a pulmonary angio-TC and a Doppler ultrasound on the lower extremities. A history of VTE was significantly more common in patients in which PE was clinically probable, whereas a history of cancer was more common for patients in which PE was clinically improbable. Patients with probable PE presented symptoms suggestive of PE and DVT more often than patients with improbable PE (Table 1).

There was a 40% prevalence of VTE (53 out of 132 patients). The median (25^{th}-75^{th} percentiles) in this group of patients was 8985 ng/mL (8672-10000). Thirty three patients (25%; CI 95%, 18-32%) were diagnosed with PE through objective methods. 15 of those presented concomitant DVT. 20 patients (15.1%; CI 95%, 9.0-21.3%) were diagnosed with isolated DVT (without PE). The clinical suspicion of VTE had a significant influence on the prevalence of the disease (odds ratio [OR] 3.0; CI 95%, 1.4-6.6; P<0.01). The diagnosis of VTE in 66 patients was objectively excluded (49%; CI 95%, 41-57%). The median (25^{th}-75^{th} percentiles) in this group of patients was 9796.5 (8552.5-10000). The final diagnoses for the patients excluded from VTE were: infections (n=23), cardiovascular diseases (n=14), fractures/traumas (n=12), disseminated malignancy (n=5), brain disease (n=5), and others (n=6). Of those 6 patients, 2 underwent a prostatectomy for a prostatic adenoma, 1 patient started to experience chest pain during a hemodialysis session and died before receiving an etiological diagnosis, 1 presented lumbar radiculopathy, there was 1 with pneumothorax, and 1 patient was diagnosed with an overdose of acenocumarol (Table 2). Diagnostics tests were not undertaken for VTE on 14 cases (10.6%; CI 95%, 5.3-15.9%). Cardiovascular disease was the most common diagnosis in patients with clinically probable PE, whilst a cancer diagnosis was most common in patients with clinically improbable PE (Table 2). The inter-observer agreement for the final diagnosis was 0.87.

Disease, n (%)	All patients N=132	Probable PE N=82	Improbable PE N=50	P
VTE	53 (40%)	38 (46%)	15 (30%)	0.07
Infections	23 (17%)	14 (17%)	9 (18%)	1
Cardiovascular disease	14 (11%)	13 (16%)	1 (2.0%)	0.02
Fractures/traumatism	12 (12%)	8 (9.7%)	4 (8.0%)	1
Cancer	5 (3.8%)	1 (1.2%)	4 (8.0%)	0.07
Brain disease	5 (3.8%)	2 (2.4%)	3 (6.0%)	0.37
Others	6 (4.5%)	3 (3.6%)	3 (6.0%)	0.67
No diagnosis	14 (11%)	8 (9.7%)	6 (12%)	0.77

Table 2: Final diagnoses in the studied set, Abbreviations: PE: Pulmonary Embolism; VTE: Venous Thromboembolism.

Mortality

30 of 132 patients included in the study died whilst hospitalized (23%; CI 95%, 16-30%). There were 6 deaths among the 53 patients diagnosed with VTE (11.3%; CI 95%, 2.8-19.8%), 20 deaths among the 65 patients excluded from VTE (31%; CI 95%, 20-42%) (p<0.01), and 4 deaths from 14 cases that didn't have diagnostic tests for VTE (28.5%; CI 95%, 20-36%) (Table 3).

Cause of death, n (%)	Group 1 N=53	Group 2 N=65	Group 3 N=14
VTE	4 (0.07)	-	-
Infections	-	9 (0.13)	-
Cardiovascular disease	1 (0.01)	5 (0.07	1 (0.07)
Cancer	-	3 (0.04)	3 (0.21)
Brain disease	-	1 (0.01)	-
Unknown	1 (0.01)	2 (0.03)	-

Table 3: Cause of death of patients in the study, Abbreviations: VTE: Venous Thromboembolism; Group 1: Objectively confirmed VTE; Group 2: Objectively excluded VTE; Group 3: No evidence to confirm or exclude VTE.

PE was the cause of death of four of the 6 patients (67%) in the group with confirmed VTE. The death of three of the 4 (75%) patients in the group that didn't undergo tests to confirm or exclude the presence of VTE was caused by a malignancy.

Discussion

The aim of this observational study was to evaluate whether very high D-dimer values are specific to VTE. Our results indicate that a D-dimer threshold >8000 ng/mL is not specific for the diagnosis of VTE. Statistically speaking, combining the D-dimer result with the clinical probability results in a significant increase for specificity but only a moderate increase in clinical terms. In this way, although the combination of clinical probability and a high D-dimer increases specificity, the proportion of patients who meet these criteria was very low in clinical practice. Hospitalized patients with an elevated D-dimer value presented a significantly worse prognosis when VTE is excluded by objective methods.

Some researchers have evaluated the positive predictive value for VTE of elevated levels of D-dimer and have found that VTE probability increases [25]. This study, in agreement with other recently

published works [26], confirms that D-dimer has a low specificity for the diagnosis of VTE, independently of the levels in the plasma. Despite all the individuals in our study having a D-dimer concentration of >8000 ng/ml, VTE was only diagnosed in 40% of the cases, a similar percentage to the work carried out by Ho and collaborators (43%). In their set, over half of the patients presented non-VTE diagnoses, such as massive hemorrhaging in the digestive system or other locations, cardiac arrest, sepsis with disseminated intravascular coagulation, HELLP syndrome (postnatal hemolysis with elevated liver enzyme levels, thrombocytopenia, pulmonary edema, and acute kidney failure), or polytrauma. In our set, the increase in D-dimer values was linked to many causes, some of which include infection, cardiovascular disease, fractures and malignancies. Since all these patients had a clinical suspicion of pulmonary embolism (PE) and D-dimer was positive, guidelines strongly recommend performing a Multidetector Computed Tomographic Pulmonary Angiography (MDCTPA) [27]. Studies and metaanalyses have demonstrated the high sensitivity and specificity of MDCTPA for the diagnosis of PE. Once the diagnosis of PE has been excluded (because of a negative MDCTPA), differentiation between infection, cardiovascular disease or cancer should be performed on a clinical basis.

In our study, the presence of clinically probable VTE increased the specificity of the elevated levels of D-dimer to approximately 50%. The American College of Chest Physicians (ACCP) recommends initiating anticoagulant treatment in patients with a high clinical suspicion of PE, whilst objective tests are being carried out (level of evidence 2C) [28]. This is recommendation is particularly valid when the diagnostic tests are not available 24 hours a day, every day of the year. However, one of the most important findings of our study is that the mortality of patients with elevated levels of D-dimer and objectively excluded VTE was significantly higher than in patients with VTE confirmed through objective methods. However, it is important to note that this study is not powered to address mortality, and the rigorous analysis strategy is not enough to address that. In any case, if these data are confirmed, the clinical consequences could be very significant. Our results underline the importance of objectively confirming or excluding VTE as early as possible, with a view to initiating a specific treatment. However, without robust evidence, we would like to emphasize that the efficacy and certainty of this method of diagnostic and therapeutic management should be evaluated prospectively.

There are limitations to our study. Firstly, it is a retrospective study. Nevertheless, the use of mortality from all causes as the primary event and the elevated inter-observer agreements in the etiological diagnosis of patients reduces the bias associated with the study design. Secondly, we chose the D-dimer threshold arbitrarily. Although a higher threshold could increase the specificity of the determination, its clinical usefulness (the proportion of patients with an elevated D-dimer value) would have decreased considerably.

In summary, it was found that a D-dimer threshold >8,000 ng/ml/mL is not specific for the diagnosis of VTE. Patients with a D-dimer value higher than this threshold have a significantly worse prognosis than when VTE is excluded by objective methods.

Conflict of Interest

The authors report no conflicts of interest.

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