Diagnosis of venous thrombosis and the post-thrombotic syndrome

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CHAPTER 5

High D-dimer levels increase the likelihood of pulmonary embolism

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Objective to determine the utility of high quantitative D-dimer levels in the diagnosis of pulmonary embolism.

Methods D-dimer testing was performed in consecutive patients with suspected pulmonary embolism. We included patients with suspected pulmonary embolism with a high-risk for venous thrombo-embolism, i.e., hospitalized patients, patients older than 80 years, with malignancy or previous surgery. Presence of pulmonary embolism was based on a diagnostic management strategy using a clinical decision rule (CDR), D-dimer testing and computed tomography.

Results a total of 1515 patients were included with an overall pulmonary embolism prevalence of 21%. The pulmonary embolism prevalence was strongly associated with the height of the D-dimer level, and increased fourfold with D-dimer levels greater than 4000 ng mL^{-1} compared to levels between 500 and 1000 ng mL^{-1}. Patients with D-dimer levels higher than 2000 ng mL^{-1} and an unlikely CDR had a pulmonary embolism prevalence of 36%. This prevalence is comparable to the pulmonary embolism likely CDR group. When D-dimer levels were above 4000 ng mL^{-1}, the observed pulmonary embolism prevalence was very high, independent of CDR score.

Conclusions strongly elevated D-dimer levels substantially increase the likelihood of pulmonary embolism. Whether this should translate into more intensive diagnostic and therapeutic measures in patients with high D-dimer levels irrespective of CDR remains to be studied.

Introduction

D-dimer measurement is widely used in the diagnostic work-up of patients with suspected venous thromboembolism (VTE) [1]. D-dimers are formed by the degradation of cross-linked fibrin [2] and are the best currently available laboratory marker of coagulation activation [3]. Several large management studies have used an algorithm combining normal D-dimer tests with low clinical probability to rule out pulmonary embolism [4-7]. Using well-evaluated quantitative D-dimer tests, levels below 500 ng mL^{-1} are regarded as a sensitive cut-off level in excluding VTE [8]. The sensitivity ranges from 91 to 97% in various studies and the specificity varies between 40 and 70% [9]. It is possible to increase the specificity of D-dimer tests by increasing D-dimer cut-off levels. Specificity of D-dimer levels exceeding 4000 ng mL^{-1} (Asserachrom Ddi ELISA) was 93% in a study evaluating outpatients with suspected pulmonary embolism [10]. Another study showed a seven-fold increased risk of pulmonary embolism when D-dimer levels exceed 2000 ng mL^{-1} (STA-Liatest D-Di®; Diagnostica Stago, Asnieres, France) compared with D-dimer levels between 500 and 1000 ng mL^{-1} [11]. However, it should be noted that these two studies were restricted to populations with a lowrisk for VTE. It has been suggested that in patients with high risk for VTE, i.e., hospitalized patients, patients older than 80 years and patients with malignancy or previous surgery the use of D-dimer is inefficient because of a high rate of false-positive tests, leading to pulmonary embolism exclusion in less than 5% of patients [12,13]. Combining a quantitative high D-dimer level with a high clinical probability score can improve the positive predictive value of pulmonary embolism and it has been suggested that the combination of these tests might be sufficient for establishing the diagnosis of VTE [14,15]. In the present study our aim was to assess the clinical consequences of high quantitative D-dimer levels combined with clinical probability score in the management strategy in patients with suspected pulmonary embolism.

Patients and Methods

This study was part of a large management study in 12 teaching hospitals in the Netherlands, evaluating a diagnostic algorithm consisting of a clinical decision rule (CDR), D-dimer assay and spiral computed tomography [7]. Patients were included between November 2002 and September 2004. The Institutional Review Boards of all participating hospitals approved the study protocol, and written or oral informed consent was obtained from all participants.

Patients

Consecutive patients with clinically suspected pulmonary embolism and quantitative D-dimer results from five teaching hospitals were included in this analysis. Baseline demographic clinical characteristics were fully comparable to the original management study. Exclusion criteria were: treatment with therapeutic doses of unfractionated or low-molecular weight heparin for more than 24 h, life expectancy <3 months, pregnancy, geographical inaccessibility precluding follow-up, age younger than 18 years, allergy to intravenous contrast agents, renal insufficiency (creatinine clearance <30 ml min^{-1}), logistic reasons or hemodynamic instability.

Diagnostic Algorithm

Patients with clinically suspected pulmonary embolism were evaluated by an attending doctor using a validated CDR [4]. Pulmonary embolism was considered unlikely if the CDR score was $\leq$ 4 points, and considered likely if the CDR score > 4 points. In the five teaching hospitals included in this analysis, D-dimer tests were performed in all patients irrespective of the CDR score. The D-dimer results were only communicated to the attending doctor in case of a CDR indicating pulmonary embolism unlikely. Three hospitals used the Vidas D-dimer assay (Biomerieux, Marcy L'Etoile, France) and two used the Tinaquant assay (Roche Diagnostica, Mannheim, Germany). A D-dimer concentration of 500 Fibrinogen Equivalent Units ng mL^{-1} or less was defined as normal. In patients with an unlikely CDR and a normal D-dimer concentration, the diagnosis of pulmonary embolism was considered excluded and anticoagulation treatment was withheld. All other patients underwent spiral computed tomography. All patients were followed up for a period of 3 months.

Outcome

The primary outcome of the study was the incidence of symptomatic VTE events during 3 months of follow-up, defined as fatal pulmonary embolism, nonfatal pulmonary embolism, or deep vein thrombosis (DVT). An independent adjudication committee, whose members were unaware of the results of the diagnostic algorithm, evaluated all suspected VTE and deaths. A diagnosis of pulmonary embolism or DVT was based on a priori defined and generally accepted criteria [16]. Deaths were classified as caused by pulmonary embolism in case of confirmation by autopsy, in case of an objective test positive for pulmonary embolism prior to death, or if pulmonary embolism could not be confidently excluded as the cause of death.

Follow-up consisted of a scheduled outpatient visit or telephone interview at 3 months. In addition, patients were instructed to contact the study centre or their general practitioner immediately in the case of complaints suggestive of DVT or pulmonary embolism. On each visit, information was obtained on complaints suggestive of VTE and use of anticoagulants. In case of clinically suspected DVT or pulmonary embolism, appropriate objective tests (compression ultrasound for suspected DVT, ventilation-perfusion scintigraphy or computed tomography for suspected pulmonary embolism) were required to confirm or refute the diagnosis. In case of death, information was obtained from the general practitioner, from the hospital records or from autopsy.

Statistical Analysis

D-dimer increments of 500-4000 ng mL^{-1} and unlikely or likely CDR score were used as the varying units of analysis. Sensitivities reflect the proportion of patients with disease who had a positive D-dimer, while specificities reflect the proportion of patients without disease who had a negative D-dimer result, depending on the cut-off level. The reference test for calculation of the test characteristics sensitivity and specificity was the diagnosis of pulmonary embolism at baseline by spiral computed tomography or the occurrence of an objectively diagnosed venous thrombo-embolic event during the 3 months of follow-up.

Results

Of 1704 eligible patients, 90 were excluded because of predefined exclusion criteria or declined informed consent. Data regarding D-dimer results were missing in 99 patients, resulting in a total of 1515 patients (94%) available for analysis. The mean age was 54 years, 16% of patients had a malignancy, 6% underwent surgery in the previous three weeks and 76% were outpatients (Table 1). The overall prevalence of pulmonary embolism was 21% (324 of 1515 patients).

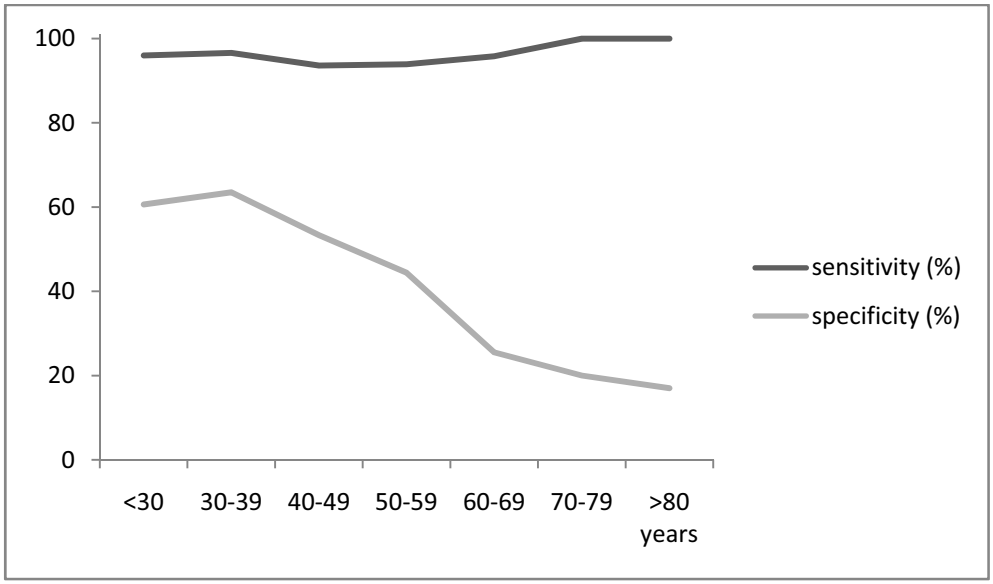
Table 1. Baseline demographic and clinical characteristics of the study population (*n* = 1515)

Characteristic	Value
Age, mean (SD), years	54 (19)
Female	824 (54.4)
Previous venous thromboembolism	209 (13.8)
Malignancy	239 (15.8)
Recent surgery	95 (6.3)
Outpatients	1158 (76.4)
Pulmonary embolism prevalence	324 (21.4)

Data are presented as *n* (%).

In 314 of 324 patients with pulmonary embolism the D-dimer concentration was above the cut-off value (500 ng mL^{-1}), resulting in a sensitivity of the D-dimer test of 96.9% (95% CI: 94.3-98.4). This sensitivity was not influenced by age and varied from 93.6% to 100% (Figure 1).

Figure 1. Performance of D-dimer in the diagnosis of pulmonary embolism according to age



In 519 of the 1191 patients without pulmonary embolism plasma levels were normal (<500 ng mL^{-1}) resulting in a specificity of the D-dimer test of 43.6% (95% CI: 40.8-46.4).

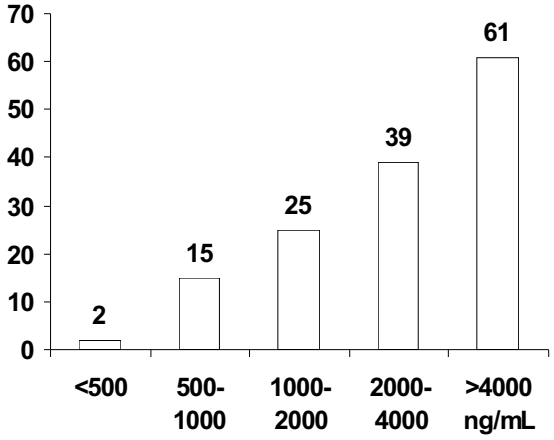
The specificity of the D-dimer concentration was influenced by age. The maximum value was 63.5 % in the 30- to 39- year group and the lowest value was 17% in the group above 80 years of age (Figure 1).

Overall, in 986 out of 1515 patients, D-dimer levels were abnormal (more than 500 ng mL^{-1}) and 314 of these 986 patients had pulmonary embolism (prevalence 32%). In the 125 of 545 patients with a CDR indicating PE unlikely, but a D-dimer more than 500 ng mL^{-1} pulmonary embolism was present (prevalence 23%) whilst 189 of 441 patients with a CDR, indicating PE likely, and a D-dimer more than 500 ng mL^{-1} had pulmonary embolism (prevalence 43%) (p-value < 0.001).

High D-dimer Levels and Prevalence of Pulmonary Embolism

Pulmonary embolism prevalence increased with higher D-dimer levels. The increase was nearly twofold for D-dimer levels between 1000 and 2000 ng mL^{-1}, nearly threefold for levels between 2000 and 4000 ng mL^{-1} and fourfold for levels greater than 4000 ng mL^{-1} compared to D-dimer levels between 500 and 1000 ng mL^{-1} (Figure 2).

Figure 2. Observed pulmonary embolism prevalence accrding to the quantitative level of D-dimers



In the unlikely CDR group with D-dimer levels between 500 and 1000 ng mL^{-1}, the observed pulmonary embolism prevalence was close to the prevalence observed in the overall unlikely CDR group (12 versus 13%) with a moderate increase in the likely CDR group (12 vs. 19%) (Table 2).

Table 2. Observed pulmonary embolism (PE) prevalence for each interval of D-dimer (DD) levels (ng mL^{-1}) and for each level of clinical PE probability

Study population	CDR ≤ 4	CDR > 4
n = 1515	(*n* = 994) (66)	(*n* = 521) (34)
PE prevalence, %	129/994 (13)	195/521 (37)
DD <500 (*n* = 529)	4/449 (0.9)	6/80 (8)
DD 500-1000 (*n* = 276)	21/175 (12)	19/101 (19)
DD 1000-2000 (*n* = 297)	40/191 (21)	35/106 (33)
DD 2000-4000 (*n* = 236)	32/118 (27)	60/118 (51)
DD >4000 (*n* = 177)	32/61 (53)	75/116 (65)

Values within parenthesis are expressed as *n* (%) unless otherwise stated.

D-dimer levels between 1000 and 4000 ng mL^{-1} showed almost a two-fold increased pulmonary embolism prevalence in the unlikely CDR group compared with the overall unlikely CDR group (23% vs. 13%), in the likely CDR group a higher pulmonary embolism prevalence was seen than in the overall CDR likely group (42% vs. 37%). When D-dimer levels were above 4000 ng mL^{-1} the observed pulmonary embolism prevalence was systematically higher than expected, independent of CDR score (53% and 65%). Even with these high D-dimer levels, the CDR score influenced the pulmonary embolism prevalence although the influence of CDR score was limited in patients with the highest D-dimer levels. Among patients with D-dimer levels higher than 2000 ng mL^{-1}, 179 had an unlikely CDR with a pulmonary embolism prevalence of 36%. This is comparable to the CDR likely group with a pulmonary embolism prevalence of 37%. These results were substantiated by logistic regression, showing a fourfold increased risk of pulmonary embolism with a likely CDR score or when D-dimer levels were between 2000 and 4000 ng mL^{-1}. CDR and D-dimer levels were independently and significantly associated with pulmonary embolism prevalence (Table 3). The Vidas and Tinaquant

D-dimer assays showed fully comparable results for the observed pulmonary embolism prevalence for each cut-off level and with logistic regression analysis (data not shown).

Table 3. Logistic regression for the risk of pulmonary embolism

Study population	Odds ratio	95% CI
CDR		
unlikely	1	
likely	4.0	(3.1-5.2)
D-dimer		
500-1000	1	
1000-2000	2.0	(1.3-3.1)
2000-4000	3.8	(2.5-5.8)
>4000	9.0	(5.7-14.2)

CDR, clinical decision rule, CI, confidence interval.

Discussion

It has been repeatedly demonstrated that, due to its low specificity, D-dimer levels above 500 ng mL^{-1} have a low capability of establishing the diagnosis of pulmonary embolism. In our study, the prevalence of pulmonary embolism increased significantly with increasing D-dimer levels. Pulmonary embolism prevalence was 15% in the 500-1000 ng mL^{-1} group and 61% in the group with D-dimer levels above 4000 ng mL^{-1}. In addition, we and others have previously shown an association between the level of D-dimer and the severity of pulmonary embolism which is reflected by the extent of embolic obstruction in the pulmonary arteries [17, 18]. The results of the present study therefore contain several potential clinical consequences of high quantitative D-dimer levels.

First, the integration of high to very high D-dimer levels may refine the diagnostic process in pulmonary embolism and improve medical management. Based on our results, clinicians may consider initiating anticoagulant treatment in patients with either a combination of D-dimer levels higher than 2000 ng mL^{-1} and likely CDR, or D-dimer levels higher than 4000 ng mL^{-1} independent of the CDR score, given the 50 % prevalence of pulmonary embolism in this group in our study. This consideration may be especially relevant when imaging diagnostic facilities are not available 24 h

around the clock. In addition, the positive D-dimer value could be taken into account to decide the urgency of further imaging testing. In absence of evidence however, we would like to stress the safety and efficiency of this potential management approach should be prospectively evaluated.

Secondly, as D-dimer specificity decreases with advancing age and elevated D-dimer levels are present in hospitalized patients with malignancy or recent surgery, several authors have stated that evaluating the use of D-dimer in the diagnostic management of pulmonary embolism should only be performed in predefined low-risk populations [11]. However, in our study we observed a ninefold increased risk of pulmonary embolism with D-dimer levels higher than 4000 ng mL^{-1} compared with D-dimer levels between 500 and 1000 ng mL^{-1}, independent of CDR score. We conclude that D-dimer testing is useful in an unselected population with risk factors for VTE such as older age, inpatients, malignancy or recent surgery.

Thirdly, assessment of CDR is an important step in the diagnostic management of pulmonary embolism. A likely CDR showed a fourfold increased risk of pulmonary embolism independent of D-dimer results. The influence of CDR on pulmonary embolism prevalence was still present even when D-dimer levels exceeded 4000 ng mL^{-1}.

We conclude that strongly elevated D-dimer levels increase the likelihood of pulmonary embolism. Whether the integration of high to very high D-dimer levels in the diagnostic management of pulmonary embolism should translate into more intensive diagnostic and therapeutic measures in patients with high D-dimer levels, irrespective of CDR, remains to be studied.

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