The use of D-dimer testing and Wells score in patients with high probability for acute pulmonary embolism

Mårten Söderberg MD,[1] Johan Brohult MD PhD,[2] Lennart Jorfeldt MD PhD[3] and Gerd Lärfars MD PhD[4]

[1]Senior Consultant, [2]Associated Professor, [4]Head of Department and Senior Consultant, Department of Internal Medicine, Karolinska Institutet, Södersjukhuset, Stockholm, Sweden

[3]Professor, Department of Molecular Medicine and Surgery, Division of Clinical Physiology, Karolinska Institutet, Karolinska University Hospital, Solna, Stockholm, Sweden

Keywords
computed tomography, D-dimer, pre-test probability score, pulmonary angiography, pulmonary embolism

Correspondence
Mårten Söderberg
Department of Internal Medicine
Karolinska Institutet
Södersjukhuset
SE-118 83 Stockholm
Sweden
E-mail:
marten.soderberg@sodersjukhuset.se

Accepted for publication: 4 December 2007

doi:10.1111/j.1365-2753.2008.00967.x

Abstract

Rationale, aims and objective To investigate if a combination of Wells pre-test probability score and D-dimer testing could be used as a safe base for making clinical decisions on further investigations for patients with intermediate to high risks of pulmonary embolism (PE).

Methods One hundred and twenty patients with signs or symptoms of acute PE were investigated with pulmonary angiography (PA) or contrast enhanced computed tomography of the pulmonary arteries (CTPA), D-dimer testing (Tinaquant®) and clinical scoring using the Wells pre-test probability score during their first 48 hours at the hospital. Patients were recruited consecutively from emergency departments at two teaching hospitals.

Results The cut-off value of 0.5 mg L^{-1} in D-dimer analysis is proved adequate with a negative predictive value (NPV) of 92% in this group of patients with intermediate to high risks. The combination of D-dimer testing and Wells score increases the NPV to 94%. The specificities of both tests were low.

Conclusion D-dimer and Wells pre-test probability scores are safe to rule out acute PE even in patients with at least an intermediate risk of PE, but the specificity is low. D-dimer testing had a higher NPV than Wells score and the combination improved the algorithm further. The cut-off level for a high risk of PE measured with the Wells score was four and it seems reasonable to use that cut-off level in future algorithms. In addition, both PA and CTPA can present false positive and negative results difficult to interpret.

Introduction

Pulmonary embolism (PE) is a common disease encountered in the emergency departments (ED). Some patients have clinical signs and symptoms indicating a high clinical probability of PE, but for a majority the symptoms are diverse and there are a number of other possible diagnoses to consider [1,2]. Several studies have addressed the problem of ruling out PE in patients with low pre-test probability and normal D-dimer tests [2]. Patients with intermediate or high risk of disease are less well studied. The importance of clinical findings to predict the prevalence of PE has been shown by several authors supporting the advantages of a pre-test probability score for selecting those patients in whom the diagnosis needs to be established with one or more radiological investigations [3–6]. The Wells pre-test probability score is the most validated instrument and is used widely. In the original papers of Wells *et al*. [4–6], the pre-test probability score was divided into three groups (low, intermediate and high) based on the PIOPED study from 1990. The prevalence of PE varied considerably between these groups [3]. In studies using perfusion and ventilation scintigraphy as diagnostic tools, the prevalence for PE in a group with low clinical probability according to Wells was 5–6% and in the intermediate group it was 19–24% [5], but it is obvious that the prevalence found depends on the kind of objective testing performed [7]. In later studies, the algorithm was simplified using only two subgroups (low and high probability), but different cut-off levels, three or four, have been used in the studies [5,6,8].

D-dimer testing has become a biochemical marker used widely to eliminate deep venous thrombosis and PE [i.e. venous thromboembolism (VTE)] from the list of diagnoses to consider, mainly in patients with a low risk of disease [9,10]. Different kinds of D-dimer tests have varying sensitivities and specificities, but methods using latex agglutination or enzyme-linked immunosorbent assay (ELISA) technology all appear highly sensitive [11]. A combination of a low pre-test probability score and a negative D-dimer test is widely accepted to exclude a VTE, especially in outpatients and in patients with a low probability for developing the disease [8]. However, for patients with intermediate to high

risks it is less well validated. In previous studies, concerning PE the use of ventilation and perfusion scintigraphy as diagnostic tools is widespread. There are only a few studies where the diagnosis has been verified using pulmonary angiography (PA) or computed tomography of the pulmonary arteries (CTPA) [12–14].

The objectives of this study were to evaluate Wells score and D-dimer testing in ruling out PE in patients with intermediate to high risks of disease. All patients were investigated with PA, CTPA or both to optimize the diagnostic accuracy.

Methods

Patients

Patients were recruited from the ED at two major hospitals in Stockholm, Sweden (Karolinska University Hospital, Solna and Södersjukhuset). Inclusion criteria were a high clinical suspicion of PE and clinical symptoms or signs of PE and that a PA or CTPA could be performed within 24 hours from admittance. Exclusion criteria were: (1) age younger than 18 or older than 80 years; (2) advanced psychiatric disease; (3) severe malnutrition or excepted survival time less than 6 months; (4) signs of massive unstable PE or two or more previous PE or deep-vein thromboses; (5) ongoing anticoagulation therapy; (6) thrombocytes $<70 \times 10^9$ L^{-1} or prolonged activated thromboplasmin time >40 seconds; (7) known HIV or hepatitis C infections; (8) pregnancy; (9) acute myocardial infarction; (10) serum creatinine >150 μmol L^{-1}; (11) ongoing treatment with metformine; and (12) contraindication to the use of contrast media. The local ethics committee at Karolinska Institutet, Stockholm, Sweden, approved the study.

Study design

After informed consent, the patients were evaluated at the ED according to a special protocol (not shown) with questions about symptoms, medical history and clinical signs of PE. Of the 146 eligible patients, 120 underwent a D-dimer test and a PA or CTPA or both tests within 48 hours from admission. The D-dimer analysis was performed after the clinical investigations and the doctors were not aware of the result. All patients with a high clinical suspicion of PE received low molecular weight heparin in a dose of 175–200 U kg^{-1} subcutaneously or unfractioned heparin (5.000 IU intravenously) before the radiological investigations. All patients with an established diagnosis of PE received further treatment with dalteparin-sodium (Fragmin®, Pharmacia, 200 U kg^{-1} OD s.c.) or tinzaparin (Innohep®, Leo Pharma, 175 U kg^{-1} OD s.c.) for at least 5 days and concomitant anticoagulation therapy with warfarin (Waran®, Nycomed) with a target international normalized ratio (INR) of 2.1–3.0. No patient received thrombolytic therapy.

For the D-dimer test we used a rapid latex agglutination procedure (Tinaquant®, Roche). Blood samples were obtained on arrival at the hospital and the citrate plasma was frozen and stored at –70 C pending analysis at the local coagulation unit of each hospital. The cut-off level of the D-dimer test used was set at <0.5 mg L^{-1}.

A scoring, using Wells pre-test probability score, was performed for all patients. This scoring was done retrospectively since the original Wells paper was not published when the study started. All variables in the Wells score were included in our study protocol.

Table 1 Clinical characteristic of the study population. Values are shown in mean ± SD, numbers or percentages

Characteristic	PE	Non-PE
n (%)	47 (39)	73 (61)
Median age in years (range)	57 (27–80)	57 (20–80)
Female, *n* (%)	25 (53)	47 (64)
Diagnosed with PA, *n* (%)	34 (72)	54 (74)
Diagnosed with CTPA, *n* (%)	13 (28)	19 (26)
Known malignant disease, *n* (%)	5 (10)	6 (8)
Known coagulopathy, *n*	0	2
Previous VTE, *n* (%)	14 (29)	12 (16)
Heart rate, per minute	91 ± 19	87 ± 16
Peripheral saturation, %*	94 ± 4	96 ± 3
Respiratory rate, per minute*	22 ± 8	17 ± 3

*Some values are missing.

CTPA, computed tomography of the pulmonary arteries; non-PE, patients without pulmonary embolism; PA, pulmonary angiography; PE, patients with pulmonary embolism; VTE, venous thromboembolism.

Because of the inclusion criteria, all patients were considered to comply with 'Pulmonary embolism as likely as or more likely than an alternative diagnosis'. The patients thus scored 3.0 points or more [4]. We used the cut-off level of four as introduced by the Christopher Study Investigators [8], but analysed also data for the cut-off levels of three and six.

The radiological investigations were carried out by two chest radiologists, blinded to all other data, initially by means of individual readings and then by means of consensus readings. The patients were finally diagnosed with a PE if one or both of the investigations fulfilled the criteria.

Statistical analysis

Data were analysed using Students' *t*-test, Wilcoxon rank sum test or logistic regression as appropriate. Significance was set at $P < 0.05$. The areas beneath the receiver operating characteristics (ROC) curves were used to compare the power of Wells scoring and D-dimer testing in ruling out the diagnosis of PE. Data are presented as mean ± standard deviation.

Results

One hundred and twenty symptomatic outpatients were evaluated in this study. The characteristic of the study population is presented in Table 1. There were no statistically significant differences between the PE and non-PE groups concerning age, sex and main clinical findings**.** Forty-seven of 120 (39%) patients had a PE confirmed by either PA ($n = 34$) or contrast enhanced CTPA ($n = 13$). Thirty-four patients had both investigations done. In five of these, PA and CTPA showed different results; for safety reasons all these patients were diagnosed as having PE and received treatment. Eight out of 47 of the PE patients had a Wells score of ≤4 and 39/47 had a score >4, compared with the non-PE group where 35/73 had a low score (≤4) and 38/73 had a high score (>4). Fifty of the 120 patients (42%) had a low D-dimer (< 0.5 mg L^{-1}) and only one patient had a PE diagnosed with Wells score of 4 and D-dimer <0.5 mg L^{-1}. The results are summarized in Tables 2–4.

Table 2 Wells score and D-dimer in patients with (PE) and without (Non-PE) pulmonary embolism.

	Wells score (points) $n = 120$		D-dimer (mg L^{-1}) $n = 120$		D-dimer <0.5 mg L^{-1} $n = 50$	
	WS ≤ 4 ($n = 43$)	WS > 4 ($n = 77$)	DD < 0.5 ($n = 50$)	DD ≥ 0.5 ($n = 70$)	WS ≤ 4 ($n = 26$)	WS > 4 ($n = 24$)
PE	8	39	4	43	1	3
Non-PE	35	38	46	27	25	21

DD, D-dimer; WS, Wells score.

Table 3 Patients with pulmonary embolism at different low Wells score and D-dimer levels

	Wells score = 3	Wells score ≤ 4	Well score ≤ 6
D-dimer < 0.5 mg L^{-1}	1	1	2
D-dimer ≤ 0.67 mg L^{-1}	1	1	7
D-dimer ≤ 1 mg L^{-1}	3	3	11

Table 4 Diagnostic performance of D-dimer and Wells score

	Wells score (≤4 points)	D-dimer (<0.5 mg L^{-1})
Sensitivity	83.0	91.5
Specificity	47.9	63.0
Positive predictive value	50.6	61.4
Negative predictive value	81.4	92.0

Values are shown in percentage.

Table 5 Logistic regression analysis

Variable	OR	B	SE	*P*-value
Wells score	1.75	0.56	0.17	0.001
D-dimer	5.01	1.61	0.56	0.004
Wells score and D-dimer	0.82	–0.19	0.08	0.013
Constant	–	–4.2	0.96	–

'Wells score and D-dimer' denotes the interaction between the two variables.
B, regression coefficient; OR, odds ratio; SE, standard error.

The regression coefficient, calculated by a multiple logistic regression model, was statistically significant for D-dimer ($P < 0.01$) and Wells score ($P < 0.01$). The interaction term Wells score by D-dimer was significant ($P = 0.013$) (Table 5). The logistic regression analysis was combined with calculations of ROC curves, showing an area under the curves of 70.5% ± 4.9 [standard error (SE)] for Wells score and 86.7% ± 3.5 (SE) for D-dimer level (Fig. 1). We used the Wells score as the a priori probability method and D-dimer level as the post priori test for estimating the risk of PE. Using the regression coefficients, the probability for PE with a Wells score of 4 and a D-dimer level of 0.5 mg L^{-1} was 0.18 compared with 0.25 with a D-dimer level of 1.0 mg L^{-1} at the same Wells score. This indicates a relative increase of risk for disease of

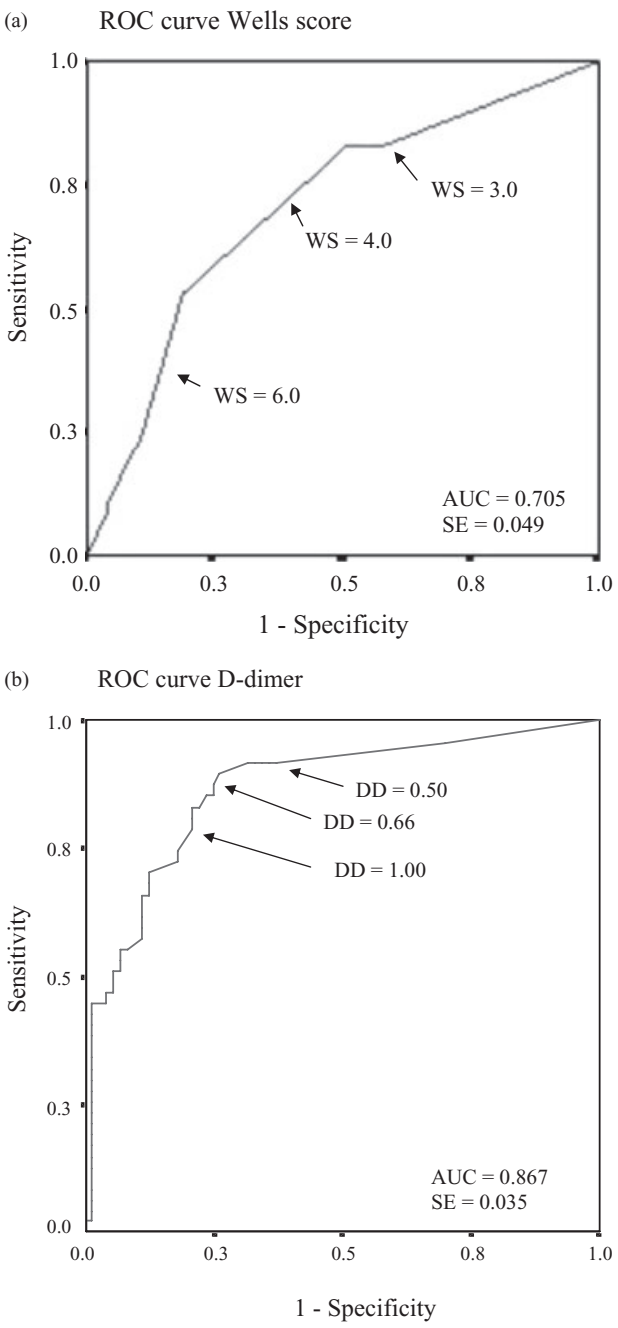

Figure 1 Receiver-operating characteristics (ROC) curve for (a) Wells score and (b) D-dimer with different cut-off levels. AUC, area under the curve; DD, D-dimer; SE, standard error; WS, Wells score.

40%. With an increased Wells score, the significance of a normal D-dimer level decreased. The negative predictive value of the combination of the score and D-dimer is 94%.

Discussion

Our conclusion from this medium size study is that a combination of a Wells pre-test probability score <4 and a D-dimer level <0.5 mg L^{-1} could be used in ruling out PE in patients with an

intermediate to high risk for the disease. This is based on our ROC curves (Fig. 1). The diagnosis was established with PA and CTPA, the best available diagnostic tools. This study had a population with higher prevalence of PE (39%) than reported in other studies, such as PIOPED (33%) [3] and recent management studies by Kearon *et al*. (14.2%) [9]. The Christopher study by van Belle *et al.* showed a prevalence of 37.1% in patients with a high risk for the disease [8]. A management study using PA as the reference method had a prevalence of 25% [15]. Thus, our study population belonged to the intermediate to high-risk group. A clinical problem, clearly shown in the present study, is that PA and CTPA occasionally give diverging results, although both are considered highly accurate and safe [16]. We found conflicting results in five of the 34 patients who had both investigations done, indicating that the diagnosis of PE in some patients might always be difficult to establish, even though the investigations here were reviewed. Three patients with a normal CTPA had a pathological PA, and two patients with a normal PA had a pathological CTPA. These contradictory interpretations only concerned small emboli below the subsegmental level. In the five patients with different results on PA and CTPA, three had a negative D-dimer level and low Wells score points. However, all five were considered as having PE and received treatment. What happens with those patients who undergo only one radiological investigation or when the emboli are too small to be detected by the method used? The studies by van Belle *et al*. [8] and Kruip *et al.* [17] used a dichotomized clinical decision rule (CDR), facilitating the original Wells CDR with three likelihood levels: low, intermediate and high and introducing a two-level score [4–6]. In the Christopher study [8], involving both inpatients and outpatients, an algorithm using CDR, D-dimer and CTPA could be applied successfully to 98% of the studied patients. Thirty-two per cent of the patients had an improbable CDR and a negative D-dimer measure; in these patients only 0.5% (95% confidence interval 0.2–1.1%) suffered a thrombosis or PE during 3-months follow-up, showing the safety of this algorithm. Probably some patients with small emboli were left untreated in these studies without any increased risk for a fatal PE.

Another source of error for patients with a suspicion of having a VTE is that the D-dimer level can also be increased in patients with non-thromboembolic diseases and patients with other diseases can have high Wells scores. A problem with D-dimer testing at the ED is that it could increase the number of clinical investigations of patients with suspected PE but does not increase the diagnosis of PE, indicating a need to follow established algorithms [18].

One difficulty with the Wells score is that it forces the doctor to decide whether a PE is likely and the most likely diagnosis before confirmatory tests influences the probability. In the clinical model designed by Wells *et al*., the authors discussed the dependency of a thorough consideration of an alternative diagnosis and noted that this decision can strongly influences the final probability. This was also shown by Kabrhel *et al.* [19], as when diseases such as asthma, anxiety and chronic obstructive pulmonary disease were considered the most likely diagnosis, the physician diagnose PE infrequently. Kruip *et al*. showed the same situation for hospitalized patients obtaining a decision rule (improbable CDR and negative D-dimer) in only 10% of the patients studied [17]. Sixty-eight per cent of the patients with a high CDR (>4 points) had disease other than PE diagnosed by CTPA, demonstrating that a high CDR score in hospitalized patients with other diseases is non-diagnostic.

In summary, we found that the combination of Wells score and D-dimer testing was superior to the sole use of the score itself to exclude the disease and that the D-dimer level was superior to the Wells score. The initial evaluation of patients with Wells score was accurate until the result of the D-dimer test was available. Wells score had a higher specificity than D-dimer level in selecting patients with a higher risk of PE, whereas the sensitivity for D-dimer is higher. According to the ROC we suggest, in concordance with other authors [8,17], that a cut-off level in the dichotomized Wells score of 4 is accurate and that the cut-off level of D-dimer of 0.5 mg L^{-1} is accurate and should be used. CTPA is sufficient for most patients, but some false cases both positive and negative might occur. The model could be used at all ED where a D-dimer test can be obtained.

Acknowledgements

We thank Hans Pettersson, PhD at Karolinska Institutet, Södersjukhuset for help with the statistics. This study was supported by grants from the Swedish Heart and Lung Foundation, Stockholm County Council, Karolinska Institutet and from the Swedish Medical Research Council (project no. 04139).

References

1. Goldhaber, S. Z. & Elliott, C. G. (2003) Acute pulmonary embolism, part I. Epidemiology, pathophysiology, and diagnosis. *Circulation*, 108, 2726–2729.
2. Kline, J. A., Mitchell, A. M., Kabhrel, C., Richman, P. B. & Courtney, D. M. (2004) Clinical criteria to prevent unnecessary diagnostic testing in emergency department patients with suspected pulmonary embolism. *Journal of Thrombosis and Haemostasis*, 2, 1247–1255.
3. The PIOPED Investigators (1990) Value of the ventilation/perfusion scan in acute pulmonary embolism: results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). *Journal of the American Medical Association*, 263, 2753–2759.
4. Wells, P. S., Ginsberg, J. S., Anderson, D. R., *et al.* (1998) Use of a clinical model for safe management of patients with suspected pulmonary embolism. *Annals of Internal Medicine*, 129, 997–1005.
5. Wells, P. S., Anderson, D. R., Rodger, M., Stiell, I., Dreyer, J. F., Barnes, D., Forgie, M., Kovacs, G., Ward, J. & Kovacs, M. J. (2001) Excluding pulmonary embolism at the bedside without diagnostic imaging: managing of patients with suspected pulmonary embolism presenting to the department by using a simple clinical model and D-dimer. *Annals of Internal Medicine*, 135, 98–107.
6. Wells, P. S., Anderson, D. R., Rodger, M., *et al.* (2000) Derivation of a simple clinical model to categorize patients' probability of pulmonary embolism: increasing the model's utility with the SimpliRED D-dimer. *Thrombosis and Haemostasis*, 83, 416–420.
7. Nilsson, T., Måre, K. & Carlsson, A. (2001) Value of structured clinical and scintigraphic protocols in acute pulmonary embolism. *Journal of Internal Medicine*, 250, 213–218.
8. van Belle, A., Büller, H. R., Huisman, M. V., Huisman, P. M., Kaasjager, K. & Kamphuisen, P. W. for the Christopher Study Investigators (2006) Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. *Journal of the American Medical Association*, 295, 172–179.
9. Kearon, C., Ginsberg, J. S., Douketis, J., *et al.* (2006) An evaluation of D-dimer in the diagnosis of pulmonary embolism. *Annals of Internal Medicine*, 144, 812–821.
10. Brown, A. M., Rowe, B. H., Reeves, M. J., Bermingham, J. M. & Goldhaber, S. Z. (2002) The accuracy of the enzyme-linked immun-

osorbent assay D-dimer test in the diagnosis of pulmonary embolism: a meta-analysis. *Annals of Emergency Medicine*, 40, 133–144.
11. Bockenstedt, P. (2003) D-Dimer in venous thromboembolism. *New England Journal of Medicine*, 349, 1203–1204.
12. Hayashino, Y., Goto, M., Noguchi, Y. & Fukui, T. (2005) Ventilation-perfusion scanning and helical CT in suspected pulmonary embolism: meta-analysis of diagnostic performance. *Radiology*, 234, 740–748.
13. van Strijen, M. J., de Monye, W., Kieft, G. J., Pattynama, P. M., Prins, M. H. & Huisman, M. V. (2005) Accuracy of single-detector spiral CT in the diagnosis of pulmonary embolism: a prospective multicenter cohort study of consecutive patients with abnormal perfusion scintigraphy. *Journal of Thrombosis and Haemostasis*, 3, 17–25.
14. Stein, P. D., Fowler, S. E., Goodman, L. R., *et al.* (2006) Multidetector computed tomography for acute pulmonary embolism. *New England Journal of Medicine*, 354, 2317–2327.
15. Kruip, M. J., Slob, M. J., Schijen, J. H., van der Heul, C. & Büller, H. R. (2002) Use of a clinical decision rule in combination with D-dimer concentration in diagnostic workup of patients with suspected pulmonary embolism: a prospective management study. *Archives of Internal Medicine*, 162, 1631–1635.
16. Nilsson, T., Carlsson, A. & Måre, K. (1998) Pulmonary angiography: a safe procedure with modern contrast media and technique. *European Radiology*, 8, 86–89.
17. Kruip, M. J. H. A., Söhne, M., Nijkeuter, M., *et al.* (2006) A simple diagnostic strategy in hospitalized patients with clinically suspected pulmonary embolism. *Journal of Internal Medicine*, 260, 459–466.
18. Kabrhel, C., Matts, C., McNamara, M., Katz, J. & Ptak, T. (2006) A highly sensitive ELISA D-dimer increases testing but not diagnosis of pulmonary embolism. *Academic Emergency Medicine*, 13, 519–524.
19. Kabrhel, C., McAfee, A. T. & Goldhaber, S. Z. (2006) The probability of pulmonary embolism is a function of the diagnoses considered most likely before testing. *Academic Emergency Medicine*, 13, 471–474.

