Further validation and simplification of the Wells clinical decision rule in pulmonary embolism

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Summary

The Wells rule is a widely applied clinical decision rule in the diagnostic work-up of patients with suspected pulmonary embolism (PE). The objective of this study was to replicate, validate and possibly simplify this rule. We used data collected in 3,306 consecutive patients with clinically suspected PE to recalculate the odds ratios for the variables in the rule, to calculate the proportion of patients with PE in the probability categories, the area under the ROC curve and the incidence of venous thromboembolism during follow-up. We compared these measures with those for a modified and a simplified version of the decision rule. In the replication, the odds ratios in the logistic regression model were found to be lower for each of the seven individual variables (p=0.02) but the proportion of patients with PE in the probability categories in our study group were comparable to those in the original derivation and validation groups. The area under the ROC of the original, modified and simplified decision rule was similar: 0.74 (p=0.99; p=0.07). The venous thromboembolism incidence at three months in the group of patients with a Wells score ≤ 4 and a normal D-dimer was 0.5%, versus 0.3% with a modified rule and 0.5% with a simplified rule. The proportion of patients safely excluded for PE was 32%, versus 31% and 30%, respectively. This study further validates the diagnostic utility of the Wells rule and indicates that the scoring system can be simplified to one point for each variable.

Keywords

Pulmonary embolism, clinical studies, thrombosis, venous thrombosis

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Introduction

The diagnostic work-up of patients with clinically suspected pulmonary embolism is challenging because of the relatively low prevalence of the disease in this population. In the past, several attempts have been made to include clinical information in the diagnostic process in order to rule out pulmonary embolism and withhold expensive and time-consuming imaging techniques without compromising patient's safety. However, the majority of these attempts have not been clinically successful (1–5). The main concern with these assessments of clinical probability involved the use of many variables, including subjective elements as well as the often complicated scoring methods. Furthermore, clinical judgment by the doctor, also called 'gestalt', is the simplest method of selecting low risk patients. Yet when this method is used, it appears that only a low percentage of patients can be withheld from additional imaging testing (6–8).

The quantitative clinical decision rule, published by Wells and colleagues in 2000, incorporated seven items from the medical history and physical examination easily obtained in the initial diagnostic work-up (9). Because of its relative comprehensiveness and ease of use in a clinical setting this rule is now widely accepted in the exclusion of pulmonary embolism. It has been incorporated in several guidelines, despite certain limitations (10–15).

The decision rule was obtained by selecting variables that were significantly associated with the presence or absence of pulmonary embolism from an extended 40 item list. These variables were initially tested in a univariate logistic regression analysis. Those variables that were also significant after a step-

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wise regression analysis were selected for the final rule. According to the value of the odds ratios in the regression analysis 1, 1.5 or 3 points are assigned for each feature (Table 2). The rule can be used to assign patients to one of three probability categories (low, moderate and high), or to classify them as 'pulmonary embolism unlikely' or 'likely'.

There is evidence that odds ratios, calculated this way for the decision rule, show an upwards bias and that replication studies produce lower values for the same variables. This mechanism has been suggested as one of the explanations for the phenomenon that many decision rules tend to loose their discriminative power in subsequent evaluations (16, 17).

If the true odds ratios in the clinical decision rule are lower than the ones reported by Wells and colleagues, there may be less need to use three different sets of points: 1, 1.5 or 3 points. It is possible that unit weights produce very similar, if not identical, results, as the original rule. If so, a more simplified rule could be used in practice, one that is easier to memorize and leads to fewer summing mistakes in the acute care setting.

The three purposes of this study were a replication of the weights in the decision rule developed by Wells and colleagues, a validation of the rule, and, if possible, simplification. For these aims we used the data of a large management study (18).

Methods

Data were obtained in a large prospective diagnostic management study that included patients with clinically suspected pulmonary embolism between November 2002 and August 2004 in 12 hospitals in the Netherlands. . That study, described in detail elsewhere, demonstrated that a diagnostic management strategy with a clinical decision rule, a D-dimer test and spiral CT, is safe in the work-up of patients with clinically suspected pulmonary embolism (18).

Patients and management

Consecutive in- and outpatients with clinically suspected acute pulmonary embolism were eligible for this study. Patients were excluded if they had received (low molecular weight) heparin for more than 24 hours, were younger than 18 years of age, were pregnant, had a known hypersensitivity for iodinated contrast fluid or renal failure, had a life expectancy of less than three months, if there was geographic inability for follow-up, or if informed consent had not been obtained. The institutional review boards of all participating hospitals approved the study protocol.

Eligible patients were asked for written or oral informed consent. At presentation the clinical decision rule of Wells and colleagues was used by the treating physician (9). The physician assigned three points for clinical signs and symptoms of deep venous thrombosis (DVT), three more points when pulmonary embolism was more likely than an alternative diagnosis, one and a half points each for a heart rate greater than 100, immobilization or surgery in the previous four weeks, and a previous episode of DVT or pulmonary embolism, and one point each for hemoptysis and malignancy. The total score was obtained by summing these points. It takes values in the range from 0 to 12.5.

Pulmonary embolism was considered unlikely with a score of 4 or lower, and a D-dimer test was performed (Tinaquant, Roche Diagnostica, Mannheim, Germany or Vidas D-dimer, Biomerieux, Marcy L'Etoile, France) (18). The D-dimer test was defined as normal if the concentration was ≤0.5 mg/l. The combination of a score over 4 and a normal D-dimer result was considered to rule out pulmonary embolism and anticoagulant treatment was withheld.

In all other patients a spiral CT scan was performed. The CT scan was considered positive for pulmonary embolism if contrast material outlined an intraluminal filling defect or if a vessel was totally occluded by low-attenuation material on at least two adjacent slices. The decision on the presence or absence of pulmonary embolism was made by a trained attending radiologist.

Follow-up was performed in all patients without pulmonary embolism at baseline by the study physician, through a hospital visit, or a telephone interview at three months, and the instruction to contact the study centre or the general practitioner in case of complaints suggestive of DVT or pulmonary embolism. In case of clinically suspected DVT or pulmonary embolism during the follow-up period, compression ultrasound for suspected DVT and ventilation-perfusion scintigraphy or CT 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.

Replication of the Wells clinical decision rule

We fitted a multivariable logistic regression model to our data that contained the same variables as used by Wells and colleagues to develop the clinical decision rule. The estimated coefficients and the 95% confidence intervals were transformed to odds ratios and compared to the odds ratios as reported by Wells et al. (9). We used the sign test to test the directions of the differences for significance.

Validation of the Wells clinical decision rule

The original study by Wells and colleagues assigned patients to one of three probability categories, based on their score: low (0 to 1 points), moderate (2 to 6 points) and high (more than 6 points). We calculated the prevalence of pulmonary embolism in these three probability categories in our study group and compared those with the prevalence in the corresponding categories in the derivation and validation groups of Wells et al. (9).

Simplification of the Wells clinical decision rule

To evaluate whether the original Wells rule could be simplified, we developed a *modified* and a *simplified* rule. Instead of assigning one, one and a half, or three points for each of the features, the modified rule assigns two points for the presence of the two variables with the highest odds ratios and one point to the remaining variables in the model.

We also developed a *simplified* rule, one that assigns unit weights for the presence of all individual variables in the model. With this simplified rule, a patient receives a score between zero and seven, depending on the presence or absence of each of the seven variables in the Wells decision rule.

We calculated the scores for all patients in our study with the modified and the simplified rule. To evaluate the performance of the modified and the simplified rules, the area under the Receiver Operating Characteristic (ROC) curve was calculated and

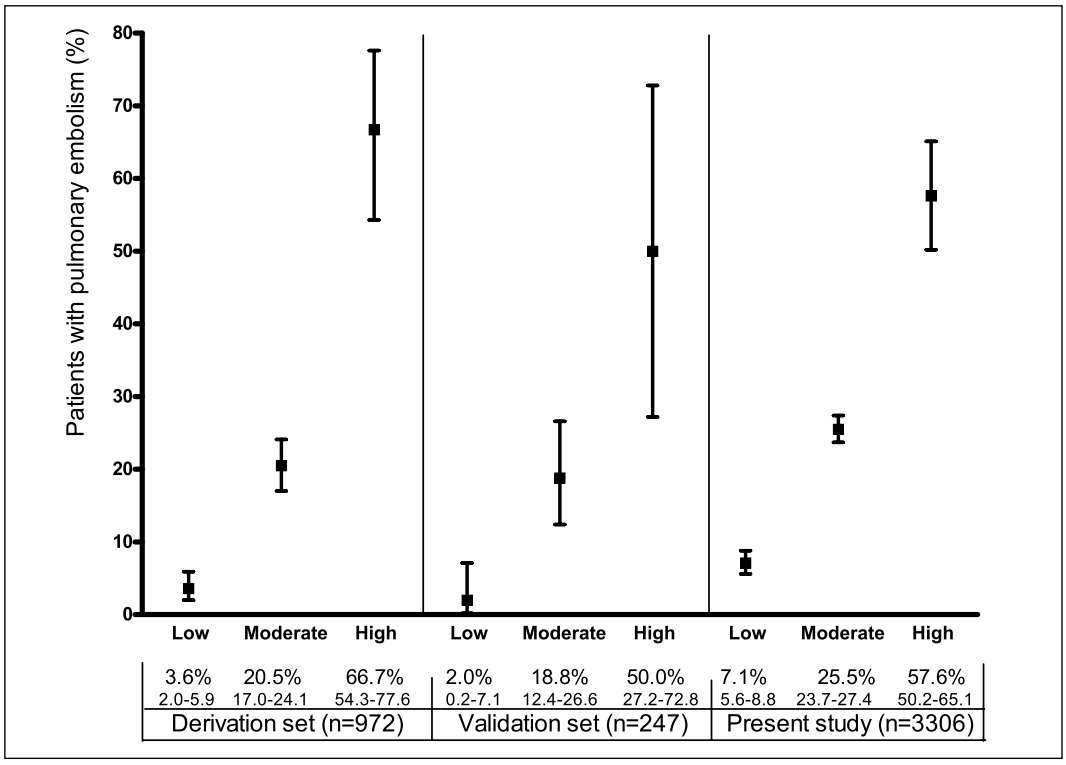

Figure 1: Prevalence of pulmonary embolism with 95% CI in the three probability groups with the original Wells rule in the study of Wells et al. (9) (derivation and validation set), as well as in the present study.

compared to the area under the curve for the original Wells rule. ROC curves show the discriminatory performance of a test; the area under the curve of a perfectly discriminating rule would be 1.00 and that of a useless rule 0.50. We used the bivariate binormal method to estimate the respective ROC curves and test the differences of these correlated rules for significance, using the ROCkit computer program 1.1B2 (19).

We also calculated and compared the proportion of patients in the 'likely' and 'unlikely' categories for the original Wells rule (using a cut-off ≤4 for 'unlikely'), the modified rule (using a cut-off of ≤2) and the simplified rule (cut-off ≤1) (9).

Safety and clinical utility of the clinical decision rules combined with D-dimer testing

Since the clinical decision rule is never used as the only test to rule out pulmonary embolism, the diagnostic safety and utility of the combination of the decision rules and the D-dimer test were also evaluated. The *safety* of this strategy was defined in terms of the observed incidence of symptomatic venous thromboembolism during the three months of follow-up in patients in whom pulmonary embolism was considered unlikely, based on the clinical decision rule cut-off and a normal D-dimer test result. The clinical *utility* was assessed by calculating the proportion of patients in whom further diagnostic testing could be safely withheld. The safety as well as the clinical utility of the two simplified rules was compared to those of the original decision rule, using the cut-off values mentioned earlier (18).

The 95% confidence interval for the three months venous thromboembolism incidence rate for each possible score in combination with a normal D-dimer result were calculated. A strategy was defined as acceptable if the confidence interval was located below 3.0%.

Results

Patient characteristics

Of the 3,503 screened patients with clinically suspected pulmonary embolism, 184 had to be excluded because of predefined exclusion criteria. A total of 3,306 consecutive patients with clinically suspected acute pulmonary embolism could be included in the study. The mean age in the study group was 53 years (range 18 to 110 years) and there were 2,701 outpatients (82%).

The score on the clinical decision rule was available for 3,298 patients (99.8%). Of the variables in the decision rule the one most frequently observed was 'pulmonary embolism is more likely than an alternative diagnosis' (n=2032, 62%). The two variables with the lowest frequency were 'clinical signs and symptoms of DVT' (n=190, 6%) and 'hemoptysis' (n=176, 5%). The prevalence of the other variables varied from 11% (malignancy) to 26% (tachycardia).

D-dimer results were available in 98% of the 2,199 patients with a score of four or lower on the decision rule. Of these 2,199 patients, 1,105 had a D-dimer test result ≥0.5 mg/l. The prevalence of proven pulmonary embolism at baseline in the entire study group was 20% (n=674).

Replication of the Wells clinical decision rule

The second column of Table 2 shows the odds ratios of the variables in the decision rule, as obtained in the multivariable regression analysis of our data as well as the odds ratios in the comparable analysis of the data obtained by Wells and colleagues (9). The odds ratios for all seven variables are lower in the analysis in our study group compared to those obtained in the Wells study (p=0.02).

Table 1: Scoring of the various variables in the original, the modified and simplified Wells rule.

	Original	Modified	Simplified
1. Clinical signs & symptoms DVT	3	2	1
2. Tachycardia (>100/min)	1.5	1	1
3. Immobilization or surgery in the previous four weeks	1.5	1	1
4. Previous DVT/PE	1.5	1	1
5. Hemoptysis	1	1	1
6. Malignancy	1	1	1
7. An alternative diagnosis is less likely than PE	3	2	1
Cut-off for PE unlikely	≤ 4	≤ 2	≤ 1

DVT, Deep Venous Thrombosis; PE, Pulmonary Embolism.

Table 2: Odds ratios for the variables of the Wells clinical decision rule and those observed in the present study.

	Odds ratio with 95%CI for the present study	
Variable	Wells et al. [9]	Present study
1. Clinical signs & symptoms DVT	5.8	4.3 (3.1–5.9)
2. Tachycardia (>100/min)	3.0	1.8 (1.5–2.2)
3. Immobilization or surgery in the previous four weeks	2.5	2.1 (1.7–2.6)
4. Previous DVT/PE	2.4	1.8 (1.4–2.3)
5. Hemoptysis	2.4	1.9 (1.3–2.6)
6. Malignancy	2.3	1.4 (1.1–1.8)
7. An alternative diagnosis is less likely than PE	4.6	3.6 (2.9–4.5)

DVT, Deep Venous Thrombosis; PE, Pulmonary Embolism.

Validation of the Wells clinical decision rule

A comparison of the prevalence of pulmonary embolism in the three probability categories is shown in our study group, and in the derivation and validation groups of Wells et al. (Fig. 1). The prevalence in the respective categories in the derivation group, the validation group and in our study group is very similar. Differences between the Wells validation group and our group were not statistically significant (p=0.06, 0.09 and 0.63 for the low, intermediate and high probability group, respectively).

Simplification of the Wells clinical decision rule

Table 1 details the two new rules. In the modified rule two points are assigned to 'clinical signs and symptoms of DVT' and to 'pulmonary embolism is more likely than an alternative diagnosis'. In the simplified rule all variables are assigned one point if present.

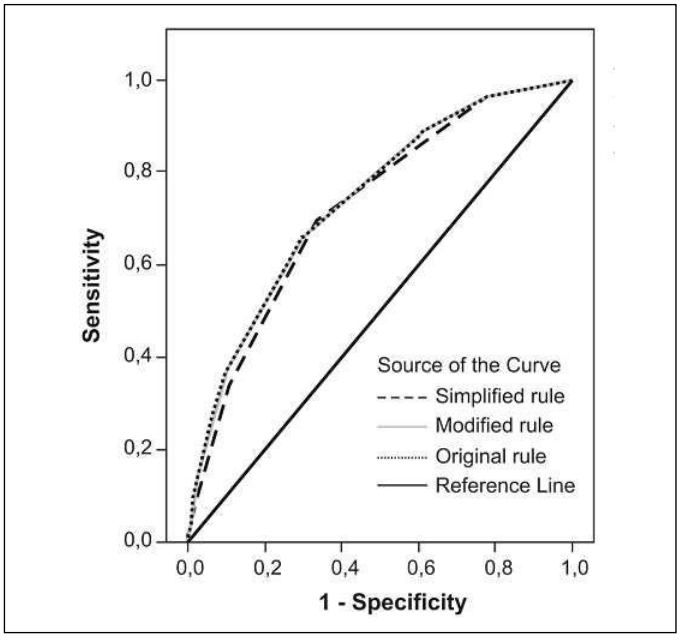

Figure 2: ROC curve. The area under the ROC of the original, modified and simplified decision rule was similar: 0.74 (p=0.99; p=0.07).

In Figure 2 the ROC curves of the original scoring method of Wells et al. of the modified and the simplified rule are depicted. The area under the curve was 0.744 for the original Wells rule (95% CI: 0.724 to 0.764), 0.744 for the modified rule (95% CI: 0.724 to 0.764), and 0.736 (95% CI: 0.715 to 0.756) for the simplified rule. The differences between the original decision rule and the modified rule, and the original and the simplified rule, were not significant (p=0.99 and p=0.07, respectively).

Safety and clinical utility of the different scoring options of the clinical decision rules combined with D-dimer testing

Figure 3 shows the proportion of patients with pulmonary embolism in the 'unlikely' and 'likely' categories for the original rule and the modified (cut-off score ≤ 2) and the simplified rule (cut-off score ≤ 1). The proportions were very similar. There were no significant differences between the three rules, neither for the 'likely' nor for the 'unlikely' categories.

We also calculated the three month incidence of VTE in case of an 'unlikely' result on the decision rule in combination with a normal D-dimer test result (Table 3). For comparison, the results with the original dichotomized Wells score combined with D-dimer, as used in our study, are also shown. Follow-up was incomplete in three of the 2632 patients without pulmonary embolism at baseline. The modified rule and the simplified rule, in combination with a normal D-dimer, had similar incidence rates of VTE during follow-up: 0.3% (95% CI: 0.1 to 0.9%) and 0.5% (95% CI 0.2 to 1.0%), respectively. None of the differences in incidence rate was significant (p>0.70).

The clinical utility, in terms of the ability to reliably exclude patients for pulmonary embolism without further imaging, was around 30% for all three decision rules when combined with a normal D-dimer test.

If the cut-off score of the modified rule was increased to ≤3, the three month incidence of VTE would increase to 1.0% (95%

CI 0.5% to 1.8%). The additional patient group with a score of three points consisted of 109 patients of whom five patients had VTE (4.6%). Similarly, as six of 135 patients with two points using the simplified rule had pulmonary embolism, the incidence of VTE in those patients would be 4.4% (95% CI: 1.7% to 9.4%).

A cut-off score of ≤ 1 on the simplified rule indicates that pulmonary embolism can be considered unlikely if one or less of the seven features in the clinical decision rule is present. No further multiplication or summation is required.

Discussion

Although the literature indicates that shrinkage and regression to the mean are often seen in the life span of prediction rules (16, 17), the present analysis shows that the discriminative power of the Wells decision rule compares favourably with the original derivation and validation set.

Our findings indicate that in general the odds ratios of the seven variables were lower than observed by Wells et al., however, this occurred without affecting the validity of the rule. Moreover, the two most informative variables remained the same: 'alternative diagnosis less likely than pulmonary embolism' and 'clinical signs & symptoms of DVT'.

In the original rule three different weights were assigned to the various variables based on their odds ratios in order to produce a user friendly decision rule (Tables 1 and 2). When we simplified this rule by giving two different weights to the variables – two points for the two variables with the highest odds ratios and one point to the other variables – little diagnostic information was lost. Most interestingly, when using unit weights – one point for each variable – in what we call the *simplified rule* the diagnostic accuracy remained unchanged (Fig. 2).

The simplified Wells rule indicates diagnostic testing is required if two or more of the seven variables are present, or if the D-dimer test is positive. If only one, or none of the variables, is present and the D-dimer test is normal, a less than one percent incidence rate of VTE during follow-up can be expected. With this combination of tests approximately 30% of patients with suspected pulmonary embolism can be safely withheld from further diagnostic imaging, a proportion similar to that observed with the original Wells rule.

Unit weight decision rules are not new. It has been shown before that a linear model containing equally weighted variables may be just as good at prediction in a validating sample as a model containing variables whose weights have been more precisely estimated in a different study group (20). Having unit weights makes decision rules also more parsimonious. In this case, as the seven variables are either present or absent in a patient, the physician should only check to see whether two or more of these features are available.

Our study results show that assigning different weights to the variables does not improve the diagnostic efficiency of the clinical decision rule. This could be caused by the upward bias in the odds ratios and a slight regression to the mean. Theoretically, the explanations for regression to the mean are diverse. It could be

Table 3: Safety and clinical utility; venous thromboembolic events during three-month follow-up in untreated patients for the three scoring models of the clinical decision rule.

	n	Total VTE n (%;95% CI)	Proportion of patients in whom spiral CT can be withheld
Original score ≤ 4 and normal D-dimer	1028	5 (0.5%; 0.2 to 1.1%)	32% (95% CI 30–33%)
Modified score ≤ 2 and normal D-dimer	1010	3 (0.3%; 0.1 to 0.9%)	31% (95% CI 29–32%)
Simplified score ≤ 1 and normal D-dimer	1119	5 (0.5%; 0.2 to 1.0%)	30% (95% CI 28–31%)

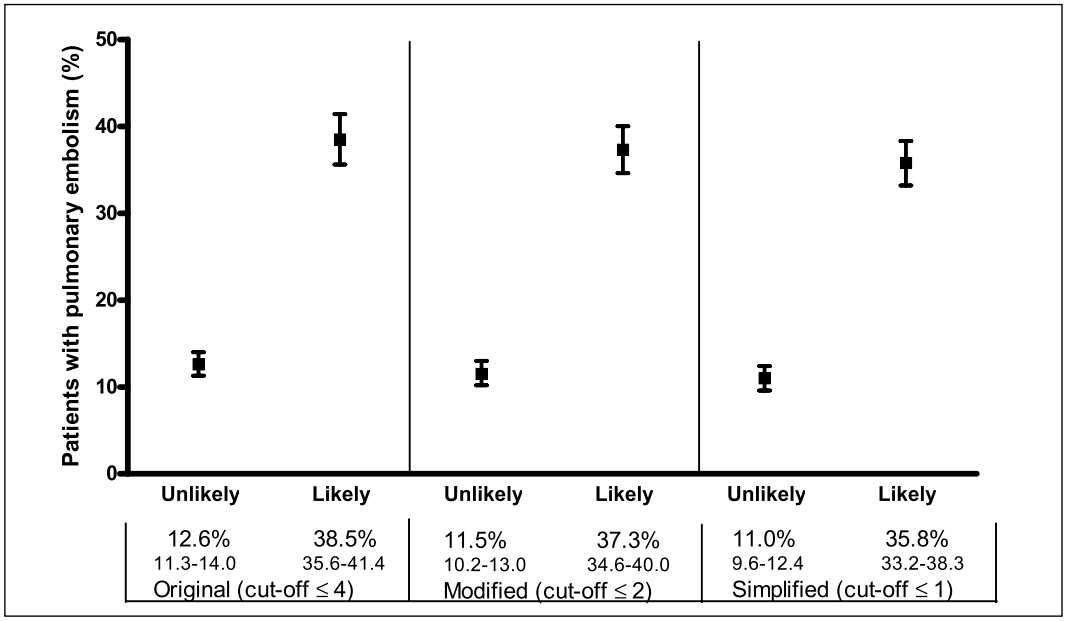

Figure 3: Prevalence of pulmonary embolism with 95% CI depicted for the original, the modified and the simplified Wells rule, using pulmonary embolism likely and unlikely categories.

caused by the influence of interobserver variability, differences in interrater reliability and variation in referral pattern (13). Yet chance is also a decisive factor. A variable with an overestimated regression coefficient is more likely to be selected for the specific decision rule than an underestimated one. Consequently, the selected variables were likely to have too large coefficients (17).

It is tempting to speculate why the Wells rule has been widely accepted while previous attempts with sometimes similar variables have failed (1–5, 21). This could partly be due to the fact that the variables in these rules were too numerous and were complicated by the need for additional tests, such as blood gas analysis, electrocardiography or chest X-ray.

The strategy of neural networks which are computerized clinical decision rules, popular in the early nineties, was also quickly forgotten, most likely because the networks were perceived to be too complicated (22, 23). More recently the application of multivariable logistic regression techniques gave more insight into the predictive strength and independency of the signs and symptoms for pulmonary embolism, and therefore reliable diagnostic models could be created which became more appealing to clinicians (3).

The wide acceptance of the Wells rule is possibly due to the inclusion of only seven relevant variables which are simple to obtain at the bedside (24). The addition of the clinical opinion of the clinician in the subjective variables 'clinical signs and symptoms of DVT' and 'alternative diagnosis less likely than pulmonary embolism' probably further contributed to its popularity.

Several aspects of our study require comment. Our analysis was based on data collected previously and the simplified rule would benefit from validation in another prospective study. Since the data were carefully collected in a large cohort of consecutive patients and the simplified rule builds on the work of Wells and colleagues, we are confident that this simplified rule will survive such further validation.

The safety of excluding pulmonary embolism was determined by the subsequent incidence of VTE during the three month follow-up. Using follow-up has increasingly been accepted as an appropriate reference standard for clinical outcome, if some basic methodological principles are adhered to, such as withholding anticoagulant treatment, complete follow-up and appropriate diagnostic work-up in case of suspected recurrence of VTE (25).

We used the combination of an unlikely clinical probability and a normal D-dimer test to rule out pulmonary embolism. It should be noted that the addition of D-dimer testing is mainly responsible for the low subsequent incidence of VTE during follow-up.

In summary, we validated the Wells rule and although the odds ratios did diminish slightly, the performance of the rule was more than adequate. Simplification of the rule by assigning only one point to each of the seven variables had a similar diagnostic accuracy and clinical utility. This simplified rule requires prospective validation.

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