

Derivation of a Simple Clinical Model to Categorize Patients Probability of Pulmonary Embolism: Increasing the Models Utility with the SimpliRED D-dimer

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Key words

Pulmonary embolism, diagnosis, D-dimer, clinical assessment, regression analysis

Summary

We have previously demonstrated that a clinical model can be safely used in a management strategy in patients with suspected pulmonary embolism (PE). We sought to simplify the clinical model and determine a scoring system, that when combined with D-dimer results, would safely exclude PE without the need for other tests, in a large proportion of patients. We used a randomly selected sample of 80% of the patients that participated in a prospective cohort study of patients with suspected PE to perform a logistic regression analysis on 40 clinical variables to create a simple clinical prediction rule. Cut points on the new rule were determined to create two scoring systems. In the first scoring system patients were classified as having low, moderate and high probability of PE with the proportions being similar to those determined in our original study. The second system was designed to create two categories, PE likely and unlikely. The goal in the latter was that PE unlikely patients with a negative D-dimer result would have PE in less than 2% of cases. The proportion of patients with PE in each category was determined overall and according to a positive or negative SimpliRED D-dimer result. After these determinations we applied the models to the remaining 20% of patients as a validation of the results. The following seven variables and assigned scores (in brackets) were included in the clinical prediction rule: Clinical symptoms of DVT (3.0), no alternative diagnosis (3.0), heart rate >100 (1.5), immobilization or surgery in the previous four weeks (1.5), previous DVT/PE (1.5), hemoptysis (1.0) and malignancy (1.0). Patients were considered low probability if the score was <2.0, moderate of the score was 2.0 to 6.0 and high if the score was over 6.0. Pulmonary embolism unlikely was assigned to patients with scores ≤4.0 and PE likely if the score was >4.0. 7.8% of patients with scores of less than or equal to 4 had PE but if the D-dimer was negative in these patients the rate of PE was only 2.2% (95% CI = 1.0% to 4.0%) in the derivation set and 1.7% in the validation set.

Importantly this combination occurred in 46% of our study patients. A score of <2.0 and a negative D-dimer results in a PE rate of 1.5% (95% CI = 0.4% to 3.7%) in the derivation set and 2.7% (95% CI = 0.3% to 9.0%) in the validation set and only occurred in 29% of patients. The combination of a score ≤4.0 by our simple clinical prediction rule and a negative SimpliRED D-Dimer result may safely exclude PE in a large proportion of patients with suspected PE.

Introduction

Pulmonary embolism, the third leading cause of cardiovascular mortality in North America, has an estimated annual incidence of 23 cases per 100,000 population per year (1). Since PE is present in less then 35% of investigated patients unnecessary presumptive anticoagulation, admission to hospital and testing occurs in a large number of patients without PE (2). A bedside method that safely excludes PE would be desirable. Since untreated PE has a high hospital mortality rate, which falls with appropriate treatment (3), a bedside method needs to be highly sensitive (i.e. very few false negatives). In addition, for a bedside test to be clinically useful it must exclude a large proportion of patients who do not have the disease. Until recently the clinical diagnosis of PE was also felt to be inaccurate and of little value. The PIOPED investigators revisited the accuracy of the clinical diagnosis and demonstrated that experienced clinicians were able to separate cohorts of patients with suspected PE into high, moderate and low probability groups using the clinical assessment alone in a multicentre study in which the diagnosis of PE was confirmed by pulmonary angiography (2). Realizing the potential utility of identifying pretest probability we recently developed an explicit clinical model to determine likelihood for PE using clinical findings, ECG and chest x-ray results (4). The clinical model was rather complex (Fig. 1). It consisted of consideration of whether the patients clinical presentation based on symptoms, signs and risk factors, was typical for PE and whether there was an alternative diagnosis at least as likely as PE to account for their symptoms. Evaluating over 1200 inpatients and outpatients with suspected PE we were able to distinguish low, moderate, and high probability cohorts in whom the incidence rates of PE were 3%, 28% and 78%, respectively (4). Consideration of clinical probability was a

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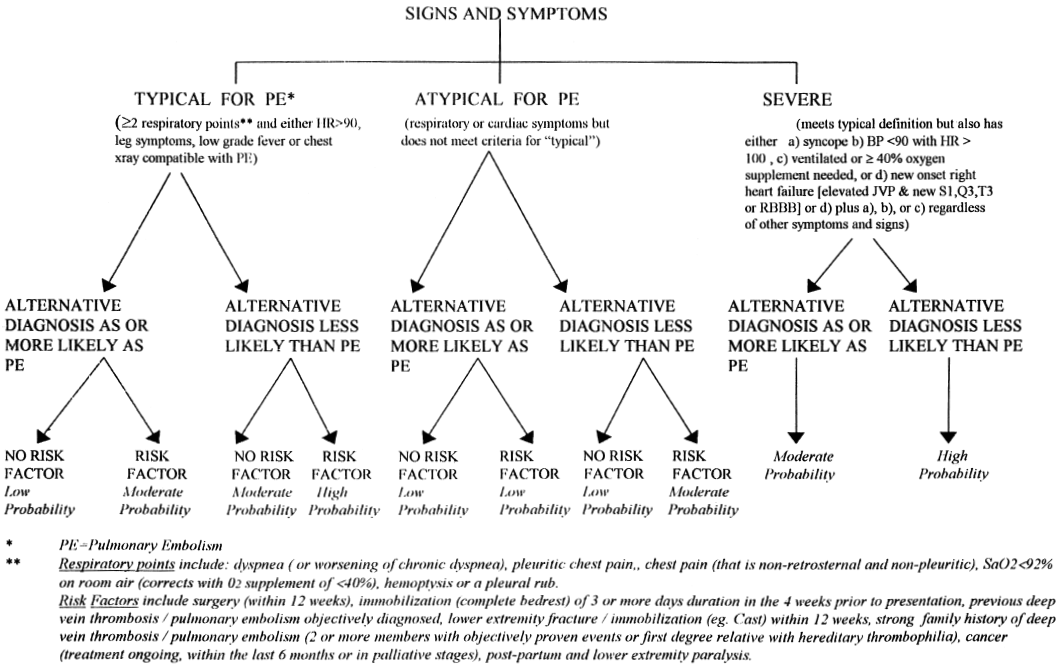

* *PE=Pulmonary Embolism*

** *Respiratory points include: dyspnea (or worsening of chronic dyspnea), pleuritic chest pain,, chest pain (that is non-retrosternal and non-pleuritic), SaO2<92% on room air (corrects with 02 supplement of <40%), hemoptysis or a pleural rub.*
Risk Factors include surgery (within 12 weeks), immobilization (complete bedrest) of 3 or more days duration in the 4 weeks prior to presentation, previous deep vein thrombosis / pulmonary embolism objectively diagnosed, lower extremity fracture / immobilization (eg. Cast) within 12 weeks, strong family history of deep vein thrombosis / pulmonary embolism (2 or more members with objectively proven events or first degree relative with hereditary thrombophilia), cancer (treatment ongoing, within the last 6 months or in palliative stages), post-partum and lower extremity paralysis.

Fig. 1 Algorithm for the clinical model to determine the pretest probability for pulmonary embolism

useful adjunct to imaging procedures and we determined a safe management strategy (Fig. 2). Assessment of clinical probability reveals that if there is discordance between the clinical assessment of pre-test probability and the lung scan finding, further diagnostic tests beyond leg vein ultrasound are necesary. In our management strategy patients in whom PE was excluded had a three month thromboembolic event rate of <0.6%. However, the algorithm was relatively complicated. We sought to simplify the clinical model and examine the potential safety and clinical utility of combining the new model with D-dimer results to enable exclusion of PE at the bedside in a large proportion of at risk patients.

Methods

Our original clinical model (Fig.1) was prospectively validated in consecutive inpatients and outpatients with suspected PE. The pretest clinical probability for PE using the clinical model was determined prior to diagnostic tests, as was the D-dimer result using the SimpliRED™ D-Dimer assay (5). V/Q scans were subsequently performed and interpreted by the nuclear medicine physicians in the respective hospitals without knowledge of other results and their interpretations were used to manage patients. After the V/Q scan bilateral compression ultrasound from the common femoral vein to the trifurcation of the calf veins was performed. Lack of vein compressibility was the sole

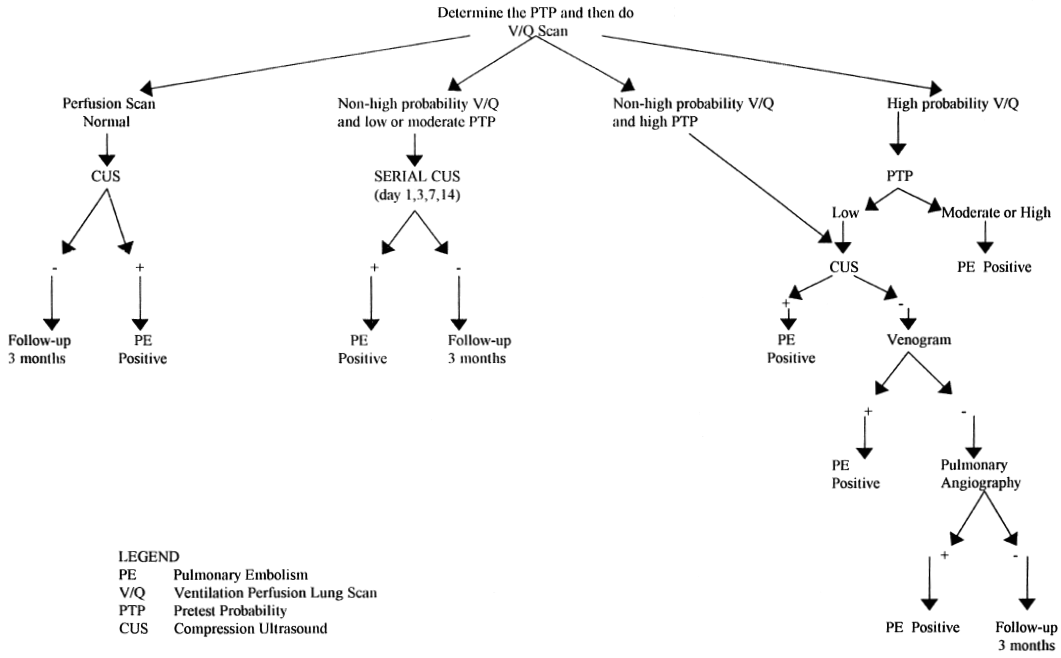

Fig. 2 Diagnostic strategy used in patients with suspected pulmonary embolism (PE)

Variable	MULTIPLE REGRESSION Coefficient	Odds Ratio	UNIVARIATE REGRESSION Odds Ratio	P-Value
Tachycardia (> 100/min)	1.1	3.0	-	0.001
Hemoptysis	0.87	2.4	2.0	0.01
S&S of DVT*	1.8	5.8	5.1	0.001
Cancer	0.81	2.3	1.7	0.002
Immobilization/surgery	0.92	2.5	2.4	0.001
Previous DVT/PE	0.87	2.4	2.8	0.001
Alternative Diagnosis	1.5	4.6	6.2	0.001
Syncope	-	-	2.1	0.02
Chest Pain	-	-	0.6	0.007
Resp Rate	-	-	-	0.02
AbN chest exam	-	-	1.6	0.001
AbN ECG	-	-	1.5	0.07
Dyspnea	-	-	1.4	0.09
Oxygen Sat'n	-	-	1.8	0.03
Diastolic Blood Pressure	-	-	-	0.01
Negative D-dimer **	-	-	0.2	0.001

Odds ratios not determined for continuous variables in the univariate analysis
* = signs and symptoms of DVT; ** = not run in the multiple regression analysis

Table 1 Factors significantly associated with pulmonary embolism in stepwise logistic regression analysis and univariate analysis

diagnostic criterion for a diagnosis of deep-vein thrombosis. The management strategy we used is outlined in Figure 2. D-dimer was not used in management. Patients were classified as pulmonary embolism-positive if one or more of the following occurred: abnormal pulmonary angiography; abnormal ultrasound or venography; high probability VQ scan plus moderate or high pretest probability; or venous thromboembolic event within the three month follow-up period. All other patients were classified as pulmonary embolism-negative.

Derivation of the New Simple Clinical Prediction Rule

We randomly selected 80% of our study population (the derivation set) and performed a univariate regression analysis to identify the variables in our original clinical model (40 variables) to include in a stepwise logistic regression. Variables with p values <0.15 were considered significant for inclusion in the stepwise regression analysis. Variables in the stepwise analysis with p values <0.05 were considered significant (6). For each significant variable a regression coefficient was obtained. These coefficients and the variables that were significant in the univariate and stepwise analysis are listed in Table 1. Points for the clinical prediction rule were assigned by doubling the value of the regression coefficients from the stepwise logistic regression and rounding to the nearest 0.5. We then created cut points to classify patients as having low, moderate and high probability of PE with rates similar to those obtained in our original study i.e. 3%, 28% and 78%, respectively. In addition, we sought to determine a score to be designated PE unlikely such that a negative D-dimer in these patients would result in a rate of PE close to 2.0%.

Validation of the Simple Clinical Prediction Rule

The final clinical prediction rule was then applied to the remaining 20% of our study population (the validation set). The proportion of patients with PE in each category, according to whether the D-dimer was positive or negative was also determined. True negative rates were determined for the relevant categories. Confidence limits were calculated from the binomial distribution.

Results

Patient Population

From the original study 1260 patients were used in the derivation of the new model but only 1211 had D-dimer results and enough clinical variables to include in the analysis broken-down by D-dimer results. 160 patients had previous deep-vein thrombosis or PE. Of the 1260 patients analyzed 354 (28%) had normal perfusion scans, 737 (58%) had nonhigh probability VQ scans and 169 (13%) had high probability VQ scans. Including events in the three month follow-up period four patients (1.1%) were PE-positive in the normal perfusion scan group, 64 patients were PE-positive in the nonhigh probability VQ scan group (8.0%), and 154 (91%) were PE-positive in the high probability VQ scan group. Overall 17.6% of patients had PE.

Seven variables were significantly related to PE and assigned scores for the final clinical prediction rule (see Fig. 3): 1) Clinical signs and symptoms of DVT (minimum of leg swelling and pain elicited upon palpation of the deep veins [3.0 points]; 2) No alternative diagnosis [3.0 points]; 3) Heart rate greater than 100 [1.5 points]; 4) Immobilisation or surgery in the previous four weeks [1.5 points]; 5) Previous DVT/PE [1.5 points]; 6) Hemoptysis [1.0 points]; 7) Malignancy (on treatment, treated in the last six months or palliative) [1.0 points]. Some of the more common symptoms such as dyspnea, chest pain and high respiratory rate, that were significant in the univariate analysis, did not reach significance in the stepwise logistic regression analysis.

If a patient had <2 points the probability of PE was low with 3.6% having PE in the derivation set and 2.0% in the validation set. A score of 2.0 to 6.0 was moderate probability with 20.5% having PE in the derivation set and 18.8% in the validation set; a score of >6.0 was high probability for PE with 66.7% in the derivation set and 50% in the validation set. These results, the 95% confidence intervals and the PE rates according to D-dimer results are in Tables 2 and 3.

We designated a score of ≤4.0 as PE unlikely and this gave a PE rate of 7.8% in the derivation set and 5.1% in the validation set. A score >4.0 gave a PE rate of 40.7% in the derivation set and 39.1% in the validation set and is designated PE likely (see Table 4 and 5). If the D-dimer result was negative the rate of PE in patients designated PE

- Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins [3.0 points]
- An alternative diagnosis is less likely than PE [3.0 points]
- Heart rate greater than 100 [1.5 points]
- Immobilization or surgery in the previous four weeks [1.5 points]
- Previous DVT/PE [1.5 points]
- Hemoptysis [1.0 points]
- Malignancy (on treatment, treated in the last six months or palliative) [1.0 points]

Fig. 3 Variables and to determine patient score and points assigned (in [])

Table 2 Pulmonary embolism rates in the derivation group using low, moderate and high pretest probability categories

Score by Model	PE rate with – DD	PE rate with + DD	PE rate overall
<2 (low)	1.5% [4/276] (0.4% - 3.7%)	8.6 % [10/116] (4.2% - 15.3%)	3.6% [14/392] (2.0% – 5.9%)
2-6 (moderate)	7.6% [21/278] (4.7% – 11.3%)	36.1% [84/233] (29.9% – 42.2%)	20.5% [105/511] (17.0% – 24.1%)
>6 (high)	20% [3/15] (4.3% – 48.1%)	79.6% [43/54] (66.5% – 89.4%)	66.7% [46/69] (54.3% – 77.6%)

( ) = 95% confidence interval: DD = D-dimer

Table 3 Pulmonary embolism rates in the validation group using low, moderate and high pretest probability

Score by Model	PE rate with – DD	PE rate with + DD	PE rate overall
<2 (low)	2.7% [2/73] (0.3% – 9.0%)	0% [0/26] (0% – 13.2%)	2.0% [2/99] (0.2% – 7.1%)
2–6 (moderate)	2.9% [2/69] (0.4% – 10%)	37.3% [22/59] (25% – 50.9%)	18.8% [24/128] (12.4% – 26.6%)
>6 (high)	20% [1/5] (5.1% – 71.6%)	60% [9/15] (32.3%– 83.7%)	50% [10/20] (27.2% – 72.8%)

( ) = 95% confidence interval: DD = D-dimer

Table 4 Pulmonary embolism rates in the derivation group using PE likely and unlikely categories

Score by Model	PE rate with – DD	PE rate with + DD	PE rate overall
≤ 4	2.2% [10/448] (1% - 4%)	18.3 % [44/241] (13.4% – 23.1%)	7.8% [54/689] (5.9% – 10.1%)
>4	16.1% [18/112] (9.8% – 24.2%)	57.7% [94/163] (49.7% – 65.4%)	40.7% [112/275] (34.9% – 46.5%)

( ) = 95% confidence interval: DD = D-dimer

Table 5 Pulmonary embolism rates in the validation group using PE likely and unlikely categories

Score by Model	PE rate with – DD	PE rate with + DD	PE rate overall
≤ 4	1.7% [2/118] (0.2% – 6.0%)	11.7% [7/6] (4.8% – 22.6%)	5.1% [9/17] (2.3% – 9.4%)
>4	10.3% [3/29] (2.2%– 27.4%)	60% [24/40] (43.3% – 75.1%)	39.1% [27/69] (27.6% – 51.6%)

( ) = 95% confidence interval: DD = D-dimer

unlikely was 2.2% (95% CI = 1.0% to 4.0%) in the derivation set and 1.7% in the validation set (95% CI = 0.2% to 6.0%). These results occurred in 45% and 46% of the total patient population, respectively. These PE rates are not significantly different than the rates in patients categorised as low probability [1.5% (95% CI = 0.4% to 3.7%) and 2.7% (95% CI = 0.3% to 9.6%)] in the derivation and validation groups, with p = 0.46 and 0.93, respectively. Patients without D-dimer results were not included in the above tables since the rates of PE were similar to those obtained in patients with D-dimer results and it was the combined results we were interested in.

When the D-Dimer results were combined with clinical probability only 1.5% and 2.7% of patients with a negative D-dimer and a score <2.0 had PE in the derivation and validation sets and this result occurred in 27% of patients. In patients designated PE unlikely with scores ≤4.0 only 2.2% of patients with a negative d-dimer had PE in the derivation set and only 1.7% in the validation set. This represented 46% of all patients with suspected PE, i.e. true negative rate of 46%.

Discussion

We have shown that a new simple clinical prediction rule, derived from our previously published clinical model management study, can accurately categorise the probability of PE when performed prior to diagnostic tests and independent of D-dimer results. The revised model when combined with the SimpliRED D-Dimer assay may be able to safely exclude PE without further testing in a large proportion of patients with suspected PE. We created two scoring systems. One system divides patients into low, moderate and high probability and could be easily applied as in our previous published strategy. However, the second scoring system may be easier to use since it classifies patients as PE unlikely or PE likely, and it may have more utility since almost 50% of patients with suspected PE have a negative SimpliRED D-dimer and are PE unlikely. These patients with a negative SimpliRED D-dimer who are PE unlikely had PE in only 2.2% (95% CI = 1.0% to 4.0%) in the derivation set and 1.7% (95% CI = 0.2% to 6.0%) of patients of cases in the validation group. This rate is similar to the PE rate in patients with normal VQ scans and normal angiograms (7) but the upper limit of the 95% confidence interval is 6% in the validation set.

Perrier et al have demonstrated the utility of D-dimer testing in patients presenting to the emergency department with suspected PE (8). Using a D-dimer test with higher sensitivity than the SimpliRED 36% of the patients had PE excluded on the basis of a normal D-dimer. However, the assay they utilized is considerably more expensive than the SimpliRED D-dimer. The use of serial ultrasound testing in our original study, from which we derived the new model, has limitations also. Only 10% of all patients with suspected PE had an abnormal ultrasound result and serial conversions occurred in only 2% of patients in whom it was performed. We performed confirmatory venography in the low and moderate probability patients with abnormal ultrasound results in our original study and recommend venography is considered especially in patients with a previous history of DVT. Depending on local costs for ultrasound and angiography the serial ultrasound approach, although very safe, may not save money.

We undertook this analysis because the diagnosis and exclusion of PE remains problematic. The diagnostic gold standard, pulmonary angiography, is an invasive and expensive procedure, with limited availability and potentially serious complications (7). Ventilation-perfusion scans provide a definitive diagnosis in less than 40% of cases (2, 9). These limitations may be the reason many clinicians often do not pursue definitive objective tests in patients with suspected PE (10-12). Our study enables physicians to predict which patients do not need further testing. The combination of the clinical prediction rule score of four or less and a negative SimpliRED D-Dimer assay had a true negative rate of 46% in our study. The true negative rate reflects the proportion of patients suspected of PE that are safely excluded. We

have already demonstrated that when clinical probability and the VQ scan are discordant further testing is necessary to diagnose PE. The models we present should also enable such a strategy. For example if the probability is low or unlikely and the VQ scan is high probability than confirmatory tests are needed. If the probability is high or likely and the VQ scan is nonhigh than confirmatory tests are also necessary. New noninvasive imaging tools for the diagnosis of PE have been examined, including spiral computerized tomographic imaging of the thorax and magnetic resonance imaging (13, 14). However, these tools are expensive, not widely available in many countries and most importantly their use has not been validated in large studies. Indeed in the only management study to date using spiral CT over 5% of patients felt to have PE excluded by CT had PE in the three-month follow-up (15). Prior to adopting our clinical prediction rule into practice several points of caution must be considered. Firstly, clinical decision rules often do not perform as well in future validation studies as in their derivation studies (16). This often results from differences in surveillance strategies and definitions of outcome between the original studies and the validation studies. Our study design uses a random part of a large study population as a validation group so this concern may not be warranted. Secondly, our clinical model is very dependent on a careful consideration of an alternative diagnosis. It is probably important that clinicians know the exact rule as they evaluate patients and complete the model checklist because consideration of alternative diagnosis and the way it changes the final probability, may have altered the way this question was answered in the original study. The inter-rater reliability of the clinical prediction rule must be tested further before it can be applied by a wide variety of clinicians. Third, the model is not a screening tool but must be applied in patients in whom pulmonary is a diagnostic consideration. Fourth, the D-dimer as part of the strategy has not been tested prospectively and its utility combined with clinical model must be confirmed. Finally, it is important to note that the higher the pretest probability for PE the less useful a negative D-dimer becomes. Indeed if the pretest probability is high or if we use the PE likely designation then PE will still be present in 20% and at least 10% of patients, respectively.

Application of our new PE unlikely and PE likely prediction rule and its use in the strategy described above should result in a safe, effective and largely noninvasive means to manage patients with suspected PE. Our novel bedside technique to exclude PE must be validated in other unselected patient populations prior to adoption into clinical practice. If validated and adopted, the application of our bedside method has the potential to save health care resources, avoid inconveniencing patients and limit risks to patients by averting unnecessary presumptive treatment and further diagnostic testing for suspected PE.

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