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REGULAR ARTICLE

Excluding pulmonary embolism at the bedside with low pre-test probability and D-dimer: Safety and clinical utility of 4 methods to assign pre-test probability

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Abstract

Introduction: Less than 35% of patients suspected of having pulmonary embolism (PE) actually have PE. Safe bedside methods to exclude PE could save scarce health care resources if they exclude large proportions of patients with suspected PE and are widely applicable. Non-Elisa D-dimer in combination with pre-test probability of suspected PE can safely exclude PE at the bedside. Pre-test probability can be assigned by gestalt or by using clinical models (Wells, Wicki, Rodger).

Materials and methods: We combined two databases from studies of patients with suspected PE and retrospectively compared the diagnostic test characteristics of the different methods of assigning pre-test probability.

Results: 535 patients were studied. PE was confirmed in 20.8% of study patients. Two clinical predictive models (Rodger and Wells) and overall diagnostic impression have similar sensitivities ranging from 96% (95% confidence interval (CI) 89–99%) to 99% (93–100%). Wicki's model has a sensitivity of 89% (77–96%). The Wells' model with a cutoff of less than 2 points in association with semi-quantitative D-dimer has a specificity of 11% (CI 7–15%). The specificities for the other clinical predictive model are ranging from 21% (17–25%) to 49% (CI 42–55%).

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Conclusion: Semi-quantitative D-dimer must be combined with safe clinical probability assessment to safely exclude PE in a significant proportion of patients. Wicki's model in association with semi-quantitative D-dimer has the lowest sensitivity and should be used carefully to exclude PE at the bedside. The Wells' model with a cutoff of less than 2 points when combined with semi-quantitative D-dimer excluded very few patients and therefore limits its clinical utility.

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Introduction

Pulmonary embolism (PE) is a common disease with an estimated incidence of 23–69 per 100,000 person per year [1–3]. Untreated PE has a high mortality and accounts for 5–10% of all in hospital deaths [3–5]. The risk of death is reduced significantly with anticoagulation [6].

The diagnosis of PE remains one of the most difficult problems confronting physicians. PE is considered in the differential diagnosis of many clinical presentations and in a wide variety of clinical settings. However, less than 35% of patients suspected of having PE actually have PE [7–9]. Safe bedside methods to exclude PE could save scarce health care resources if they exclude large propor-

tions of patients with suspected PE (i.e., have high true negative proportion) and are widely applicable.

Clinical signs and symptoms, arterial blood gas and ECG are not sensitive nor specific when used in isolation for the diagnosis of PE [10–15]. Clinical prediction models have combined symptoms, signs and laboratory investigations to categorize patient's probability of PE. Pre-test probability and semi-quantitative D-dimer, when used in combination, have been previously shown to safely exclude PE at the bedside (i.e., have high negative predictive values) [16–18]. Pre-test probability can be assigned by overall diagnostic impression (clinical gestalt) or by using clinical prediction models. Three different prediction models have been proposed [19–21].

Table 1 Prediction models for suspected pulmonary embolism

Wicki's criteria	Points	Wells' criteria	Points	Rodger's model
Recent surgery	3.0	Clinical signs of deep vein thrombosis	3.0	Previous venous thromboembolic event
<i>Age</i>				
60–79 years old	1.0	Recent surgery or immobilization	1.5	Recent surgery
≥80 years old	2.0			
Heart rate >100 beats per minutes	1.0	Heart rate >100 beats per minutes	1.5	Leg pain or Leg swelling
<i>Chest radiography</i>				
Atelectasis	1.0	Previous history of pulmonary embolism or deep vein thrombosis	1.5	Heart rate over 110 beats per minute
Elevated hemidiaphragm	1.0			
<i>PaO₂</i>				
<48.7 mm Hg (6.5 kPa)	4.0	Hemoptysis	1.0	Positive D-dimer
4.8–5.19 mm Hg (6.5–7.99 kPa)	3.0	Malignancy	1.0	
60–71.2 mm Hg (8–9.49 kPa)	1.0	Alternative diagnosis less likely than pulmonary embolism	3.0	
71.3–82.4 mm Hg (9.5–10.99 kPa)	1.0			
<i>PaCO₂</i>				
<36 mm Hg (4.8 kPa)	2.0			
36–38.9 mm Hg (4.8–5.2 kPa)				
<i>Clinical probability</i>				
Low	0–4	Unlikely	≤4	Absence of all of the five variables—PE unlikely
Intermediate	5–8	Likely	>4	
High	≥9			

The Rodger's clinical prediction model excludes PE if all of the five following clinical variables are absent: positive semi-quantitative D-dimer, heart rate >110 beats per minute, leg pain or swelling, previous venous thromboembolic events and recent surgery. The negative predictive value of the Rodger's prediction model was 97.8% (95% CI 96.0–99.0%) in the original derivation and validation sets [19].

The other two models stratify patients into categories of an increasing risk of PE. The Wells' model uses seven variables derived from a mixed population of inpatients and outpatients presenting with suspected PE (Table 1) [20]. One of the variables is a subjective judgment of whether an alternative diagnosis is as or less likely than PE. More recently, Wicki's model based on entirely objective variables has been developed and validated (Table 1) [21]. However, the Wicki's model requires an arterial blood gas on room air and was only validated in patient presenting in the emergency department. Both prediction models seem to have similar predictive accuracy for patients in an emergency department [22], but they have never been compared in a mixed sample of inpatients and outpatients.

We sought to compare the pre-test probabilities assigned by three different clinical models (Wicki, Wells and Rodger) and clinical gestalt in combination to the semi-quantitative D-dimer results to safely exclude PE at the bedside in a mixed population of patients (inpatients and outpatients).

Methods

Databases

We combined two databases from studies of patients with suspected PE and retrospectively compared the diagnostic test characteristics of the different methods of assigning pre-test probability.

The first database includes consecutive inpatients and outpatients at the Ottawa Hospital (General Campus) referred to our nuclear medicine department for suspected PE (from January 1996 to August 1998). The second database includes consecutive patients with suspected PE that were referred to our nuclear medicine departments (General Campus (October 1998 to February 2002) and Civic Campus (February 2000 to July 2001)) for a ventilation/perfusion scan (V/Q scan). Patients were ineligible if they (1) were less than 18 years of age, (2) were unable to give informed consent, (3) had an expected survival <3 months, (4) were

ventilated, (5) were known to have chronic PE or PE diagnosed in the last 3 months, (6) were already on full dose anticoagulants, (7) had venal caval filter.

Clinical evaluation and diagnostic tests

Clinical information was collected from all study participants using standardized forms. The referring physician completed a standardized patient's assessment including all the variables of the Wells' clinical model and additional clinical parameters. Physicians also recorded the variables necessary for the Wicki's clinical model (Table 1), which was calculated retrospectively. Physicians were asked to indicate their index of clinical suspicion of PE to establish an overall diagnostic impression (clinical gestalt). After completing the form, physicians were asked to indicate their overall diagnostic impression (clinical gestalt) of PE as either low (<20%), moderate (20–80%) or high (>80%).

Semi-quantitative D-dimer analysis was performed with the SimpliRED whole-blood agglutination D-dimer test (AGEN Biomedical, Ltd., Brisbane, Australia) or the Accuclot (Sigma Diagnostics, St. Louis, MO, USA) latex agglutination D-dimer if the SimpliRED was not available ($n=51$). The sensitivity of these assays is, respectively, 90% and 80% [23].

All patients underwent a ventilation/perfusion scan (V/Q scan). The V/Q scans were independently interpreted utilizing the PLOPED criteria. All patients with an intermediate V/Q scan were recommended to proceed to pulmonary angiography or spiral CT but this decision was left to the patient's treating physician.

In our study, pulmonary embolism was defined by (1) patients with a high/intermediate pre-test

Table 2 Characteristic of the study sample ($N=535$)

Characteristic	Number (%) or median (range)
Age	52 (17–96)
Female sex	350 (65.4)
Confirmed pulmonary embolism	95 (17.8)
Clinical presentation	
Dyspnea	365 (68.2)
Hemoptysis	28 (5.2)
Signs and symptoms of DVT	169 (31.7)
Risk factors	
Recent immobilization or surgery	176 (32.9)
Malignancy	105 (19.3)
Tachycardia	184 (34.4)
Previous history of PE or DVT	79 (14.8)
Chest Radiography ($N=429$)	
Elevated of hemidiaphragm	10 (2.3)
Plate-like atelectasis	62 (14.5)
Elevated hemidiaphragm + atelectasis	12 (2.8)

Table 3 Diagnostic criteria to define pulmonary embolism in the study sample ($n=95$)

Diagnostic criteria	Number (%)
High-probability lung scan	39 (41)
Pulmonary embolism on pulmonary angiogram	21 (22)
Deep vein thrombosis on lower limb ultrasonography	18 (19)
Pulmonary embolism on helical CT scan	7 (7)
Venous thromboembolism during 3-month follow-up	10 (11)

probability (Wells' model >4) + high probability V/Q scan; (2) positive pulmonary angiogram; (3) spiral CT demonstrating intraluminal filling defect in a vessel larger than a segmental artery; or (4) proximal DVT on venous compression ultrasonography. Pulmonary embolism was excluded by (1) negative semi-quantitative D-dimer and Wells' model score less than or equal to 4.0 points and absence of venous thrombotic events on a 3-month follow-up; (2) normal or near normal V/Q scan and absence of venous thrombotic events on a 3-month follow-up; (3) patients with a low pre-test probability who had a low probability V/Q scan and absence of venous thrombotic events on a 3-month follow-up; or (4) patients with low probability scans with a negative leg ultrasound at presentation and absence of venous thrombotic events on a 3-month follow-up.

Follow up

Anticoagulant therapy was withheld in-patients in whom a diagnosis a PE was excluded. After 3 months, patients were followed up for development of venous thromboembolic events at a return appointment or by telephone contact.

Statistical analysis

Sensitivity, specificity and positive and negative predictive values and 95% confidence intervals (CI) were calculated. The true positive proportion

corresponds to the proportion of patients correctly diagnosed with PE out of the total number of patients tested whereas the true negative proportion corresponds to the proportion of patients correctly excluded out of the total number of patients tested.

Results

Five hundred and thirty five patients were evaluated. The study participant's characteristics are displayed in [Table 2](#). The median age was 52 years old (range 17–96) and 65% were female (see [Table 2](#)). Most patients presented with dyspnea and signs and symptoms of DVT. The most common clinical finding was tachycardia.

Pulmonary embolism was diagnosed in 95 patients (18%) according to our study criteria (see [Table 3](#)). Of the 95 confirmed PE, most were identified ($n=39$) with a high probability V/Q scan (see [Table 3](#)). Among the patients initially classified as not having a PE, ten were confirmed over 3-month follow-up (2 high probability V/Q scans, 4 new proximal DVTs on ultrasound, 2 positive pulmonary angiograms and 2 positive spiral CTs). None of the 10 patients who had a VTE diagnosed during the 3-month follow-up had new exposures that could have placed them at increased risk of VTE.

Two of the clinical predictive models (Wells, Roger) and clinical gestalt classified similar proportions of patients into the low and intermediate/high (non-low) clinical probability categories ([Table 4](#)). Wicki's model classified a majority of patients into the low probability category. The frequency of PE in the low probability category was higher for the Wicki's model (42%) compared to the other models.

[Table 5](#) compares the sensitivities, specificities, negative predictive values and likelihood ratios of the four clinical models in combination with semi-quantitative D-dimer. The Wells' model was

Table 4 Proportion of patients and frequency of pulmonary embolism in the four clinical probability categories according to each clinical prediction model

Clinical probability	Wicki's model	Well's model (≤ 2)	Well's model (≤ 4)	Rodger's model	Gestalt
	($n=280$)	($n=413$)	($n=413$)	($n=399$)	($n=432$)
Pre-test probability	n (%)	n (%)	n (%)	n (%)	n (%)
Low	194 (69.3)	69 (16.7)	150 (36.3)	95 (23.8)	146 (33.8)
Inter/High	86 (30.7)	344 (83.3)	263 (63.7)	304 (76.2)	286 (66.2)
Frequency of PE in pre-test probability category	n (%)	n (%)	n (%)	n (%)	n (%)
Low	21 (42.0)	4 (5.3)	13 (17.1)	3 (3.7)	11 (14.1)
Inter/High	29 (58.0)	72 (94.7)	63 (82.9)	76 (96.2)	67 (85.9)

Table 5 Safety and clinical utility of D-dimer and pre-test probability assessment (using 4 different methods) in excluding pulmonary embolism at the bedside

	D-dimer alone	Wicki (≤ 4) and D-dimer	Wells (≤ 2) and D-dimer	Wells (≤ 4) and D-dimer	Rodger	Gestalt ($< 20\%$) and D-dimer
<i>n</i>	483	264	403	403	399	415
Sensitivity (%, 95% CI)	83.9 (75–91)	89.1 (77–96)	98.7 (93–100)	96.0 (89–99)	96.2 (89–99)	97.4 (91–100)
Specificity (%, 95% CI)	52.1 (47–57)	48.6 (42–55)	11.0 (8–15)	23.5 (19–28)	28.8 (24–34)	20.7 (17–25)
NPV (%, 95% CI)	93.1 (89–96)	95.5 (90–100)	97.3 (86–100)	96.3 (89–99)	96.8 (91–99)	97.2 (90–100)
LR+ (%, 95% CI)	1.75 (1.5–2.0)	1.74 (1.5–2.0)	1.11 (1.1–1.2)	1.26 (1.2–1.4)	1.54 (1.3–1.9)	1.23 (1.2–1.3)
LR– (%, 95% CI)	0.31 (0.2–0.5)	0.22 (0.1–0.5)	0.12 (0.0–0.9)	0.17 (0.1–0.5)	0.31 (0.1–0.9)	0.13 (0.0–0.5)
True negative (%, 95% CI)	42.0 (38–47)	40.2 (34–46)	8.9 (6–12)	19.1 (15–23)	23.1 (19–28)	16.9 (13–21)

NPV: negative predictive value; LR+: positive likelihood ratio; LR–: negative likelihood ratio.

studied using two different definitions of low probability pre-test probability for PE (2 vs. 4 points). Two clinical predictive models (Rodger and Wells) and overall diagnostic impression have similar sensitivities ranging from 96% (89–99%) to 99% (93–100%). Wicki's model has the lowest sensitivity (89%). The four clinical predictive models in combination with semi-quantitative D-dimer have similar negative predictive values, ranging from 96% to 97%. Similarly the positive likelihood ratios ranged from 1.1 to 1.8 and the negative likelihood ratios ranged from 0.1 to 0.3. The Wells' model, using a low pre-test probability defined as being less than 2 points, has the lowest true negative rate (8.9%).

Discussion

Previous studies have compared different clinical predictive models in the assessment of patients with suspected PE. Wicki's and Wells' models appeared to have similar predictive accuracy for suspected PE in emergency department patients [22]. We provide the safety of these clinical models combined with semi-quantitative D-dimer to exclude PE in a mixed population of inpatients and outpatients.

We found that two clinical predictive models (Rodger and Wells) and overall diagnostic impression (clinical gestalt) in combination with semi-quantitative D-dimer performed equally well in a mixed sample of inpatients and outpatients. Semi-quantitative D-dimer alone has a negative predictive value of 93.1% and therefore cannot be safely used to exclude PE. The Wells' model with a cutoff of less than 2 points when combined with semi-

quantitative D-dimer excluded very few patients (low true negative rate) and therefore limits its clinical utility.

The prediction models classified the patients differently. The clinical probability changed markedly from low to high in a large number of patients depending on the prediction rule used. In our population, Wicki's model classified a majority of patients into the low probability category, missing 42% of the PE in the study population. These results suggest that the Wicki's model should be used carefully when assessing pre-test probability of PE in a mixed population of inpatients and outpatients. However, Wicki's model was applied retrospectively, and in a large proportion of patients, it could not be applied hence no firm conclusions can be drawn from our study. Randomised or prospective comparisons of the clinical models would be required to definitively determine their comparative safety and clinical utility.

We acknowledge some limitations to our study. First, missing data in 103 patients (24% of our total sample) resulted in incomplete datasets to calculate the models. This accounts for the different numbers of patients for which the clinical models could be calculated. Second, as mentioned previously, Wicki's model was calculated retrospectively which eliminates clinician's ability to 'gamble' in assigning points. A sizeable proportion of patients could not be included in the analysis (possible selection bias). Many patients did not undergo arterial blood gas sampling or were receiving supplemental oxygen. Third, the overall diagnostic impression (clinical gestalt) determination was performed after completing a data form that included variables in the clinical prediction rules. These prompts may have influenced the way physicians categorize PE. Overall diagnostic

impression (clinical gestalt) without a data collection form may be less useful. Fourth, a potential bias is introduced by using the Wells clinical model in outcome determination in the PE negative group, however, the combination of use of the Wells clinical model and a negative D-dimer to exclude PE has been validated in a large number of studies [8,16,20,24]. Finally, another potential limitation of our study is that some PE patients with a previous VTE may have been misclassified as having acute PE due to residual defects from previous VTE as not all patients in our study had baseline imaging after their previous VTE.

In conclusion, semi-quantitative D-dimer must be combined with safe clinical probability assessment to safely exclude PE in a significant proportion of patients. Further work is required to identify methods to assign pre-test probability that are safe, widely applicable, reproducible, and that exclude a large proportion of patients with suspected PE (i.e., are clinically useful).

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