Does this patient have pulmonary embolism?

Does This Patient Have Pulmonary Embolism?

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Context Experienced clinicians' gestalt is useful in estimating the pretest probability for pulmonary embolism and is complementary to diagnostic testing, such as lung scanning. However, it is unclear whether recently developed clinical prediction rules, using explicit features of clinical examination, are comparable with clinicians' gestalt. If so, clinical prediction rules would be powerful tools because they could be used by less-experienced health care professionals to simplify the diagnosis of pulmonary embolism. Recent studies have shown that the combination of a low pretest probability (using a clinical prediction rule) and a normal result of a D-dimer test reliably excludes pulmonary embolism without the need for further testing.

Objective To evaluate and demonstrate the accuracy of pretest probability assessment for pulmonary embolism using clinical gestalt vs clinical prediction rules.

Data Sources The MEDLINE database was searched for relevant articles published between 1966 and March 2003. Bibliographies of pertinent articles also were scanned for suitable articles.

Study Selection To be included in the analysis, studies were required to have consecutive, unselected patients enrolled; participating physicians in the studies, blinded to the results of diagnostic testing, had to estimate pretest probability of pulmonary embolism; and validated diagnostic methods had to be used to confirm or exclude pulmonary embolism.

Data Extraction Three reviewers independently scanned titles and abstracts for inclusion of studies. An initial MEDLINE search identified 1709 studies, of which 16 involving 8306 patients were included in the final analysis.

Data Synthesis A clinical gestalt strategy was used in 7 studies, and in the low, moderate, and high pretest categories, the rates of pulmonary embolism ranged from 8% to 19%, 26% to 47%, and 46% to 91%, respectively. Clinical prediction rules were used in 10 studies, and 3% to 28%, 16% to 46%, and 38% to 98% in the low, moderate, and high pretest probability groups, respectively, had pulmonary embolism.

Conclusions The clinical gestalt of experienced clinicians and the clinical prediction rules used by physicians of varying experience have shown similar accuracy in discriminating among patients who have a low, moderate, or high pretest probability of pulmonary embolism. We advocate the use of a clinical prediction rule because it has shown to be accurate and can be used by less-experienced clinicians.

JAMA. 2003;290:2849-2858 www.jama.com

CLINICAL SCENARIOS

Do These Patients Have Pulmonary Embolism?

Case 1. A 28-year-old woman with recently diagnosed systemic lupus erythematosus presents with 2 days of pleuritic chest pain and breathlessness. She has no leg symptoms and no personal or family history of venous thromboembolism. She is taking a second-generation oral contraceptive pill. Examination reveals a finding of mild tachypnea (20/min) and minimal tenderness over the right lateral chest wall. Examination finding of the legs is normal, and a red blood cell agglutination D-dimer test shows a negative result.

Case 2. A 78-year-old man presents with 3 days of worsening pleuritic chest pain and breathlessness. He was discharged from the hospital 2 weeks earlier after a 14-day admission with acute cholecystitis. Surgery was not performed. His past history includes 2 episodes of idiopathic, right-leg deep vein thrombosis. He has controlled hyper-

See also Patient Page.

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Table 1. Risk Factors for Venous Thromboembolism

Risk Factors[8-10]	Odds Ratio (95% Confidence Interval)
Surgery	21 (9.4-49.9)
Trauma	12.7 (4.1-39.7)
Immobility (hospital or nursing home)	8.0 (4.5-14.2)
Cancer	
With chemotherapy	6.5 (2.1-20.2)
Without chemotherapy	4.1 (1.9-8.5)
Neurological disease with lower extremity paresis	3.0 (1.3-7.4)
Oral contraceptive pill[10]	3.0 (2.6-3.4)*
Hormone therapy[9]	2.7 (1.4-5.0)†

*Relative risk from case-control studies.
†Relative hazard.

tension and previous left ventricular failure. The examination reveals tachypnea (20/min) but findings are otherwise normal. Chest radiograph and electrocardiogram findings are normal, and a red blood cell agglutination D-dimer test shows a negative result.

Background

Pulmonary embolism occurs in 1 to 2 persons per 1000 annually in the United States.[1,2] If untreated, it is associated with a high mortality rate, but anticoagulant therapy is highly effective in reducing mortality.[3,4] The diagnosis of pulmonary embolism is challenging because of the wide spectrum of symptoms and signs, and most patients with suggestive symptoms do not have the disease.[5] Typically, patients with proven pulmonary embolism present with dyspnea or acute chest pain and less frequently with cough, hemoptysis, or fainting.[6,7] These findings often occur in association with well-defined risk factors, such as lower limb surgery or immobility (TABLE 1[8-10]). Frequent findings on examination include tachycardia, tachypnea, and an accentuated pulmonary component of the second heart sound (S_2). Other features such as jugular venous distention, S_3 or S_4 (third or fourth heart sound), an audible systolic murmur at the left sternal edge, as well as hepatomegaly infrequently are present and may reflect right ventricular compromise.

Results of arterial blood gas analysis commonly show hypoxia and hypocapnia. Chest radiography results are nonspecific, and common findings include an elevated hemidiaphragm, unilateral pleural effusion, and platelike atelectasis; radiography is useful because it will sometimes provide an alternative diagnosis (eg, pneumothorax). Similarly, electrocardiography is nonspecific and may show T-wave inversion across precordial leads, the $S_1Q_3/S_1Q_3T_3$ pattern, or a right bundle-branch block.[6,7] Thus, although the above findings are seen in patients with objectively diagnosed pulmonary embolism, they also are common in patients without pulmonary embolism and lack specificity when considered individually. On the other hand, pulmonary embolism is uncommon in the absence of acute or worsening breathlessness or chest pain.[6,7] Because anticoagulant therapy reduces mortality from pulmonary embolism, the threshold for considering the diagnosis should be low.[3] We believe that pulmonary embolism at least should be considered whenever a patient presents with any of the above symptoms or symptom complexes, particularly in the presence of known risk factors or when there is no clear alternative.

Prior to the development of accurate diagnostic testing, the diagnosis of pulmonary embolism largely was based on clinical history and examination findings. Unfortunately, the clinical evaluation alone proved inaccurate in diagnosing and excluding pulmonary embolism[7,11-13] and was virtually abandoned in the evaluation of patients with suspected pulmonary embolism. Lung scanning became routine in the 1980s and was shown to be clinically useful.[5] However, lung scanning proved to be less than optimal as more than half of patients with suspected pulmonary embolism had nondiagnostic lung scans and the prevalence of pulmonary embolism in such patients was approximately 25%.[5]

Once clinicians raise the possibility of pulmonary embolism, they can further define the clinical likelihood of pulmonary embolism into a pretest probability. Rather than definitively diagnosing or excluding pulmonary embolism, pretest probability assessment categorizes patients into subgroups, such as low, intermediate, and high, with ascending order of prevalences of pulmonary embolism. The potential for clinical assessment of the pretest probability to significantly influence the posttest probability of pulmonary embolism was demonstrated in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study[5] and was confirmed in a later study by Wells et al.[14] When the participating clinicians in the PIOPED study used clinical judgment to categorize patients into low, moderate, or high pretest probability subgroups for pulmonary embolism, a moderate correlation with disease prevalence was found (9%, 30%, and 68%, respectively). In addition, in patients with a low pretest probability and a high-probability lung scan, only about 50% had pulmonary embolism, whereas in those with a moderate or high pretest probability and a high-probability lung scan, more than 90% had pulmonary embolism.[5]

Based on the history and physical examination findings, clinical prediction rules that assess pretest probability for deep vein thrombosis, a closely related condition to pulmonary embolism, have been developed and shown to simplify the diagnosis.[15,16] For example, the safety of withholding anticoagulant therapy, without additional testing, has been demonstrated in patients with a low[17] or low/moderate[18] pretest probability for deep vein thrombosis and a negative D-dimer test result. D-dimer is a plasmin-derived fibrin degradation product that is highly sensitive for deep vein thrombosis and pulmonary embolism.[19] Elevated levels of D-dimer are seen in most patients with pulmonary embolism and deep vein thrombosis, but because the available assays have moderate specificity (30%-75%), they also show elevated results in patients with nonthrombotic disorders.[19] We postulated that assessment of pretest probability of pulmonary embolism also might be useful in simplifying the diagnosis of this condition.

The objectives of this article are 2-fold: (1) to determine whether, based on their clinical impression after collecting rou-

tine data (the clinical gestalt), experienced clinicians can accurately group patients into strata distinguished by an increasing probability of pulmonary embolism and (2) to determine whether clinical prediction rules are useful in determining the pretest probability for pulmonary embolism. In the first instance, the examiner estimates the probability of pulmonary embolism based on his/her clinical gestalt. Each examiner values the information differently in quantifying an overall impression. On the other hand, clinical prediction rules rely on a prespecified list of data items, each of which is assigned a score.

METHODS

Data Sources

We searched the MEDLINE electronic database for English-language articles published between 1966 and March 2003 using the following Medical Subject Headings: *pulmonary embolism*, *prospective studies*, *EXP* (explode) *sensitivity and specificity*, *EXP probability* and *EXP models*, and *statistical*. We identified studies in which clinical assessment of patients with suspected pulmonary embolism was performed routinely. The reference lists of identified articles also were examined for additional studies missed by the MEDLINE search.

Study Selection and Data Extraction

Three independent reviewers (S.D.C., J.W.E., J.A.) identified potentially eligible articles and a senior reviewer (J.S.G.) resolved disagreements. To be eligible, studies had to include the following: (1) an estimate of the pretest probability of pulmonary embolism using the clinical gestalt or clinical prediction rule; (2) performance of the clinical assessment blind to the results of diagnostic testing; and (3) comparison of these assessments with validated methods of confirming or refuting the diagnosis of pulmonary embolism (BOX).[20-24] Additional eligibility criteria were applied to studies in which a clinical prediction rule was being derived.[25] These studies had to systematically collect all relevant clinical data from consecutive patients and have a sufficient number of patients with confirmed pulmonary embolism (N>50) to ensure accuracy of the derived rule. For each eligible study, where possible, the pretest probability categories, corresponding disease prevalences, and likelihood ratios (LRs) (and corresponding 95% confidence intervals [CIs]) are summarized.

The clinical gestalt must have been determined based on information available from the patient's history and findings from physical examination and routine investigations (eg, chest radiograph, electrocardiogram, and arterial blood gas analysis) without predetermined elements or a standardized score, and most importantly, it must have been assessed before other diagnostic testing. A clinical prediction rule used a mathematically derived formula that combined the individual contribution of each component of the history, physical examination findings, and routine laboratory results before diagnostic testing.

Data Analysis

Likelihood ratios and their 95% CIs were calculated using the program Metstat (version 1)[26] and Confidence Interval Analysis (version 1.1).[27] Summary LRs were derived using random effects measures that provide conservative CIs around the estimates.[28,29] Decisions to include or exclude studies were made before the analysis based on the reported methods, rather than their actual results. We determined the summary LRs to get a general sense of whether structured models performed as well as the clinical gestalt. Furthermore, we only pooled data from studies that derived a structured model and specifically did not include data from subsequent validation studies, as these latter studies varied substantially in their study design (retrospective assessment and concomitant use of D-dimer) from the derivative studies.

Box. Criteria for Diagnosis and Exclusion of Pulmonary Embolism

Positive for Pulmonary Embolism

Positive pulmonary angiogram[20]

High-probability lung scan (≥1 segmental perfusion defect[21] or ≥2 large [>75% of a segment] segmental perfusion defects[5] with corresponding normal ventilation)

Nondiagnostic lung scan with either a positive venogram[22] or a compression ultrasound diagnostic for deep vein thrombosis

Positive lung perfusion scan[23] (single or multiple wedge-shaped defect with or without matching chest radiograph abnormalities; wedge-shaped areas of overperfusion usually exist)

Negative for Pulmonary Embolism

Normal perfusion lung scan[23] and a normal 3-month follow-up result

Negative pulmonary angiogram[20] and a normal 3-month follow-up result

Nondiagnostic lung scan and negative venogram,[22] serial leg compression ultrasound,[14] or impedance plethysmography,[24] and a normal 3-month follow-up result

Negative spiral computed tomography scan and negative venogram or negative serial compression ultrasound and a normal 3-month follow-up result

Negative D-dimer test result and a normal 3-month follow-up result provided anticoagulants were withheld

RESULTS

Our search yielded a total of 1709 articles, and after scanning the abstracts and titles, we selected 443 abstracts for detailed review. Of these, 30 articles were selected for complete review and 16 were included in the final analysis. These studies involved a total of 8306 patients.

Clinical Gestalt

In the PIOPED study, physicians used their clinical gestalt to estimate the prob-

Table 2. Accuracy of Pretest Probability Assessment for Pulmonary Embolism Using Clinical Gestalt

Source	No. of Patients	Prevalence of Pulmonary Embolism, %	Category	Probability Estimate, %	No. of Patients	Actual Probability, %	Likelihood Ratio (95% Confidence Interval)*
PIOPED,[5] 1990	887	28	Low	0-19	228	9	0.26 (0.17-0.4)
			Moderate	20-79	569	30	1.1 (0.96-1.2)
			High	80-100	90	68	5.3 (3.5-8.0)
Miniati et al,[23] 1996	783	44	Unlikely	10	349	8	0.13 (0.09-0.18)
			Possible	50	179	47	1.1 (0.86-1.4)
			Very likely	90	225	91	12 (8.1-18)
Perrier et al,[30-32] 1996, 1997, 1999	985	27	Low	≤20	368	9	0.21 (0.15-0.29)
			Moderate	21-79	523	33	1.1 (1.0-1.3)
			High	≥80	94	66	4.5 (3.0-6.7)
Sanson et al,[33] 2000	413	31	Low	0-19	58	19	0.53 (0.28-0.99)
			Moderate	20-80	278	29	0.92 (0.79-1.1)
			High	>80	77	46	1.9 (1.3-2.8)
Musset et al,[34] 2002 (ESSEP)	1041	34	Low	0-19	231	12	0.26 (0.18-0.38)
			Moderate	20-79	525	26	0.67 (0.58-0.78)
			High	80-100	285	68	4.0 (3.3-5.0)

Abbreviations: ESSEP, Evaluation du Scanner Spirale dans l'Embolie Pulmonaire; PIOPED, Prospective Investigation of Pulmonary Embolism Diagnosis.
*Summary data (likelihood ratio [95% confidence interval]) for empirical pretest probability assessments are the following: low, 0.25 (0.14-0.45); moderate, 0.92 (0.71-1.2); and high, 4.7 (2.3-9.7). These summary data exclude results from the studies by Perrier et al[30-32] because the pretest probability was used to manage subgroups of patients.

ability of pulmonary embolism based on patient history and physical examination findings together with the results of a chest radiograph, an electrocardiogram, and an arterial blood gas analysis (TABLE 2).[5,23,30-34] The results of this study showed that the prevalence of pulmonary embolism correlated reasonably well with the pretest probability estimates of pulmonary embolism.

The Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED) study tested the accuracy of perfusion scan alone compared with pulmonary angiography.[23] In this study, experienced clinicians estimated the probability of pulmonary embolism from their clinical gestalt based on patient symptoms, signs, and risk factors together with the results of a chest radiograph, an electrocardiogram, and an arterial blood gas analysis.

Perrier et al[30-32] reported the clinical gestalt from 3 separate studies using a diagnostic strategy in which a ventilation/perfusion lung scan, a D-dimer assay, and a compression ultrasound followed the clinical evaluation. In the first 2 studies,[30,31] all patients underwent a ventilation/perfusion scan and then were managed according to the pretest probability assessment, D-dimer assay result, and compression ultrasound finding. In the third study,[32] patients were assessed initially with a highly sensitive (but nonspecific) enzyme-linked immunosorbent assay D-dimer laboratory analysis. The results of these studies are consistent with those reported in the PISA-PED[23] and PIOPED[5] studies.

Sanson et al[33] conducted a study in 6 Dutch teaching hospitals. The clinical gestalt was quantified into the pretest probability for pulmonary embolism, and patients underwent ventilation/perfusion lung scanning followed by angiography if the lung scan finding was nondiagnostic. The estimate of the pretest probability was performed by the attending physician on a visual analog scale; however, the results of chest radiographs, electrocardiograms, and arterial blood gas analysis were not always available at the time the pretest probability was documented. In this study, assessment of pretest probability was less predictive than other studies of the clinical gestalt.

The Evaluation du Scanner Spirale dans l'Embolie Pulmonaire study group[34] assessed the accuracy of contrast spiral computed tomography (spiral CT) of the chest for pulmonary embolism in 1041 patients. Using simple prespecified guidelines and empirical assessment based on patient history, physical examination findings, and results of routine investigations, clinicians stratified patients into low, moderate, or high pretest probability groups. The presence or absence of pulmonary embolism largely was based on the combined results of spiral CT and routine bilateral compression ultrasound of the legs. If the clinical suspicion was high and the test results were negative, or if test results were inconclusive, further assessment with lung scanning and pulmonary angiography was performed. The study demonstrated reasonable discriminative ability among the 3 pretest groups.

When interpreted together, the studies show that when experienced clinicians use clinical gestalt the prevalence of pulmonary embolism increases with increasing pretest probability. Importantly, the PIOPED and PISA-PED studies demonstrate the influence that clinical gestalt has on the interpretation of results of subsequent tests. In the PISA-PED study, a positive scan for pulmonary embolism (single or multiple perfusion defects with or without matching chest radiograph abnormalities) together with a possible or very likely clinical pretest probability was associated with pulmonary embolism in 92% and 99% of patients, re-

Table 3. Accuracy of Clinical Prediction Rules for Assessing Pretest Probability of Pulmonary Embolism in Derivative Studies*

Source	No. of Patients	Prevalence of Pulmonary Embolism, %	Prospective Validation	Pretest Probability Category	Pretest Probability, %	Likelihood Ratio (95% Confidence Interval)
Wells et al,[14] 1998 (Extended)	1239	17.5	Yes	Low	3	0.17 (0.12-0.25)
				Moderate	28	1.8 (1.5-2.1)
				High	78	17 (11-27)
Miniati et al,[35] 1999 (PISA-PED)	750	41	Yes	Unlikely	6	0.05 (0.03-0.10)
				Possible	46	0.99 (0.75-1.3)
				Very likely	97	47 (23-98)
				High	63	8.6 (5.7-13)
Wicki et al,[37] 2001 (Geneva rule)	986	27	Yes	Low	10	0.31 (0.24-0.40)
				Moderate	38	1.7 (1.5-1.9)
				High	81	11 (6.1-21)
Kline et al,[38] 2002	934	19.4	No	Nonhigh	13.3	0.64 (0.56-0.73)
				High	42.1	3.0 (2.4-3.8)
Miniati et al,[39] 2003 (PISA-PED II)	1100	40	No	Low	4	0.07 (0.04-0.11)
				Moderate	26	0.72 (0.6-0.87)
				High	98	66 (31-137)

Abbreviation: PISA-PED, Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis.
*Summary of pretest probability (likelihood ratio [95% confidence interval]) of structured clinical rules are as follows: low, 0.12 (0.05-0.31); moderate, 1.1 (0.76-1.6); and high, 23 (7.6-69). This summary excludes data from Kline et al[38] because that study only categorized patients into low and high categories and from Wells et al[14] because the pretest probability was used to guide management, which likely resulted in case-finding bias.

spectively.[34] On the other hand (similar to the PIOPED study results), when patients had an unlikely (low) clinical pretest probability but a positive finding on perfusion scan, pulmonary embolism was diagnosed in only 50% to 60% of individuals.

The findings in the study by Sanson et al[33] suggest that the clinical gestalt is not particularly discriminating. However, the study still showed increasing prevalence of pulmonary embolism according to pretest probability.

Table 4. The Simplified Wells Scoring System*

Findings	Score†
Clinical signs/symptoms of deep venous thrombosis (minimum of leg swelling and pain with palpation of the deep veins of the leg)	3.0
No alternate diagnosis likely or more likely than pulmonary emboli	3.0
Heart rate >100/min	1.5
Immobilization or surgery in last 4 weeks	1.5
Previous history of deep venous thrombosis or pulmonary emboli	1.5
Hemoptysis	1.0
Cancer actively treated within last 6 months	1.0

*Adapted from Wells et al[36] with permission.
†Category scores are as follows: low, <2; moderate, 2-6; and high, >6. Patient's clinical score is calculated by the summing of the scores (weight) of the predictor variables that are present.

Clinical Prediction Rules

The PISA-PED study group analyzed clinical data from their accuracy study (Table 2)[23] to derive a structured clinical rule.[35] Clinical variables were divided into 3 categories: (1) signs and symptoms; (2) results of routine tests (chest radiograph, electrocardiogram, and arterial blood gas analysis); and (3) evidence of an obvious alternative diagnosis.

Wells et al[14] initially developed a 40-variable clinical rule and subsequently refined the rule after a limited pilot study. This rule (extended) was used in a large multicenter study in which 1239 patients were enrolled and assigned a clinical probability of pulmonary embolism after taking a patient history, performing a physical examination, and assessing chest radiography, arterial blood gas analysis, and electrocardiography findings. A checklist of specific symptoms and signs was compiled to help assign the pretest probability. Patients were assessed for type of symptoms ("typical," "atypical," or "suggestive" of severe pulmonary embolism), the presence or absence of risk factors, and the presence or absence of an alternative diagnosis as or more likely than pulmonary embolism to account for the patient's symptoms.

The corresponding prevalence and LRs for pulmonary embolism in each of the 3 pretest probability categories are listed in TABLE 3.[14,35,37-39] The utility of pretest probability assessment in combination with lung scanning again was highlighted. Only 8 of 27 (30%) patients with a low pretest probability and a high-probability lung scan, had angiographically proven pulmonary embolism.[14]

Clinical data collected on the 1239 patients by Wells et al[36] also were used to derive a simplified clinical rule. Using a stepwise logistic regression model, 7 key variables were identified and selected for inclusion in the final rule. Cut points were identified to classify patients as low (<2), moderate (2-6), or high (>6) probability for pulmonary embolism (TABLE 4).[36] Using this simplified rule, only 3% (LR, 0.17; 95% CI, 0.11-0.27)

of patients with a low pretest probability had pulmonary embolism vs 63% (LR, 8.6; 95% CI, 5.7-13.0) of those with a high pretest probability.

Table 5. The Clinical Prediction Rule by Wicki et al (Geneva)*

Variable	Point Score†
Age, y	
60-79	1
≥80	2
Previous pulmonary emboli or deep venous thrombosis	2
Recent surgery	3
Pulse rate >100/min	1
$PaCO_2$, kPa	
<4.8	2
4.8-5.19	1
PaO_2, kPa	
<6.5	4
6.5-7.99	3
8-9.49	2
9.5-10.99	1
Chest radiograph appearance	
Platelike atelectasis	1
Elevated hemidiaphragm	1

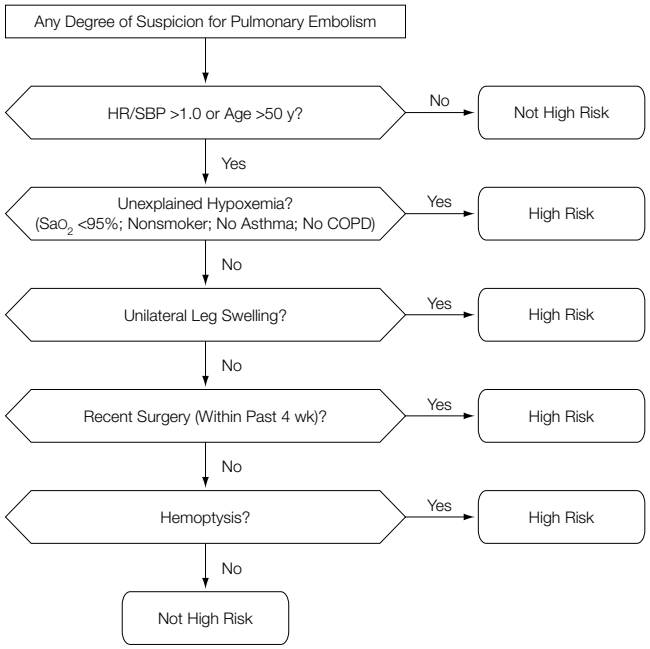
*Adapted from Wicki et al.[37]
†The pretest probability categories (clinical probability score range, prevalence of disease [95% confidence interval], and percentage of patients in the pretest probability category) are as follows: low (0-4, 10% [8%-13%], 49%); intermediate (5-8, 38% [34%-43%], 38%); and high (9-16, 81% [69%-90%], 6%), respectively.

Wicki et al[37] pooled clinical data obtained from the patient history and physical examination together with results of the chest radiograph, electrocardiogram, and arterial blood gas analysis collected during the 3 studies, involving 986 consecutive patients. A 7-variable rule was derived by logistic regression and statistically cross-validated (TABLE 5). A score, based on a weighted sum of variables present, was used to estimate the pretest probability of pulmonary embolism. Patients with scores of less than 5 had low pretest probability of pulmonary embolism, of 5 to 8 had moderate pretest probability, and of greater than 8 had high pretest probability. The prevalence of pulmonary embolism correlated well with pretest probability.

A large emergency department–based study involving 7 US centers systematically assessed 934 patients with suspected pulmonary embolism and derived a 6-variable model from this database (FIGURE).[38] This model uses 2 screening variables to assess all patients' age and shock index (heart rate divided by systolic blood pressure). Patients younger than 50 years and with a shock index less than 1 are deemed "nonhigh"; the remaining patients are then further assessed using 4 variables. The model classified 79% of patients as non–high risk patients in whom the prevalence of pulmonary embolism was 13.3%, whereas the prevalence in the high-risk group (21% of patients) was 42.1%. Two medical students subsequently were employed to assess 117 patients presenting to one of the participating centers, and they demonstrated a high degree of interobserver agreement (weighted κ, 0.83).[38]

The PISA-PED investigators have reanalyzed data from their initial study and included data on a further 350 patients; the latter were assessed and managed as in the first study.[39] Using appropriate statistical techniques, they derived and cross-validated a 15-variable model (TABLE 6). Unlike other structured models, the authors calculated and display the actual pretest probability for individual patients rather than the ordinal descriptors of low, moderate, and high probability. Nonetheless, the probability of pulmonary embolism in the low, moderate, moderately high, and very high pretest strata shows clear discrimination among the groups (for ease of comparison we have combined the moderate and moderately high groups).

Figure. Decision Rule for Pulmonary Embolism



This model uses 2 screening variables to assess all patients' age and shock index (heart rate [HR] divided by systolic blood pressure [SBP]). COPD indicates chronic obstructive pulmonary disease. Adapted from Kline et al[38] with permission from the American College of Emergency Physicians.

Validation of Derived Clinical Prediction Rules

Two hundred fifty patients with suspected pulmonary embolism were assessed prospectively by the PISA-PED group.[35] In this study, 90% of patients were categorized correctly as having or not having pulmonary embolism, which compared favorably with an 88% diagnostic accuracy of the initial study.

The extended Wells model has been tested prospectively by Sanson et al[33] and by Kruip et al.[40] The pretest probability in the study by Sanson et al was determined retrospectively by a second physician who used clinical information collected by the assessing physician; both physicians remained blind

to the results of diagnostic testing for pulmonary embolism. Unfortunately, about 50% (212 of 414 patients) of study patients enrolled were assessed. The Sanson et al[33] study assignments of low, moderate, and high pretest probabilities corresponded to rates of pulmonary embolism of 28%, 39%, and 46%, respectively. These results showed less discrimination among the subgroups than other studies. Kruip et al[40] combined the pretest probability assessment of patients with the results of D-dimer analysis and withheld objective testing and anticoagulant therapy in those patients categorized with a low pretest probability and a negative D-dimer result (normal level). All other patients were tested with the combination of compression ultrasound of the legs followed by pulmonary angiography, if the results of the ultrasound were negative. The model showed considerable discriminative ability when used by Kruip et al,[40] with the prevalence of pulmonary embolism ranging from 4% in the low pretest probability group to 28% and 63% in the moderate and high pretest probability groups, respectively. For the subgroup of patients with a low pretest probability and a negative D-dimer result, the 3-month rate of venous thromboembolism was 0% (95% CI, 0%-6%) (TABLE 7).

The simplified Wells model also was tested by 3 groups.[33,41,42] As with the extended Wells model, Sanson et al[33] used a second physician to assign retrospectively patients a pretest score based on the clinical data collected by the attending physician (Table 7). Although the attending physician was required to specify whether an alternate diagnosis, more likely than pulmonary embolism, was present, when this was not done, the second physician inferred this from reviewing the medical notes. The lack of an alternate diagnosis is a critical limitation of the study given the relative importance of this factor in the model. Sanson et al[33] reported that the simplified Wells model was less discriminating in this study than in the original Wells et al[14] study. Patients with a low pretest probability had a 28% prevalence of pulmonary embolism compared with 3% in the study by Wells et al,[36] and only 38% of patients with a high pretest probability had pulmonary embolism compared with 63% in the study by Wells et al.[36]

At variance with these data is the subsequent prospective validation of the simplified clinical prediction rule by Wells et al[41] in 4 Canadian centers and Chagnon et al[42] in 3 centers in France and Switzerland. The Canadian study included patients assessed by 1 of 43 emergency department physicians; patients with a low pretest probability and a negative D-dimer test result had no further testing performed, but were followed up for 3 months. The model reliably categorized patients into low,

Table 6. Structured Clinical Model Derived by the PISA-PED Group*

Factor	Regression Coefficient
Male sex	0.81
Age, y	
63-72	0.59
≥73	0.92
Preexisting disease	
Cardiovascular	−0.56
Respiratory	−0.97
Thrombophlebitis (ever)	0.69
Symptoms	
Dyspnea (sudden onset)	1.29
Chest pain	0.64
Hemoptysis	0.89
Temperature >38°C	−1.17
Electrocardiogram signs of acute right ventricular overload	1.53
Chest radiograph findings	
Oligemia	3.86
Amputation of hilar artery	3.92
Consolidation (infarction)	3.55
Consolidation (no infarction)	−1.23
Pulmonary edema	−2.83

Abbreviation: PISA-PED, Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis.
*Adapted from Miniati et al[39] with permission from Excerpta Medica.

Table 7. Accuracy of Clinical Prediction Rules for Pulmonary Embolism When Tested Prospectively

Source	No. of Patients	Prevalence of Pulmonary Embolism, %	Rule Prospectively Tested	Pretest Probability Category	Posttest Probability, %	Likelihood Ratio (95% Confidence Interval)
Sanson et al,[33] 2000	237	38	Extended Wells[14]	Low	28	0.66 (0.4-1.1)
				Moderate	39	1.1 (0.86-1.3)
				High	46	1.4 (0.81-2.5)
Sanson et al,[33] 2000	414	29	Simplified Wells[36]	Low	28	0.93 (0.69-1.3)
				Moderate	30	1.0 (0.88-1.2)
				High	38	1.4 (0.35-5.9)
Wells et al,[41] 2001	930	9.5	Simplified Wells[36]	Low	1.3	0.13 (0.06-0.26)
				Moderate	16.2	1.9 (1.6-2.3)
				High	40.6	5.9 (3.7-9.3)
Kruip et al,[40] 2002	234	22	Extended Wells[14]	Low	4	0.15 (0.07-0.33)
				Moderate	28	1.5 (1.01-2.2)
				High	63	5.85 (3.51-9.74)
Chagnon et al,[42] 2002	277	26	Simplified Wells[36]	Low	12	0.39 (0.26-0.58)
				Moderate	40	2.0 (1.5-2.6)
				High	91	29 (3.8-223)
Chagnon et al,[42] 2002	277	26	Wicki (Geneva)[37]	Low	13	0.44 (0.30-0.65)
				Moderate	38	1.8 (1.4-2.3)
				High	67	5.8 (1.8-19)

Table 8. Estimated Accuracy Indices of 3 D-Dimer Assays

D-Dimer Assay	% (95% Confidence Interval)		Likelihood Ratio (95% Confidence Interval)	
	Sensitivity	Specificity	Positive	Negative
Organon Teknika latex immunoassay[45]	96 (90-99)	45 (40-49)	1.7 (1.5-1.9)	0.09 (0.04-0.11)
Vidas Rapid ELISA assay[46]	90 (81-96)	45.1 (39-51)	1.6 (1.4-1.8)	0.22 (0.11-0.44)
SimpliRED D-dimer assay[43]	84.8 (79-89)	68.4 (65-71)	2.7 (2.4-3.0)	0.22 (0.16-0.3)

Abbreviations: ELISA, enzyme-linked immunosorbent assay.

moderate, and high pretest probability subgroups with the prevalence of disease being 1.3%, 16.2%, and 40.6% (95% CI, 29.7%-54%), respectively.[41]

In the study by Chagnon et al,[42] emergency department residents collected and recorded clinical data on 277 consecutive patients with suspected pulmonary embolism to create a score. Although the final score was calculated retrospectively, all the variables were documented clearly. Subsequent management of patients was determined by the results of D-dimer testing. Patients with a positive D-dimer result were further investigated with a combination of ultrasound testing of the legs, lung scanning, and pulmonary angiography.[32] Consistent with the prospective validation by Wells et al,[41] the emergency department residents were able to stratify patients into low, moderate, and high pretest probability categories with ascending prevalences of pulmonary embolism.

The clinical model derived by Wicki et al[37] has been validated prospectively by Chagnon et al.[42] Emergency department residents collected all the relevant data on consecutive patients with suspected pulmonary embolism and assigned each patient a pretest probability based on the Wicki model. The results of the assessment of patients using the Wicki model showed that patients identified as low, moderate, or high pretest probability for pulmonary embolism showed ascending prevalences of pulmonary embolism.

Precision of the Examination and Components of the Clinical Prediction Rules

To be useful, the pretest probability for pulmonary embolism needs to be reproducible. Put simply, when assessing the same patient, 2 clinicians' clinical gestalt should yield similar estimates of the pretest probability. None of the individual studies documented interobserver variability for the clinical gestalt.

Wells et al[14] documented observer variability for the pretest probability using the extended model ($\kappa = 0.86$). Kline et al[38] employed 2 medical students to test the observer variability of their rule and demonstrated excellent observer agreement (weighted κ, 0.83). Chagnon et al[42] did not document concordance between 2 observers for either of the 2 models they tested, but they documented modest agreement between Wells simplified model and the Wicki model (weighted κ, 0.43) and found that in only 2 of 277 cases was there extreme disagreement in the pretest probability assessment.

D-Dimer Assay

D-dimer, a specific fibrin degradation product, is generated by the action of plasmin on cross-linked fibrin.[19,43-47] D-dimer assay is sensitive for the presence of venous thrombosis and can be used to help exclude deep vein thrombosis and pulmonary embolism. Although several assays are available, to be useful, a D-dimer assay must be highly sensitive for pulmonary embolism so that patients with this disease are not missed. In addition, for the assay to be useful, the specificity should be high enough so that the number of false-positive results is sufficiently low. Newer assays can be performed rapidly, making them suitable for use in individual patients.[43-47] The D-dimer assay is complementary to the clinical pretest probability because pulmonary embolism can be reliably excluded in patients with a negative D-dimer result and a low pretest probability.[41] The accuracy indices of 3 currently available D-dimer assay types are summarized in TABLE 8.[43,45,46]

Unfortunately, D-dimer assays vary in their sensitivities and specificities so the posttest probability for a given patient with suspected pulmonary embolism will vary according to which D-dimer assay is used. Before clinicians use a particular D-dimer assay to revise their pretest probability, they should be aware of the differences and interpret the results of the assay accordingly.[44,47]

SCENARIO RESOLUTIONS

Case 1

This young woman has no risk factors or signs of pulmonary embolism (no tachycardia, features of deep vein thrombosis, or hemoptysis). No clear alternate diagnosis is present that is at least as likely, or more likely, than pulmonary embolism. Based on the Wells simplified clinical prediction rule, her score would be 3, a moderate pretest probability for pulmonary embolism (approximately 20%). Her whole-blood red cell agglutination D-dimer assay result is negative (negative LR, 0.22).[43] Therefore, the probability of pulmonary embolism after the results of the D-dimer assay are obtained is about 5%. The finding from a perfusion scan is normal (LR for pulmonary embolism with a normal lung scan, 0.1).[48] Therefore, her posttest probability after the above combination of tests is 0.5%, and pulmonary embolism can be ruled out.

Case 2

This elderly patient has a high pretest probability for pulmonary embolism

(approximately 65%) using the simplified Wells rule because of the combination of immobilization, tachycardia, previous deep vein thrombosis/pulmonary embolism, and the absence of an alternate diagnosis as or more likely than pulmonary embolism. This combination of findings results in a score of 7, which falls into the category of a high pretest probability. In combination with a negative whole-blood red cell agglutination D-dimer asssay result (LR, 0.22),[43] the revised pretest probability is approximately 30%. A ventilation/perfusion scan is reported as intermediate probability (LR, 1.2)[48]; therefore, his posttest probability of pulmonary embolism is about 33% and pulmonary embolism has not been ruled out. Further testing with compression ultrasonography and, if the finding is normal, pulmonary angiography should be considered.

BOTTOM LINE

Clinical assessment alone is insufficient to diagnose or rule out pulmonary embolism, although experienced clinicians can use clinical gestalt to assign a pretest probability of pulmonary embolism with reasonable accuracy. Clinical prediction rules appear to have similar accuracy to that of the clinical gestalt for patients in the low- and high-probability categories. We advocate the use of any one of the clinical prediction rules because they are simple and maintain their accuracy when used by less-experienced clinicians. In deciding which of the several rules to use, clinicians could justifiably make decisions on the scale that is easiest for them to use consistently. Factors that could affect the decision are availability of the rule in clinical reminder systems and the availability of the required clinical data. We are unable to say with confidence whether one structured clinical rule performs better than another. In outpatients with new onset of or recent worsening of symptoms within the preceding 3 days, the combination of pretest probability assessment with the results of D-dimer testing improves diagnostic accuracy. Furthermore, there is emerging evidence that outpatients with a low pretest probability for pulmonary embolism can have anticoagulant therapy safely withheld when the results of D-dimer testing are negative.[41,43]

Author Contributions: *Study concept and design:* Chunilal, Panju, Ginsberg.
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Administrative, technical, or material support: Chunilal, Attia, Simel.
Study supervision: Panju, Simel, Ginsberg.
Funding/Support: Dr Chunilal is the recipient of the Noonan Fellowship, McMaster University. Dr Eikelboom is the recipient of a research fellowship from the Heart and Stroke Foundation of Canada. Dr Ginsberg is the recipient of a Career Investigator Award from the Heart and Stroke Foundation of Ontario, and a research chair from CIHR-AstraZeneca.
Disclaimer: Dr Simel, a section editor for the Rational Clinical Examination series, did not influence the editorial decision to publish this article.
Acknowledgment: We thank Jonathan Edlow, MD, David B. Matchar, MD, and Eugene Oddone, MD, for their important suggestions on the manuscript, as well as Arnaud Perrier, MD, Harry Buller, PhD, and Marieke J.H.A. Kruip, MD, for providing clarification of data.

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> The sole philosophy open to those who doubt the possibility of truth is absolute silence—even mental.
> —Jacques Maritain (1882-1963)