CLINICAL STUDIES

A Structured Clinical Model for Predicting the Probability of Pulmonary Embolism

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PURPOSE: To develop a structured model to predict the clinical probability of pulmonary embolism.

METHODS: We studied 1100 consecutive patients with suspected pulmonary embolism in whom a definite diagnosis had been established. We used logistic regression analysis to estimate the probability of pulmonary embolism based on patients' clinical characteristics; the probability was categorized as low (≤10%), intermediate (>10%, ≤50%), moderately high (>50%, ≤90%), or high (>90%).

RESULTS: The overall prevalence of pulmonary embolism was 40% (n = 440). Ten characteristics were associated with an increased risk of pulmonary embolism (male sex, older age, history of thrombophlebitis, sudden-onset dyspnea, chest pain, hemoptysis, electrocardiographic signs of acute right ventricular overload, radiographic signs of oligemia, amputation of the hilar artery, and pulmonary consolidation suggestive of infarction), and five were associated with a decreased risk (prior cardiovascular or pulmonary disease, high fever, pulmonary consolidation other than infarction, and pulmonary edema on the chest radiograph). With this model, 432 patients (39%) were rated a low probability, of whom 19 (4%) had pulmonary embolism; 283 (26%) were rated an intermediate probability, of whom 62 (22%) had pulmonary embolism; 72 (7%) were rated a moderately high probability, of whom 53 (74%) had pulmonary embolism; and 313 (28%) were rated a high probability, of whom 306 (98%) had pulmonary embolism.

CONCLUSION: This prediction model may be useful for estimating the probability of pulmonary embolism before obtaining definitive test results. **Am J Med. 2003;114:173–179.** ©2003 by Excerpta Medica Inc.

The clinical diagnosis of pulmonary embolism is deemed unreliable because the signs, symptoms, and laboratory data are often nonspecific (1). However, certain clinical findings, such as unexplained dyspnea or chest pain, raise the suspicion of pulmonary embolism and may be useful in selecting patients for further diagnostic testing (2,3). Furthermore, the results of three prospective studies (4–6) have indicated that physicians' estimates of the clinical likelihood of pulmonary embolism, even if based on empirical assessment, do have predictive value, and that the clinical probability of pulmonary embolism can be used as pretest probability before objective testing.

Several attempts have been made to develop prediction models for pulmonary embolism (7–9). We previously described a clinical diagnostic algorithm based on the presence of one or more of three relevant symptoms (sudden-onset dyspnea, chest pain, or fainting) in association with one of four abnormalities (electrocardiographic [ECG] signs of right ventricular overload, radiographic signs of oligemia, amputation of the hilar artery, or pulmonary consolidation suggestive of infarction). In comparison with pulmonary angiography, this algorithm had a sensitivity of 84% and a specificity of 95% (8).

In the present study, we used logistic regression models to identify parameters significantly associated with pulmonary embolism in 1100 consecutive patients admitted to our institution with clinically suspected pulmonary embolism. In most patients, pulmonary angiography was used as the reference diagnostic standard.

METHODS

Sample

The sample consisted of 1100 consecutive patients who were referred to our institution for suspected pulmonary embolism between November 1, 1991, and December 31, 1999, and in whom the disease was diagnosed or excluded. The clinical characteristics of 500 of these patients have been described (8). All patients were examined according to a standardized protocol that included clinical evaluation, perfusion lung scanning, and pulmonary angiography (5,8).

Clinical Evaluation

Upon study entry, patients were examined by one of 12 on-call pulmonary physicians, all of whom had experi-

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ence with the diagnostic procedures for pulmonary embolism. The clinical evaluation included a detailed clinical history, physical examination, interpretation of the ECG and the chest radiograph, and measurement of the partial pressures of oxygen (Pa_{O_2}) and carbon dioxide (Pa_{CO_2}) in arterial blood. All clinical and laboratory data were recorded by the physician on a standard form before any further objective testing.

Immobilization was defined as strict bed rest for more than 3 consecutive days within the previous 4 weeks. History of thrombophlebitis required a documented episode treated with anticoagulant therapy. Major surgical procedures and radiologically confirmed fractures of the lower extremity within the previous 4 weeks were noted. Estrogen use was defined as use of estrogen-containing drugs within the previous 3 months. The postpartum period was defined as pregnancy within the previous 3 months.

Ischemic heart disease was considered to be present if a patient had typical angina on exertion, used antianginal medication, or had a prior myocardial infarction documented by ECG or cardiac enzyme elevation. Hypertension was diagnosed if there was documented persistent elevation of arterial pressure (systolic >160 mm Hg or diastolic >95 mm Hg) or if the patient was receiving antihypertensive medication. Cerebrovascular disorders included prior transient ischemic attack or stroke. Valvular disease was recorded if there was hemodynamic or echocardiographic evidence of mitral or aortic stenosis or regurgitation. Chronic obstructive pulmonary disease was recorded if there was evidence of fixed airflow obstruction, chronic mucous hypersecretion, or emphysema. Cancer was recorded if there was evidence of clinically active disease with pathologic diagnosis within the previous 3 months. Diabetes mellitus was diagnosed if the patient was on long-term therapy with insulin or oral hypoglycemic drugs. Thyroid dysfunction requiring treatment was noted.

In evaluating dyspnea, attention was paid to establish whether it was sudden or gradual in onset, and whether it was associated with orthopnea. Chest pain was categorized as pleuritic or substernal. Unilateral leg swelling with tenderness and redness of the skin were regarded as a sign suggestive of deep vein thrombosis.

Arterial blood samples were obtained upon study entry in all patients while they were breathing room air. Electrocardiograms obtained within 24 hours before study entry were evaluated by the on-call physician. The following abnormalities, if new, were regarded as suggestive of right ventricular overload: S wave in lead I and Q wave in lead III, each of amplitude >1.5 mm, with or without T-wave inversion in lead III ($S_1Q_3T_3$ or S_1Q_3); S waves in leads I, II, and III, each of amplitude >1.5 mm ($S_1S_2S_3$); T-wave inversion in right precordial leads; transient right bundle branch block; and pseudoinfarction (10).

Chest radiographs were obtained in all patients at the time of study entry using a stationary X-ray unit. In most patients, posteroanterior and lateral views were taken in the upright or seated position. For patients who were unable to stand or sit (30% in our study), anteroposterior chest radiographs were obtained in the supine or semirecumbent position. Chest radiographs were examined by the physician according to a standard form that included the following items: size and shape of the heart and hilar arteries, position of the diaphragm, presence or absence of pulmonary parenchymal abnormalities (e.g., consolidation, atelectasis, oligemia, edema), and pleural effusion. When evaluating the hilar arteries, attention was paid to the presence of abrupt vascular amputation that gave the hilum a "plump" appearance (11,12). In retrospective studies, this radiographic abnormality has been strongly associated with pulmonary embolism (13,14). Pulmonary consolidation was considered suggestive of infarction if it had a semicircular or half-spindle shape and was arranged peripherally along the pleural surface (so-called Hampton's hump) (15,16). Oligemia was considered to be present if, in a given lung region, the pulmonary vasculature was greatly diminished with concomitant hyperlucency of the lung parenchyma (17).

Criteria for Diagnosing or Excluding Pulmonary Embolism

Diagnosis was based on angiographic or autopsy documentation of pulmonary embolism. Exclusion criteria were a normal pulmonary angiogram, absence of pulmonary emboli at autopsy, or a normal or near-normal perfusion scan. Performing pulmonary angiography in patients with normal or near-normal scans was deemed unethical because available data indicate that such a scintigraphic pattern, in itself, makes the diagnosis very unlikely (4,18–20). Six-month clinical follow-up was obtained in patients with normal or near-normal scans.

Statistical Analysis

The univariate relations between baseline characteristics and the diagnosis of pulmonary embolism were assessed with the Fisher exact test or the Wilcoxon rank sum test. Two-sided P values <0.05 were considered statistically significant.

To estimate the probability of pulmonary embolism, we developed a logistic regression model that initially included all demographic, clinical, and laboratory data. Continuous variables were split into tertiles. A stepwise procedure was used, and variables with a P value >0.20 were removed from the model. Remaining variables were examined individually and kept in the model if they were statistically significant or appeared to be confounders, defined as variables whose removal changed another variable's coefficient by >10%. Next, all variables that had been removed were reintroduced one at a time and kept in the model if they were statistically significant or con-

founders. Finally, all pairwise interactions were tested; none were statistically significant.

The area under the receiver operating characteristic (ROC) curve of the final model was calculated. To estimate 95% confidence intervals, 1000 bootstrap samples were generated, each of which consisted of 1100 observations selected randomly with replacement from the original data. The area under the ROC curve was calculated for each bootstrap sample, and the 95% confidence interval was obtained as the 5th and 95th percentiles of the 1000 bootstrap values (21).

The logistic regression model was cross-validated to check for overfitting of the data according to the following steps: step 1, the data set was split randomly into 10 equal subsamples; step 2, regression coefficients were estimated for nine subsets (training set); step 3, the prediction equation was applied to the remaining subset (validation set) and the area under the ROC curve was calculated; step 4, steps 2 and 3 were repeated for each subset in turn. The 10 areas under the ROC curves were compared with those obtained on the same 10 validation sets by using the original prediction equation developed from the whole study sample.

RESULTS

The 1100 patients had a median age of 68 years (range, 15 to 94 years); 498 (45%) of them were male (Table 1). Eighty-one percent (n = 891) were hospitalized at the time of study entry. The median time between onset of symptoms and study entry was 1 day (range, 0 to 30 days). Based on angiography and autopsy data, the prevalence of pulmonary embolism was 40% (n = 440). Among patients without pulmonary embolism, 242 had the diagnosis excluded based on a normal or near-normal perfusion scan. None of these patients had symptomatic venous thromboembolism during a 6-month follow-up.

Patients with confirmed pulmonary embolism did not differ in age and sex from those without pulmonary embolism. The median Pa_{O_2} was 63 mm Hg (range, 31 to 108 mm Hg) in patients with pulmonary embolism and 66 mm Hg (range, 30 to 129 mm Hg) in those without ($P = 0.03$). The median Pa_{CO_2} was 33 mm Hg (range, 20 to 49 mm Hg) in patients with pulmonary embolism and 34 mm Hg (range, 14 to 65 mm Hg) in those without ($P = 0.02$).

Multivariate Predictors of Pulmonary Embolism

Ten characteristics were associated with an increased likelihood of pulmonary embolism: male sex, older age, history of thrombophlebitis, sudden-onset dyspnea, chest pain, hemoptysis, ECG signs of acute right ventricular overload, radiographic signs of oligemia, amputation of the hilar artery, and pulmonary consolidation suggestive of infarction (Table 2). Variables associated with a decreased likelihood of pulmonary embolism included prior cardiovascular or pulmonary disease, high fever, pulmonary consolidation other than infarction, and pulmonary edema on the chest radiograph. The area under the ROC curve for the logistic regression model was 0.95 (95% confidence interval: 0.93 to 0.96).

Assessing the Clinical Probability of Pulmonary Embolism

The probability of pulmonary embolism in a given patient—based on the characteristics of that patient that are listed in Table 2—can be derived from the formula in Table 2, or by using the Figure, which displays the relation between the sum of the regression coefficients and the predicted probability of pulmonary embolism. There was a very close agreement between the probability of pulmonary embolism predicted by the model and the actual prevalence (Figure).

When the probability of pulmonary embolism was divided into four categories: low (≤10%), intermediate (>10%, ≤50%), moderately high (>50%, ≤90%), and high (>90%), the actual prevalence of pulmonary embolism among patients in each of the categories was consistent with the predicted risks (Table 3).

Cross-Validation

The models developed from the training sets all included the same covariates as the final model, except for one model that did not include pulmonary edema. The prediction equations developed from the 10 training sets, when applied to the 10 validation sets, yielded areas under the ROC curve that averaged 0.94 (range, 0.90 to 0.97). In the same validation sets, the prediction equation developed from the whole study sample yielded areas under the ROC curve that averaged 0.95 (range, 0.91 to 0.98).

DISCUSSION

The results of large-scale prospective studies of the diagnosis of pulmonary embolism lend support to the concept that clinical assessment is a fundamental step in the diagnostic work-up of patients (4–6). Although the diagnostic yield of individual signs, symptoms, and common laboratory tests is limited, the combination of these variables, either by empirical assessment or by a prediction rule, can be used to express the clinical probability of pulmonary embolism.

In a multicenter Canadian study (7), the clinical probability of pulmonary embolism was categorized as low, moderate, or high based on the presenting signs and symptoms, interpretation of the ECG and chest radiograph, measurement of arterial oxygen saturation, presence or absence of an alternative diagnosis, and identification of predisposing risk factors for venous thrombo-

Table 1. Characteristics of 1100 Patients with Suspected Pulmonary Embolism

Characteristic	Pulmonary Embolism (n = 440)	No Pulmonary Embolism (n = 660)	*P* Value
	Number (%)		
Male sex	205 (47)	293 (44)	0.50
Age (years)			0.19
15–62	153 (35)	240 (36)	
63–72	127 (29)	214 (32)	
73–94	160 (36)	206 (31)	
Pre-existing disease or condition			
Cardiovascular	128 (29)	273 (41)	0.0001
Pulmonary	37 (8)	132 (20)	0.0001
Neoplastic	70 (16)	92 (14)	0.39
Endocrine	35 (8)	82 (12)	0.02
Risk factors			
Immobilization	242 (55)	290 (44)	0.0001
Surgery	160 (36)	224 (34)	0.44
Thrombophlebitis (ever)	153 (35)	109 (17)	0.0001
Bone fractures (lower limb)	78 (18)	86 (13)	0.04
Estrogen use	4 (1)	6 (1)	1.00
Pregnancy or postpartum	2 (0.5)	10 (2)	0.14
Symptoms			
Dyspnea (sudden-onset)	358 (81)	210 (32)	0.0001
Dyspnea (gradual-onset)	14 (3)	143 (22)	0.0001
Orthopnea	3 (1)	62 (9)	0.0001
Chest pain	248 (56)	232 (35)	0.0001
Fainting	114 (26)	83 (13)	0.0001
Hemoptysis	31 (7)	25 (4)	0.02
Signs			
Tachycardia (>100 beats per minute)	124 (28)	180 (27)	0.78
Leg swelling (unilateral)	101 (23)	63 (10)	0.0001
Fever >38°C	28 (6)	140 (21)	0.0001
Wheezes	11 (3)	75 (11)	0.0001
Arterial blood gases			
Pa_{O_2} (mm Hg)			0.03
30–59	167 (38)	204 (31)	
60–70	145 (33)	222 (34)	
71–129	128 (29)	234 (35)	
Pa_{CO_2} (mm Hg)			0.02
14–31	161 (36)	226 (34)	
32–35	162 (37)	207 (31)	
36–65	117 (27)	227 (34)	
ECG signs of acute right ventricular overload	200 (45)	54 (8)	0.0001
Chest radiograph			
Right heart enlargement	141 (32)	68 (10)	0.0001
Oligemia	196 (45)	6 (1)	0.0001
Amputation of hilar artery	149 (34)	4 (1)	0.0001
Consolidation (infarction)	74 (17)	3 (0.5)	0.0001
Consolidation (no infarction)	17 (4)	127 (19)	0.0001
Plate-like atelectasis	123 (28)	141 (21)	0.01
Elevated diaphragm (unilateral)	185 (42)	206 (31)	0.0001
Pleural effusion	198 (45)	230 (35)	0.001
Pulmonary edema	1 (0.2)	71 (11)	0.0001

ECG = electrocardiogram; Pa_{CO_2} = partial pressure of carbon dioxide (arterial); Pa_{O_2} = partial pressure of oxygen (arterial).

Table 2. Factors Independently Associated with Pulmonary Embolism*

Factor	Regression Coefficient	Odds Ratio (95% Confidence Interval)	*P* Value
Male sex	0.81	2.3 (1.4–3.6)	0.001
Age (years)			
63–72	0.59	1.8 (1.0–3.1)	0.04
≥73	0.92	2.5 (1.4–4.6)	0.002
Pre-existing disease			
Cardiovascular	−0.56	0.6 (0.4–0.9)	0.03
Pulmonary	−0.97	0.4 (0.2–0.7)	0.005
Thrombophlebitis (ever)	0.69	2.0 (1.2–3.3)	0.007
Symptoms			
Dyspnea (sudden-onset)	1.29	3.6 (2.3–5.7)	0.0001
Chest pain	0.64	1.9 (1.2–3.0)	0.004
Hemoptysis	0.89	2.4 (1.0–6.0)	0.06
Fever >38°C	−1.17	0.3 (0.2–0.7)	0.002
ECG signs of acute right ventricular overload	1.53	4.6 (2.7–7.8)	0.0001
Chest radiograph			
Oligemia	3.86	47 (19–119)	0.0001
Amputation of hilar artery	3.92	51 (17–152)	0.0001
Consolidation (infarction)	3.55	35 (9.7–126)	0.0001
Consolidation (no infarction)	−1.23	0.3 (0.1–0.6)	0.001
Pulmonary edema	−2.83	0.1 (0.0–0.6)	0.02
Constant	−3.26		

* To estimate the probability of pulmonary embolism, add all of the regression coefficients that apply to a particular patient to the constant (−3.26). The probability of pulmonary embolism then equals 1 ÷ (1 + exp (− sum)). For example, a 50-year-old woman with a history of thrombophlebitis (0.69), sudden-onset dyspnea (1.29), and amputation of a hilar artery on chest radiograph (3.92), but no other characteristics, would have a sum of 0.69 + 1.29 + 3.92 − 3.26, or 2.64. Her probability of pulmonary embolism is 1 ÷ (1 + exp(−2.64)) = 93.3%.
ECG = electrocardiogram.

embolism. In that study (7), the clinical probability was low in 59% of the patients, of whom 3% had pulmonary embolism; moderate in 33% (28% with pulmonary embolism); and high in 8% (78% with pulmonary embolism). Because so few patients were categorized as high risk, that model seems more useful for ruling out—rather

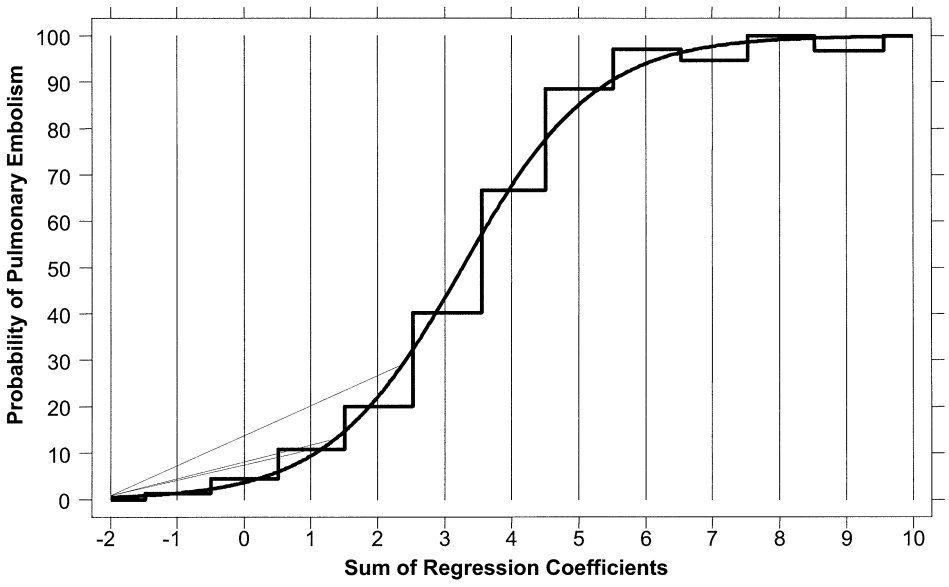

Figure. Probability of pulmonary embolism, as predicted by the model (smooth curve), and the actual prevalence of pulmonary embolism, as observed in the sample (step curve), for different sums of coefficients. See Table 2 for instructions on how to calculate the sum of the coefficients.

Table 3. Comparison between Probability Estimates and Actual Prevalence of Pulmonary Embolism

Probability of Pulmonary Embolism	Number (%)	Patients with Pulmonary Embolism	
		Number	Percentage (95% Confidence Interval)
≤10%	432 (39)	19	4 (3–7)
>10% to ≤50%	283 (26)	62	22 (17–27)
>50% to ≤90%	72 (7)	53	74 (62–83)
>90%	313 (28)	306	98 (95–99)

than ruling in—the diagnosis. The prevalence of pulmonary embolism in that study was only 17%, much lower than in other prospective studies (4–6), and only 4% of the patients had confirmation or exclusion of pulmonary embolism based on pulmonary angiography. Moreover, the model relies on the clinician's subjective judgement as to whether an alternative diagnosis is as or more likely, and is therefore difficult to standardize.

Recently, a simple clinical score was developed to stratify outpatients in an emergency department with suspected pulmonary embolism into groups of low, intermediate, or high probability (9). In that study, the prevalence of pulmonary embolism was 27%, and only a minority of patients underwent pulmonary angiography for a definitive diagnosis. In a multivariate analysis, eight factors were associated with pulmonary embolism: recent surgery, previous thromboembolic event, older age, hypocapnia, hypoxemia, tachycardia, band atelectasis, or elevated diaphragm on the chest radiograph. The score is calculated by assigning points based on these characteristics. A score ≤4 was considered low probability (49% of all patients of whom 10% had pulmonary embolism); a score of 5 to 8 was considered intermediate probability (44% of all patients of whom 38% had pulmonary embolism); and a score ≥9 was considered high probability (6% of all patients of whom 81% had pulmonary embolism) (9). Although the score is based only on standardized criteria, very few patients were high risk. In addition, the model was based on patients in an emergency department and may not be valid in assessing the clinical probability of pulmonary embolism in hospitalized patients.

In contrast, most (>80%) of our patients were hospitalized at the time of study entry. A substantial proportion had cardiovascular or pulmonary disorders that may mimic the clinical presentation of pulmonary embolism; about 50% suffered from prolonged immobilization, about 40% had recent surgery, and 15% had recent trauma. In addition, the prevalence of pulmonary embolism (40%) was substantially higher than in the previous two studies (7,9). In terms of predictive accuracy, the logistic regression model that we developed yields better results than those reported previously (7,9). The area under the ROC curve of our model was 0.95 using the original prediction equation, and 0.94 after cross-validation, compared with 0.79 (0.77 after cross-validation) in one of the previous studies (9).

Instead of using a point-scale score that is proportional to the regression coefficients, we estimated the probability of pulmonary embolism directly from the sum of the regression coefficients. Although calculation of the probability of pulmonary embolism by hand is complex, the Figure can be used as a graphical tool. The score can also be incorporated into electronic devices that would enable physicians to use the estimated probability of pulmonary embolism as the pretest probability when calculating the post-test probability after whichever objective testing they consider most appropriate in their own clinical setting. As an example, Table 4 shows the relation between the pretest and post-test probability of pulmonary embolism conditioned by lung scan results. Post-test probability was calculated by means of Bayes' theorem using sensitivity and specificity values for ventilation-perfusion

Table 4. Ranges of Post-test Probability of Pulmonary Embolism As a Function of Pretest Probability and Lung Scan Results

Pretest Probability of Pulmonary Embolism	Results of V-Q Scan*			Results of Perfusion Scan†	
	High Probability	Intermediate Probability	Low Probability	Suggestive of Pulmonary Embolism	Not Suggestive of Pulmonary Embolism
	Post-test Probability of Pulmonary Embolism (%)				
≤10%	0–60	0–8	0–3	0–58	0–2
>10% to ≤50%	61–93	9–43	3–22	59–92	2–13
>50% to ≤90%	93–99	44–87	22–71	93–99	14–58
>90%	99–100	88–100	72–100	99–100	59–100

* Based on data from reference 4. High-probability scan: segmental or greater perfusion defects with normal ventilation; intermediate-probability scan: not falling into high or low probability; low-probability scan: matched V-Q defects.

† Based on data from reference 5. Scan suggestive of pulmonary embolism: one or more wedge-shaped perfusion defects; scan not suggestive of pulmonary embolism: one or more perfusion defects other than wedge shaped.

V-Q = ventilation-perfusion.

(V-Q) and for perfusion scan (without ventilation imaging), as reported in two broad prospective studies (4,5).

Results of this analysis indicate that a high-probability V-Q scan, or a perfusion scan suggestive of pulmonary embolism, associated with a pretest probability >50% make the diagnosis of pulmonary embolism very likely and justify the institution of anticoagulant therapy. By contrast, a low-probability V-Q scan, or a perfusion scan not suggestive of pulmonary embolism, paired with a low (≤10%) pretest probability make the diagnosis of pulmonary embolism very unlikely and justify withholding of anticoagulant therapy. An intermediate-probability V-Q scan does not modify the pretest probability of pulmonary embolism and should be regarded as nondiagnostic. Finally, when the pretest probability and lung scan results are discordant, the post-test probability is neither sufficiently high nor sufficiently low to permit therapeutic decisions; under these circumstances, further diagnostic testing, such as pulmonary angiography or spiral computerized tomographic angiography, are indicated.

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