Simple and Accurate Prediction of the Clinical Probability of Pulmonary Embolism

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Rationale: Clinical probability assessment is a fundamental step in the diagnosis of pulmonary embolism.

Objectives: To develop a predictive model for pulmonary embolism based on clinical symptoms, signs, and the interpretation of the electrocardiogram.

Methods: The model was developed from a database of 1,100 patients with suspected pulmonary embolism, of whom 440 had the disease confirmed by angiography or autopsy findings. It was validated in an independent sample of 400 patients with suspected pulmonary embolism (71% were inpatients). Easy-to-use software was developed for computing the clinical probability on palm computers and mobile phones.

Measurements and Main Results: The model comprises 16 variables of which 10 (older age, male sex, prolonged immobilization, history of deep vein thrombosis, sudden-onset dyspnea, chest pain, syncope, hemoptysis, unilateral leg swelling, electrocardiographic signs of acute cor pulmonale) are positively associated, and 6 (prior cardiovascular or pulmonary disease, orthopnea, high fever, wheezes, or crackles on chest auscultation) are negatively associated with pulmonary embolism. In the validation sample, 165 (41%) of 400 patients had pulmonary embolism confirmed by angiography. The prevalence of pulmonary embolism was 2% when the predicted clinical probability was slight (0 to 10%), 28% when moderate (11 to 50%), 67% when substantial (51 to 80%), and 94% when high (81 to 100%). There was no significant difference between inpatients and outpatients with respect to the prevalence of pulmonary embolism in the four probability categories.

Conclusions: The proposed model is simple and accurate, and it may aid physicians when assessing the clinical probability of pulmonary embolism.

Keywords: pulmonary embolism; diagnosis; clinical assessment

The results of broad prospective studies lend support to the concept that clinical probability assessment is a fundamental step in the diagnosis of pulmonary embolism (1–7). When considered individually, symptoms, signs, or common laboratory tests have limited diagnostic power. Jointly, however, they may provide accurate assessment of the clinical probability of pulmonary embolism.

Over the last few years, structured prediction models for pulmonary embolism have been developed with the purpose of improving and easing the diagnostic approach (8–13).

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject
None of the available diagnostic tests for suspected pulmonary embolism can safely confirm or exclude the diagnosis without independent assessment of the clinical probability of the disease.

What This Study Adds to the Field
The proposed clinical model is accurate in predicting the probability of pulmonary embolism in both inpatients and outpatients. Easy-to-use software is available for online computation of the clinical probability of pulmonary embolism on palm computers and mobile phones.

In 2003, we introduced a clinical model that proved accurate in predicting the probability of pulmonary embolism (11). This model rests heavily on the interpretation of the chest radiograph, which requires substantial medical expertise (11).

In the present study, we propose a simpler model based on clinical symptoms, signs, and the interpretation of the electrocardiogram. To facilitate its use in clinical settings, easy-to-use software is available for the computation of the clinical probability of pulmonary embolism on palm computers and mobile phones.

METHODS

Sample of Patients
The sample consisted of 1,100 patients who were referred to the Institute of Clinical Physiology (Pisa, Italy) for suspected pulmonary embolism between November 1, 1991, and December 31, 1999. Approximately 70% of patients were referred from the medical or surgical departments, and from the emergency ward of the city hospital; about 30% came from four peripheral hospitals in northwestern Tuscany. The suspicion of pulmonary embolism had been raised on the basis of the following: presence of symptoms such as unexplained dyspnea, chest pain, fainting, or hemoptysis; electrocardiographic or echocardiographic signs of acute right ventricular overload; arterial hypoxemia with respiratory alkalosis. None of the patients had undergone any objective testing for pulmonary embolism before entering the study. Presence or absence of pulmonary embolism was firmly established in all patients. Patients’ baseline characteristics are reported in the online supplement.

All the patients were examined uniformly according to a standardized protocol that included clinical evaluation, perfusion lung scanning, and pulmonary angiography. Details on the acquisition and interpretation of lung scans and angiograms are given elsewhere (2, 3, 11). All the procedures, including pulmonary angiography, were performed in a dedicated diagnostic unit at our institution. The protocol was approved by the local ethics committee. Before angiography, an informed, written consent was obtained.

Clinical Evaluation
Upon study entry, patients were examined by 1 of 12 chest physicians who served as on-call physicians 1 day a week.
When interviewing the patients, care was taken to identify risk factors for pulmonary embolism and preexisting diseases that may mimic the clinical presentation of pulmonary embolism. In evaluating dyspnea, attention was paid to establish whether it was sudden or gradual in onset, or whether it was associated with orthopnea. Unilateral leg swelling with or without tenderness and redness of the skin was regarded as a sign suggestive of deep vein thrombosis.

Electrocardiograms obtained within 24 hours before study entry were considered for evaluation by the physicians. Acute cor pulmonale was deemed present if one or more of the following abnormalities were identified: S wave in lead I and Q wave in lead III, each of an amplitude greater than 1.5 mm; with T-wave inversion in lead III (S1Q3T3), S waves in lead I, II, and III, each of an amplitude greater than 1.5 mm (S1S2S3); T-wave inversion in right precordial leads, transient right bundle branch block, and pseudoinfarction (14, 15). If any of the above abnormalities were present in electrocardiograms taken before the onset of symptoms, they were disregarded.

All clinical and laboratory data were recorded by the physicians on a standard form before any further objective testing. The data were grouped into four classes based on the quartiles of its observed distribution (15–56, 57–67, 68–74, and 75–94 yr). The univariate relationship between patients’ baseline characteristics and the diagnosis of pulmonary embolism was assessed by Fisher’s exact test or by Mann-Whitney nonparametric test. Two-tailed \( P \) values less than 0.05 were considered statistically significant throughout.

### Diagnostic Criteria for Pulmonary Embolism

The diagnosis of pulmonary embolism was based on angiography or autopsy documentation of pulmonary emboli. Criteria for excluding pulmonary embolism were a normal pulmonary angiogram, absence of pulmonary emboli at autopsy, or a normal perfusion scan. Pulmonary angiograms were not obtained in patients with normal scans because available data indicated that such a scintigraphic pattern alone makes a diagnosis of pulmonary embolism very unlikely (16–18). A 6-month clinical follow-up was pursued in patients with normal scans at inclusion. In patients with confirmed pulmonary embolism, a scintigraphic follow-up was obtained at 1 week, 1 month, and 1 year of diagnosis to assess the restoration of pulmonary perfusion (19).

### Pulmonary Angiography

Pulmonary cineangiograms were obtained according to standardized procedures within 24 hours of study entry (2, 3). Initial filming was in the anteroposterior view, after having advanced the catheter into the main pulmonary artery of the lung that showed the greatest perfusion abnormalities on lung scanning. If there was doubt about the presence of filling defects, the appropriate vessel was selectively entered with a balloon-tipped catheter and angiograms were repeated by manual injection of contrast material. Pulmonary angiograms were examined by experienced physicians who were blinded to clinical information. Angiographic criteria for diagnosing pulmonary embolism included the identification of an embolus obstructing a vessel or the outline of an embolus within a vessel. In patients who died before angiography, the diagnosis was established at autopsy.

### Severity of Pulmonary Embolism

We estimated the extent of scintigraphically detectable pulmonary vascular obstruction at baseline as an index of disease severity. This analysis was performed by a nuclear medicine specialist, who was blinded to clinical information, according to a method originally validated against pulmonary angiography (20). Details are given in the online supplement.

### Derivation of the Predictive Model

We provided the sample prevalence for all the variables collected in the 1,100 patients, separately for patients with and those without pulmonary embolism. Age was the only continuous variable, and it was grouped into four classes based on the quartiles of its observed distribution (15–56, 57–67, 68–74, and 75–94 yr). The univariate relationship between patients’ baseline characteristics and the diagnosis of pulmonary embolism was assessed by Fisher’s exact test or by Mann-Whitney nonparametric test. Two-tailed \( P \) values less than 0.05 were considered statistically significant throughout.

We developed a logistic regression model for the probability of having pulmonary embolism. Initially, all the baseline variables were included in the model. Then, they were removed one by one, if not statistically significant. If the removal caused large changes (>10%) in the coefficients of any of the remaining variables, the removed variable was reintroduced into the model. In the model-building process, age and sex were considered known relevant predictors and were kept in the model regardless of their statistical significance. In the final model, however, all the variables included were statistically significant (Table 1). The area under the receiver operating characteristic (ROC) curve of the final model was reported, together with its 95% confidence interval (CI). All the analysis was performed on Stata (STATA 10; StataCorp, College Station, TX) and R software (http://www.r-project.org). We provided the sample prevalence for all the variables collected in the 1,100 patients, separately for patients with and those without pulmonary embolism. Age was the only continuous variable, and it was grouped into four classes based on the quartiles of its observed distribution (15–56, 57–67, 68–74, and 75–94 yr). The univariate relationship between patients’ baseline characteristics and the diagnosis of pulmonary embolism was assessed by Fisher’s exact test or by Mann-Whitney nonparametric test. Two-tailed \( P \) values less than 0.05 were considered statistically significant throughout.

### Internal Validation of the Model

To estimate the predictive accuracy of our model, when applied to a new set of patients, we used bootstrap resampling techniques (21). We estimated the area under the ROC curve from 1,000 bootstrap samples of size 1,100 that were randomly selected with replacement from the original 1,100-patient sample.

### External Validation of the Model

The predictive model, derived from the original 1,100-patient sample, was validated in an independent sample of 454 patients with suspected pulmonary embolism who were evaluated between January 1, 2003, and December 31, 2005. Fifty-four (12%) of them were excluded because of inability to obtain an informed consent (n = 28), or documented contraindications to pulmonary angiography (n = 26). The remaining 400 patients were managed according to the diagnostic protocol de-

### TABLE 1. ESTIMATES FOR REGRESSION COEFFICIENTS, ODDS RATIOS, AND 95% CONFIDENCE INTERVALS OF THE PREDICTORS OF PULMONARY EMBOLISM

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Coefficient</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>57–67</td>
<td>0.80</td>
<td>2.23</td>
<td>1.37–3.63</td>
</tr>
<tr>
<td>68–74</td>
<td>0.87</td>
<td>2.38</td>
<td>1.41–4.01</td>
</tr>
<tr>
<td>&gt;75</td>
<td>1.14</td>
<td>3.11</td>
<td>1.82–5.32</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.60</td>
<td>1.82</td>
<td>1.27–2.61</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immobilization</td>
<td>0.42</td>
<td>1.53</td>
<td>1.08–2.15</td>
</tr>
<tr>
<td>Deep vein thrombosis (ever)</td>
<td>0.64</td>
<td>1.90</td>
<td>1.23–2.95</td>
</tr>
<tr>
<td>Preexisting diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>–0.51</td>
<td>0.60</td>
<td>0.41–0.88</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>–0.89</td>
<td>0.41</td>
<td>0.24–0.72</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea (sudden onset)</td>
<td>2.00</td>
<td>7.38</td>
<td>5.18–10.51</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>–1.51</td>
<td>0.22</td>
<td>0.05–0.93</td>
</tr>
<tr>
<td>Chest pain</td>
<td>1.01</td>
<td>2.74</td>
<td>1.93–3.88</td>
</tr>
<tr>
<td>Fainting or syncope</td>
<td>0.66</td>
<td>1.93</td>
<td>1.25–2.98</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>0.93</td>
<td>2.52</td>
<td>1.19–5.35</td>
</tr>
<tr>
<td>Signs</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Leg swelling (unilateral)</td>
<td>0.80</td>
<td>2.23</td>
<td>1.35–3.70</td>
</tr>
<tr>
<td>Fever &gt; 38 °C</td>
<td>–1.47</td>
<td>0.23</td>
<td>0.13–0.40</td>
</tr>
<tr>
<td>Wheezes</td>
<td>–1.20</td>
<td>0.30</td>
<td>0.14–0.66</td>
</tr>
<tr>
<td>Crackles</td>
<td>–0.61</td>
<td>0.54</td>
<td>0.35–0.83</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Acute cor pulmonale*</td>
<td>1.96</td>
<td>7.11</td>
<td>4.66–10.87</td>
</tr>
<tr>
<td>Constant</td>
<td>–3.43</td>
<td></td>
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</tbody>
</table>

Definition of abbreviation: CI = confidence interval.

* One or more of the following abnormalities: \( S_1Q_3T_3, S_1S_2S_3, \) negative T waves in right precordial leads, transient right bundle branch block, pseudoinfarction.

Calculation of the clinical probability of pulmonary embolism: (1) Add all the coefficients that apply to a given patient and the constant (sum); (2) the probability of pulmonary embolism equals \( 1 + \exp(-\text{sum}) \).
scribed above. The clinical probability of pulmonary embolism was estimated at bedside by one of seven residents in respiratory medicine by using the proposed software on palm computers. Clinical probability was assessed before any further objective testing.

The management of the 54 patients who were excluded from the validation sample is described in the online supplement.

RESULTS

Derivation Sample

The 1,100 patients in the derivation sample had a median age of 68 years (interquartile range [IQR], 57–75 yr); 45% of them were male, and 81% were hospitalized at the time of study entry. On the basis of angiography and autopsy findings, the prevalence of pulmonary embolism was 40%. The median extent of pulmonary vascular obstruction at baseline was 42% (IQR, 30–57%). Most of the patients with pulmonary embolism showed a nearly complete restoration of pulmonary perfusion, with 90% of them having a residual vascular obstruction of less than 15% at 1 year of diagnosis.

Among the patients without pulmonary embolism, 242 had normal perfusion scans. None of these patients had symptomatic episodes of venous thromboembolism during a 6-month period of follow-up.

Predictive Model

Sixteen variables were incorporated into a multivariate logistic regression model, of which 10 were positively and 6 were negatively associated with pulmonary embolism (Table 1).

Variables associated with an increased likelihood of pulmonary embolism were as follows: older age, male sex, prolonged immobilization, history of deep vein thrombosis, sudden-onset dyspnea, chest pain, fainting (or syncope), hemoptysis, and electrocardiographic signs of acute cor pulmonale. Variables associated with a decreased likelihood of pulmonary embolism included prior cardiovascular or pulmonary disease, orthopnea, high fever, wheezes, or crackles on chest auscultation. The area under the ROC curve was 0.90 (95% CI, 0.88–0.91).

The probability of pulmonary embolism can be calculated using the proposed software on palm computers. Clinical probability was estimated at bedside by one of seven residents in respiratory medicine by using the proposed software on palm computers. Clinical probability was assessed before any further objective testing.

Internal Validation

The predictive model derived from the original 1,100-patient sample appeared to be accurate and parsimonious. The overall accuracy of the model, as measured by the ROC area, was validated based on 1,000 bootstrap samples. The area under the ROC curve on a sample of new independent patients was estimated to be 0.88.

External Validation

The 400 patients in the validation sample had a median age of 70 years (IQR, 59–76 yr); 42% were male, and 71% were inpatients at the time of study entry. Further characteristics are given in the online supplement.

Pulmonary embolism was diagnosed by angiography in 165 (41%) of 400 patients. The median extent of pulmonary vascular obstruction at baseline was 40% (IQR, 27–56%). Of the 235 patients without pulmonary embolism, 83 had normal perfusion scans. None of them presented with symptomatic episodes of venous thromboembolism over a 6-month follow-up. The proportion of patients in each of the four probability categories and the relative prevalence of pulmonary embolism are reported in Table 3 for the whole sample, and separately for inpatients and outpatients. In the validation sample, the area under the ROC curve was 0.88 (95% CI, 0.84–0.91), which was consistent with the estimate from the internal validation.

The prevalence of pulmonary embolism in outpatients (46%) was slightly but not significantly higher than in inpatients (39%, P value = 0.18 by Fisher’s test). There was no significant difference between inpatients and outpatients regarding the prevalence of pulmonary embolism in each of the four proba-

<table>
<thead>
<tr>
<th>TABLE 2. COMPARISON BETWEEN CLINICAL PROBABILITY AND ACTUAL PREVALENCE OF PULMONARY EMBOLISM IN DERIVATION SAMPLE</th>
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<tbody>
<tr>
<td>Clinical Probability (%)</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>0–10</td>
</tr>
<tr>
<td>11–50</td>
</tr>
<tr>
<td>51–80</td>
</tr>
<tr>
<td>81–100</td>
</tr>
</tbody>
</table>

Definition of abbreviation: CI = confidence interval; PE = pulmonary embolism.

* P = 0.555 compared with inpatients (Fisher’s test).
† P = 0.297 compared with inpatients (Fisher’s test).
‡ P = 0.156 compared with inpatients (Fisher’s test).
§ P = 0.091 compared with inpatients (Fisher’s test).

Figure 1. Extent of scintigraphically detectable pulmonary vascular obstruction as a function of clinical probability in 440 patients with pulmonary embolism. Line in box: 50th percentile; limits of box: 25th and 75th percentile; whiskers: 10th and 90th percentile. In parentheses, number of patients in each clinical probability category. P value < 0.0001 by Kruskal-Wallis nonparametric test.
ability categories (Table 3). In the 165 patients with pulmonary embolism at inclusion, there was a highly significant, positive relation between the clinical probability predicted by the model and the severity of pulmonary embolism on the lung scan (P value < 0.001 by Kruskal-Wallis nonparametric test).

**DISCUSSION**

Our model is entirely based on the evaluation of relevant clinical symptoms and signs, and the interpretation of the electrocardiogram. Therefore, it is applicable in any clinical context. Among the symptoms, sudden-onset dyspnea is a strong predictor of pulmonary embolism. The importance of characterizing dyspnea in terms of onset has long been recognized (22), but it was largely overlooked in most studies reported thus far (8–10, 13). Although the interpretation of the electrocardiogram requires medical expertise, the abnormalities associated with acute cor pulmonale are based on clearly defined criteria, which have been known and applied for many years (14, 15).

In terms of predictive accuracy, our model outperformed those reported by others (8–10, 13). The area under the ROC curve was 0.90 in the derivation sample, and 0.88 in the validation sample. In addition, the model performed equally well in inpatients and outpatients. Among the patients with pulmonary embolism, there was a strong relation between the clinical probability predicted by the model and the severity of embolism on lung scintigraphy—the higher the probability, the greater the extent of vascular obstruction.

Our previous model yielded somewhat better results, the area under the ROC curve being 0.95 in the derivation sample (11) and 0.94 in an independent sample of new patients (12). This model includes chest radiographic abnormalities some of which are specific for pulmonary embolism, whereas others suggest an alternative diagnosis (11). Recognizing such abnormalities, however, requires substantial medical expertise.

The present and our previous models include variables that are negatively associated with pulmonary embolism. This gives the models greater flexibility, which may explain why they perform equally well in detecting and in ruling out pulmonary embolism. Also, instead of using a point-scale score proportional to the regression coefficients, typical of other approaches (8–10, 13), we estimate the probability of pulmonary embolism directly from the sum of the regression coefficients. This allows predicting the clinical probability as a continuous function and precise estimation of likelihood ratios. The relative complexity of the calculation can be overcome by using dedicated software that permits online computation of clinical probability. Software (13 kilobytes in size) is available at http://www.ifc.cnr.it/pismodel. It can be uploaded via the Internet on desktop, laptop, and palm computers, and mobile phones.

The prevalence of pulmonary embolism in our study was higher than that reported by others (8–10, 13). This prevalence was observed as early as 1970, when our institution became a referral center for the diagnosis of pulmonary embolism, and it has remained fairly constant ever since. Most likely, this reflects the soundness of the clinical suspicion of the disease raised by the referring physicians.

The positive and negative predicted values of our model, however, are higher than those reported by others (8–10, 13), regardless of the prevalence of pulmonary embolism, which suggests that the proposed model may be applied in evaluating patients from different populations with varying prevalence of the disease.

The clinical probability predicted by the model can be used by physicians as the pretest probability in calculating the posttest probability of pulmonary embolism after appropriate objective testing. An example is given in Figure 2, which shows the relationship between pretest and posttest probability of pulmonary embolism conditioned by the results of quantitative ELISA D-dimer test (A) and multidetector computed tomographic angiography (B).

![Figure 2](image)

**Figure 2.** Relationship between pretest (clinical) probability of pulmonary embolism (PE) and posttest probability conditioned by the results of quantitative ELISA D-dimer test (A) and multidetector computed tomographic angiography (B).

This formal analysis indicates the following: (1) a D-dimer concentration of 500 ng/ml or less with a pretest probability less than < 50% makes a diagnosis of pulmonary embolism very unlikely; (2) a D-dimer concentration greater than 500 ng/ml does not modify the pretest probability and is, therefore, clinically useless; (3) a negative CTA with a pretest probability of 10% or less rules out clinically significant pulmonary embolism; (4) a positive CTA with a pretest probability of 50% or greater makes a diagnosis of pulmonary embolism very likely; (5) when pretest probability and CTA results are discordant, the posttest probability is neither sufficiently high nor sufficiently low to permit therapeutic decisions; under these circumstances further diagnostic testing is mandatory.

The model proposed may provide physicians with a diagnostic edge when evaluating patients for suspected pulmonary embolism. Even though its predictive accuracy is supported by internal and external validation procedures, further validation in patients from other centers would be desirable.
Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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