A Prediction Rule to Identify Low-Risk Patients With Pulmonary Embolism

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Background: A simple prognostic model could help identify patients with pulmonary embolism who are at low risk of death and are candidates for outpatient treatment.

Methods: We randomly allocated 15,531 retrospectively identified inpatients who had a discharge diagnosis of pulmonary embolism from 186 Pennsylvania hospitals to derivation (67%) and internal validation (33%) samples. We derived our rule to predict 30-day mortality using classification tree analysis and patient data routinely available at initial examination as potential predictor variables. We used data from a European prospective study to externally validate the rule among 221 inpatients with pulmonary embolism. We determined mortality and nonfatal adverse medical outcomes across derivation and validation samples.

Results: Our final model consisted of 10 patient factors (age ≥70 years; history of cancer, heart failure, chronic lung disease, chronic renal disease, and cerebrovascular disease; and clinical variables of pulse rate ≥110 beats/min, systolic blood pressure <100 mm Hg, altered mental status, and arterial oxygen saturation <90%). Patients with none of these factors were defined as low risk. The 30-day mortality rates for low-risk patients were 0.6%, 1.5%, and 0% in the derivation, internal validation, and external validation samples, respectively. The rates of nonfatal adverse medical outcomes were less than 1% among low-risk patients across all study samples.

Conclusions: This simple prediction rule accurately identifies patients with pulmonary embolism who are at low risk of short-term mortality and other adverse medical outcomes. Prospective validation of this rule is important before its implementation as a decision aid for outpatient treatment.

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Pulmonary embolism (PE) is a major health problem, with an estimated incidence of 23 to 69 cases per 100,000 persons annually in the United States.1,2 Data from the National Hospital Discharge Survey3 show that 101,000 patients were hospitalized in 2002 in acute care hospitals having a primary diagnosis of PE in the United States, resulting in 676,700 inpatient days. The all-cause short-term mortality of this illness varies widely, ranging from more than 95% among patients who experience cardiorespiratory arrest to less than 2% among patients with nonmassive PE,4,5 defined as PE without systemic hypotension, cardiogenic shock, or respiratory failure.6

There is growing evidence that outpatient treatment with low-molecular-weight heparin sodium is effective and safe for selected patients with nonmassive PE.7-10

See also pages 147, 176, and 181

Based on this evidence, experts11,12 and the British Thoracic Society guidelines for the management of acute PE13 recommend outpatient treatment for clinically stable patients. Outpatient treatment for nonmassive PE is not widely accepted because no explicit clinical criteria exist to accurately identify patients with PE who are at low risk of adverse outcomes. Therefore, we sought to develop an objective and easily applied clinical prediction rule to identify patients with PE at low risk of short-term mortality and other adverse medical outcomes who are candidates for outpatient treatment.

Author Affiliations are listed at the end of this article.
The baseline clinical variables necessary to derive our prediction rule were obtained from the Atlas database (MediQual, Marlborough, Mass). Clinical inpatient data from all nongovernmental acute care hospitals in Pennsylvania are represented in this proprietary database, which is compiled from patient medical records using standardized data collection instruments.

We used vital signs measured in the emergency department for all patients admitted through the emergency department; all other variables were recorded on the day of hospital admission. For patients admitted from other sources (eg, directly from a physician’s office), we abstracted all clinical variables on the day of admission. To derive our prediction rule, we used clinical variables routinely available to clinicians at the time of initial examination and previously shown to be associated with short-term mortality in patients who have PE or other acute diseases (Table 1). We did not consider other potential predictors such as right ventricular dysfunction, mean pulmonary arterial pressure, or concomitant deep vein thrombosis by sonography because these conditions are not routinely assessed among patients diagnosed as having PE.

**OUTCOME MEASURES**

The main study outcome used to derive our prediction rule was death from all causes within 30 days of each hospitalization. All-cause 30-day mortality is objective and clinically relevant and is a widely used outcome of prognostic models for other acute diseases or medical interventions. Most deaths due to PE occur within this time frame. We obtained mortality data from the National Death Index. Using Atlas database information and discharge ICD-9-CM codes from the Pennsylvania Health Care Cost Containment Council database, we also assessed whether patients classified as low risk by our prediction rule developed nonfatal cardiogenic shock (ICD-9-CM code 785.51) or cardiorespiratory arrest, defined as cardiac arrest (ICD-9-CM code 427.5), resuscitation (ICD-9-CM codes 99.60, 99.63, and 37.91), intubation (ICD-9-CM codes 96.04 and 96.05), or mechanical ventilation (ICD-9-CM codes 96.70-90.72).

**DERIVATION, INTERNAL VALIDATION, AND EXTERNAL VALIDATION OF THE PREDICTION RULE**

Of the 16,468 patient discharges that met our inclusion criteria, we excluded 937 because they were missing patient identifiers (n=867) or could not be linked to the National Death Index (n=70). Therefore, the study cohort comprised 15,531 patients who had a discharge diagnosis of PE from 186 Pennsylvania hospitals. Overall, these discharges represented 14,672 individual patients with PE; 895 discharges (6%) represented recurrent PE episodes that occurred during the study period. We randomly selected 10,354 discharges (67%) for the derivation sample and 5,177 discharges (33%) for the internal validation sample.

We derived our prediction rule using classification tree analysis, with 30-day mortality as the outcome and the demographic and clinical variables in Table 1 as predictors. Except for age, we dichotomized continuous variables using clinically meaningful cutoff points that are commonly used in clinical practice and are easily remembered by physicians (eg, systolic blood pressure <100 mm Hg and arterial oxygen saturation <90%). Unknown values were assumed to be normal, a strategy successfully used in the derivation and validation of a widely used previous prognostic model for pneumonia. Using S-Plus 2000 software, we recursively partitioned our deriva-
tion sample into progressively more homogeneous subgroups by sequentially identifying predictor variables that best discriminated between patients who died and those who did not. At each step, the program automatically examined all possible splits for age and each categorical predictor to identify the variable and cutoff point that maximized goodness of fit. The splitting process continued until the subgroups were homogeneous or contained fewer than 3 deaths. Although we did not modify the automatically generated models using subjective criteria, we rounded cutoff points to the next clinically meaningful value. We explored candidate tree models with and without laboratory variables, trying to find models that identified a low-risk group with a membership of at least 20% of the total derivation sample and a 30-day mortality of less than 1%. Although no widely accepted threshold defines low risk, prognostic models for other acute diseases such as community-acquired pneumonia or heart failure defined short-term mortality rates below 1% to 2% as low risk.31 Among candidate models meeting these criteria, we chose the one with the fewest predictors.

We then assessed the performance of our prediction rule in the internal validation sample by computing the proportion of patients who were classified as low vs higher risk and the proportion of patients who died within 30 days of initial examination. Because 7-day mortality may be more relevant for the hospital admission decision than 30-day mortality, we also estimated the proportion of patients in both samples who died 7 days after admission or experienced nonfatal cardiogenic shock or cardiopulmonary arrest in the hospital.

We externally validated our rule using data previously collected from a prospective cohort study39 that used spiral computed tomography to diagnose PE. That study enrolled patients with suspected PE from 3 emergency departments at the university hospitals of Lausanne, Geneva, and Angers between October 1, 2000, and June 30, 2002. Patients who had a contraindication to spiral computed tomography to diagnose PE. That study enrolled patients with suspected PE from 3 emergency departments at the university hospitals of Lausanne, Geneva, and Angers between October 1, 2000, and June 30, 2002. Patients who had a contraindication to spiral computed tomography to diagnose PE. That study enrolled patients with suspected PE from 3 emergency departments at the university hospitals of Lausanne, Geneva, and Angers between October 1, 2000, and June 30, 2002. Patients who had a contraindication to spiral computed tomography to diagnose PE. That study enrolled patients with suspected PE from 3 emergency departments at the university hospitals of Lausanne, Geneva, and Angers between October 1, 2000, and June 30, 2002. Patients who had a contraindication to spiral computed tomography to diagnose PE. That study enrolled patients with suspected PE from 3 emergency departments at the university hospitals of Lausanne, Geneva, and Angers between October 1, 2000, and June 30, 2002. Patients who had a contraindication to spiral computed tomography to diagnose PE. That study enrolled patients with suspected PE from 3 emergency departments at the university hospitals of Lausanne, Geneva, and Angers between October 1, 2000, and June 30, 2002. Patients who had a contraindication to spiral computed tomography to diagnose PE. That study enrolled patients with suspected PE from 3 emergency departments at the university hospitals of Lausanne, Geneva, and Angers between October 1, 2000, and June 30, 2002. Patients who had a contraindication to spiral computed tomography to diagnose PE. That study enrolled patients with suspected PE from 3 emergency departments at the university hospitals of Lausanne, Geneva, and Angers between October 1, 2000, and June 30, 2002. Patients who had a contraindication to spiral computed tomography to diagnose PE. That study enrolled patients with suspected PE from 3 emergency departments at the university hospitals of Lausanne, Geneva, and Angers between October 1, 2000, and June 30, 2002. Patients who had a contraindication to spiral computed tomography to diagnose PE. That study enrolled patients with suspected PE from 3 emergency departments at the university hospitals of Lausanne, Geneva, and Angers between October 1, 2000, and June 30, 2002. Patients who had a contraindication to spiral computed tomography to diagnose PE. That study enrolled patients with suspected PE from 3 emergency departments at the university hospitals of Lausanne, Geneva, and Angers between October 1, 2000, and June 30, 2002. Patients who had a con...
In the internal validation sample, our derived model classified 21.6% (95% CI, 20.5%-22.7%) of patients as low risk, with low-risk patients having a 30-day mortality of 1.5% (95% CI, 0.9%-2.4%) (Table 3). Although 30-day mortality was somewhat higher in the internal validation sample than in the derivation sample (P=.01), the 0.9% difference was small in absolute terms. Seven-day mortality was 0.4% (95% CI, 0.2%-0.7%) in the derivation sample and 0.9% (95% CI, 0.4%-1.6%) in the internal validation sample (P=.05). The rate of nonfatal cardiogenic shock or cardiorespiratory arrest among low-risk inpatients was 0.7% (95% CI, 0.4%-1.2%) in the derivation sample and 0.9% (95% CI, 0.4%-1.6%) in the internal validation sample (P=.58).

In the external validation sample, our prediction rule classified 33.9% (95% CI, 27.7%-40.6%) of patients as low risk, a higher proportion than in the derivation sample (P=.001) (Table 3). None of the low-risk patients in the external validation group died within 7 days or 30 days of the initial examination (P>.99 for both groups compared with the derivation sample). During the 3-month follow-up period, none of the low-risk patients in the external validation sample died, had recurrent venous thromboembolism, or experienced a major bleeding episode.

The rule had a high sensitivity (range, 97%-100%) and a high negative predictive value (range, 98%-100%) for predicting 30-day mortality (Table 4). Because the prediction rule was specifically designed to identify low-risk patients (ie, to rule out short-term mortality), the specificity (range, 23%-35%) and positive predictive value (range, 4%-12%) were low.

**COMMENT**

We developed a simple clinical prediction rule based on 10 demographic, history, and clinical findings to identify low-risk patients with PE. Among large derivation and internal validation samples of patients with PE, our rule identified more than one fifth of patients at low risk of short-term mortality and serious medical complications. In an independent validation cohort of patients with PE, we confirmed the accuracy of our prediction rule: none of the patients classified as low risk died, experienced recurrent venous thromboembolism, or had major bleeding during a 3-month follow-up. Overall, our rule had a negative predictive value for 30-day mortality of at least 98% across the derivation and 2 validation samples.

The potential clinical and economic benefit of our prediction rule can be estimated using data from a recent cost-effectiveness analysis comparing inpatient treatment with unfractionated heparin vs low-molecular-weight heparin in patients with PE. Treatment with low-molecular-weight heparin was cost saving when at least 5% of patients were treated as outpatients or 8% were discharged early. Assuming a cost difference of $4500 between inpatient and outpatient treatment of PE and an annual PE incidence of 101 000 cases, up to $91 million per year could be saved in the United States if 20% of patients were treated as outpatients. Therefore, treating patients with PE identified as low risk using our prediction rule in an ambulatory setting could result in im-

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**Figure.** The clinical prediction rule. Cerebrovascular disease includes transient ischemic attack or stroke. Altered mental status includes disorientation, lethargy, stupor, or coma.
portant cost savings. However, at the initial site of
treatment decision for patients with PE, it is important
for physicians also to consider psychosocial contraindi-
cations to outpatient care (eg, lack of treatment adher-
ence). Other potential barriers to outpatient treatment
are the lack of outpatient systems of health care and the
absence of insurance coverage for more costly low-
molecular-weight heparin.

Our prediction rule consists of 10 clinical prognostic
factors that are routinely available in all hospital set-
tings and that were previously shown to be associated
with adverse outcomes among patients with PE and other
acute diseases.16-20,22 Compared with a previous prog-
nostic model for PE,20,41 our prediction rule has distinctive
strengths. First, our rule consists of clearly defined, rou-
tinely available predictors and does not require any labo-
atory tests or radiographic procedures not routinely per-
formed in the management of PE. Second, the accuracy
and generalizability of the rule are supported by its deri-
vation and internal and external validation in 15 752 pa-
tients from 189 hospitals and 3 countries. Third, our study
samples represent a broad disease spectrum, ranging from
nonmassive PE to PE with cardiorespiratory arrest.

Investigators in a prior study9 successfully treated 81
(51%) of 158 patients with PE as outpatients using low-
molecular-weight heparin. Patients without arterial hy-
opension, arterial hypoxemia, pain requiring intrave-
nous narcotics, social contraindications to outpatient
treatment, and comorbid conditions necessitating hos-
pital treatment were eligible for that study, although the
comorbid conditions requiring hospitalization were not
specified. Moreover, patients enrolled in that study were
younger and potentially healthier than the patients in our
study samples, which may have resulted in a higher pro-
portion of patients considered as low risk. In contrast to
the unspecific eligibility criteria of the prior study,9 our
prediction rule provides clinicians a set of explicit cri-
teria to identify low-risk patients with PE.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Derivation Sample (n = 10 354)</th>
<th>Internal Validation Sample (n = 5 177)</th>
<th>External Validation Sample (n = 221)</th>
<th>Derivation vs Internal Validation Samples</th>
<th>Derivation vs External Validation Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-d Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>21.6 (20.8-22.4)</td>
<td>21.6 (20.5-22.7)</td>
<td>33.9 (27.7-40.6)</td>
<td>.99</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Higher risk</td>
<td>78.4 (77.6-79.2)</td>
<td>78.4 (77.3-79.5)</td>
<td>66.1 (59.4-72.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal cardiogenic shock or cardiorespiratory arrest†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>0.6 (0.3-1.0)</td>
<td>1.5 (0.9-2.4)</td>
<td>0 (0-4.8)</td>
<td>.01</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Higher risk</td>
<td>11.5 (10.8-12.2)</td>
<td>11.7 (10.7-12.7)</td>
<td>4.1 (1.5-8.7)</td>
<td>.79</td>
<td>.005</td>
</tr>
</tbody>
</table>

*Data are given as percentage (95% confidence interval) unless otherwise indicated.
†During the initial hospital stay.
‡Inpatient complications such as death, cardiogenic shock, and cardiorespiratory arrest were not explicitly recorded in the external validation sample.

Table 4. Accuracy of the Prediction Rule to Predict 30-Day Mortality in the Derivation and Validation Samples*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Derivation Sample (n = 10 354)</th>
<th>Internal Validation Sample (n = 5 177)</th>
<th>External Validation Sample (n = 221)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>99 (98-99)</td>
<td>97 (95-98)</td>
<td>100 (54-100)</td>
</tr>
<tr>
<td>Specificity</td>
<td>24 (23-25)</td>
<td>23 (22-25)</td>
<td>35 (29-42)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>12 (11-12)</td>
<td>12 (11-13)</td>
<td>4 (2-9)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>99 (99-100)</td>
<td>98 (98-99)</td>
<td>100 (95-100)</td>
</tr>
<tr>
<td>Positive likelihood ratio</td>
<td>1.29 (1.27-1.31)</td>
<td>1.26 (1.23-1.29)</td>
<td>1.54 (1.39-1.69)</td>
</tr>
<tr>
<td>Negative likelihood ratio</td>
<td>0.06 (0.03-0.10)</td>
<td>0.15 (0.09-0.24)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Data are given as percentage (95% confidence interval) unless otherwise indicated.

However, patients classified as higher risk by our pre-
diction rule (eg, patients with cancer) may choose to be
treated as outpatients even if their short-term prognosis
is worse than that in low-risk patients. Until random-
ized trials comparing inpatient vs outpatient treatment
of PE are conducted, it remains uncertain whether the
initial site of treatment affects mortality rates.

Our work has potential limitations. First, patients in
our derivation and internal validation samples were identi-
fied using ICD-9-CM codes for PE rather than standard-
ized clinical criteria and may be subject to study selec-
tion biases because of hospital coding procedures. How-
ever, prior studies42-44 demonstrated that 94% to 96%
of patients with specific ICD-9-CM codes for PE had ob-
jectively documented disease based on medical record
review criteria. Second, we cannot exclude the possibil-
ity that patients who were identified using a primary ICD-
9-CM code for conditions that may represent complica-

Table 3. Risk Classification and Outcomes for Patients in the Derivation and Validation Samples*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Derivation Sample (n = 10 354)</th>
<th>Internal Validation Sample (n = 5 177)</th>
<th>External Validation Sample (n = 221)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classification</td>
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<td></td>
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<td>7-d Mortality</td>
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<td>Low risk</td>
<td>0.4 (0.2-0.7)</td>
<td>0.9 (0.4-1.6)</td>
<td>0 (0-4.8)</td>
<td>.05</td>
</tr>
<tr>
<td>Higher risk</td>
<td>5.2 (4.8-5.7)</td>
<td>6.1 (5.4-6.8)</td>
<td>1.4 (0.2-4.9)</td>
<td>.06</td>
</tr>
<tr>
<td>30-d Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>0.6 (0.3-1.0)</td>
<td>1.5 (0.9-2.4)</td>
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tions of PE (eg, cardiogenic shock) developed PE as a consequence of these conditions. However, the performance of our prediction rule did not change when these patients were excluded from analysis. Third, we had no information about the timeliness or type of treatments received (eg, type of heparin) among our study samples. Therefore, we could not assess whether patients who were treated differently experienced different outcomes. Fourth, we externally validated our rule using data from a prior prospective study that was not designed to validate our prediction rule. The small sample size in that study resulted in wide 95% CIs for mortality rates. Although the healthier patients in the external validation sample may not reflect the full prognostic spectrum of patients with PE, no deaths occurred in the subgroup that was identified as low risk by our prediction rule.

We derived and validated a clinical prediction rule that accurately identifies a substantial proportion of patients with PE who are at low risk of death and other adverse outcomes and who are candidates for less costly outpatient treatment. However, before this prediction rule can be considered ready for use in clinical practice, it should be validated in a prospective study.

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Author Contributions: Dr Aujesky had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES