Prospective validation of the Pulmonary Embolism Severity Index

A clinical prognostic model for pulmonary embolism


1 Division of General Internal Medicine, University of Lausanne, Lausanne, Switzerland; 2 Department of Internal Medicine and Chest Diseases, University of Brest, Brest, France; 3 Division of General Internal Medicine, University of Pittsburgh, and Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare System, University of Pittsburgh, Pittsburgh, Pennsylvania, USA; 4 Department of Emergency Medicine, University of Angers, Angers, France; 5 Department of Respiratory and Critical Care Medicine, Hôpital Européen Georges Pompidou, Paris, France; 6 Department of Emergency Medicine, St. Luc University Hospital, Brussels, Belgium; 7 Division of General Internal Medicine, University of Geneva, Geneva, Switzerland; 8 Division of Angiology and Hemostasis, University of Geneva, Geneva, Switzerland

Introduction

Practice guidelines recommend outpatient care for selected patients with non-massive pulmonary embolism (PE), but fail to specify how these low-risk patients should be identified. Using data from U.S. patients, we previously derived the Pulmonary Embolism Severity Index (PESI), a prediction rule that risk stratifies patients with PE. We sought to validate the PESI in a European patient cohort. We prospectively validated the PESI in patients with PE diagnosed at six emergency departments in three European countries. We used baseline data for the rule’s 11 prognostic variables to stratify patients into five risk classes (I-V) of increasing probability of mortality. The outcome was overall mortality at 90 days after presentation. To assess the accuracy of the PESI to predict mortality, we estimated the sensitivity, specificity, and predictive values for low- (risk classes I/II) versus higher-risk patients (risk classes III-V), and the discriminatory power using the area under the receiver operating characteristic (ROC) curve. Among 357 patients with PE, overall mortality was 5.9%, ranging from 0% in class I to 17.9% in class V. The 186 (52%) low-risk patients had an overall mortality of 1.1% (95% confidence interval [CI]: 0.1–3.8%) compared to 11.1% (95% CI: 6.8–16.8%) in the 171 (48%) higher-risk patients. The PESI had a high sensitivity (91%, 95% CI: 71–97%) and a negative predictive value (99%, 95% CI: 96–100%) for predicting mortality. The area under the ROC curve was 0.78 (95% CI: 0.70–0.86). The PESI reliably identifies patients with PE who are at low risk of death and who are potential candidates for outpatient care. The PESI may help physicians make more rational decisions about hospitalization for patients with PE.

Summary

Practice guidelines recommend outpatient care for selected patients with non-massive pulmonary embolism (PE), but fail to specify how these low-risk patients should be identified. Using data from U.S. patients, we previously derived the Pulmonary Embolism Severity Index (PESI), a prediction rule that risk stratifies patients with PE. We sought to validate the PESI in a European patient cohort. We prospectively validated the PESI in patients with PE diagnosed at six emergency departments in three European countries. We used baseline data for the rule’s 11 prognostic variables to stratify patients into five risk classes (I-V) of increasing probability of mortality. The outcome was overall mortality at 90 days after presentation. To assess the accuracy of the PESI to predict mortality, we estimated the sensitivity, specificity, and predictive values for low- (risk classes I/II) versus higher-risk patients (risk classes III-V), and the discriminatory power using the area under the receiver operating characteristic (ROC) curve. Among 357 patients with PE, overall mortality was 5.9%, ranging from 0% in class I to 17.9% in class V. The 186 (52%) low-risk patients had an overall mortality of 1.1% (95% confidence interval [CI]: 0.1–3.8%) compared to 11.1% (95% CI: 6.8–16.8%) in the 171 (48%) higher-risk patients. The PESI had a high sensitivity (91%, 95% CI: 71–97%) and a negative predictive value (99%, 95% CI: 96–100%) for predicting mortality. The area under the ROC curve was 0.78 (95% CI: 0.70–0.86). The PESI reliably identifies patients with PE who are at low risk of death and who are potential candidates for outpatient care. The PESI may help physicians make more rational decisions about hospitalization for patients with PE.
dated a clinical prediction rule for mortality, designated the Pulmonary Embolism Severity Index (PESI) (13). The PESI, which consists of 11 clinical parameters routinely available at presentation, stratifies patients into five risk classes (I–V) with increasing risk of short-term mortality (Table 1). Patients in risk classes I and II have a risk of short-term mortality of 2.6% or less and are considered low-risk (13, 14). Thus, the PESI provides clinicians with an easily applied prognostic tool for patients with PE and may help identify appropriate candidates for outpatient care or an abbreviated hospital stay.

Temporal and follow-up period transportabilities are important components of the generalizability of a prognostic model (15). These components require that the model’s predictions remain accurate when re-tested in patients from other time periods, using different periods of follow-up. To assess these dimensions of generalizability and to further validate its prognostic accuracy, we applied the PESI to a European patient cohort with PE.

### Material and methods

#### Study sample

We prospectively validated the PESI using data from a clinical trial that evaluated a diagnostic algorithm for PE based on multidetector spiral computed tomography (CT) (16). The trial enrolled patients with suspected PE from emergency departments at six university hospitals in Switzerland, France, and Belgium between January 1, 2005, and August 31, 2006 (16). Consecutive adult outpatients who were treated in the emergency department with a clinical suspicion of PE were potentially eligible. Patients were excluded from this study if they had a contraindication to spiral CT (i.e. allergy to iodine contrast agents, creatinine clearance of less than 30 ml/minute, or pregnancy), a terminal illness with an expected survival of less than three months, a diagnosis of PE documented before the time of presentation, or were receiving anticoagulant therapy at presentation. The criteria used to establish the diagnosis of PE were a positive spiral CT or pulmonary angiography, a high-probability ventilation/perfusion lung scan, or proximal deep-vein thrombosis (DVT) documented by compression ultrasonography. Ultrasonographic diagnosis of proximal DVT has a high positive predictive value (99%) for predicting PE among patients with a clinical suspicion of PE (17). All patients diagnosed with PE were treated with heparin followed by oral anticoagulants.

#### Baseline data collection

Trained study personnel prospectively recorded baseline patient characteristics, including the predictors that comprise the PESI (age, gender, cancer, heart failure, chronic lung disease, pulse, blood pressure, respiratory rate, temperature, altered mental status, and arterial oxygen saturation) and whether patients received thrombolysis, on a standardized data collection instrument. Our definition of altered mental status (disorientation, confusion, or somnolence) was slightly different from the definition used in the original derivation of the PESI (disorientation, lethargy, stupor, or coma). Using the prognostic variables in the PESI, we calculated the risk class for each patient, and the proportion of patients classified within each risk class. Missing values for all prognostic variables were assumed to be normal, a strategy used in the original derivation of the PESI (13) and other prediction rules for mortality (18).

#### Study outcome

Our outcome measure was all-cause mortality 90 days after presentation for PE. We assessed mortality using patient or proxy interviews, interview of the patient’s primary care physician, and/or hospital chart review. Interviews were performed through telephone and administered by local study personnel. Three independent experts adjudicated all deaths as definite, fatal PE and possible, fatal PE or death from other causes. Death was judged to be definite, fatal PE if it was confirmed by autopsy, or if death followed a clinically severe PE, either initially or after an objectively confirmed recurrent event. Death in a patient who died suddenly or unexpectedly was classified as possible, fatal PE.

#### Statistical analyses

We compared the overall mortality rate of low- (risk classes I and II) versus higher-risk patients (risk classes III-V) at 90 days using Kaplan-Meier analysis, with the two groups compared by the log-rank test. To assess the accuracy of the PESI to predict overall mortality, we estimated sensitivity, specificity, and positive and negative predictive values and likelihood ratios for low-versus higher-risk patients at 90 days after presentation. A positive likelihood ratio indicates how much more likely patients who die are classified in PESI risk classes IV and V relative to those who survive; a negative likelihood ratio indicates how much less likely patients who die are classified in PESI risk classes I-II compared to those who survive (19). To assess the rule’s discriminatory power to predict mortality, we also estimated the area under the receiver operating characteristic curve (ROC). All analyses were performed using SPSS 14.0 (SPSS Inc, Chicago, IL, USA).

### Table 1: The Pulmonary Embolism Severity Index.

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Points assigned</th>
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<tbody>
<tr>
<td>Age, per year</td>
<td>Age, in years</td>
</tr>
<tr>
<td>Male sex</td>
<td>+10</td>
</tr>
<tr>
<td>History of cancer</td>
<td>+30</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>+10</td>
</tr>
<tr>
<td>History of chronic lung disease</td>
<td>+10</td>
</tr>
<tr>
<td>Pulse ≥110/minute</td>
<td>+20</td>
</tr>
<tr>
<td>Systolic blood pressure &lt; 100 mm Hg</td>
<td>+30</td>
</tr>
<tr>
<td>Temperature ≤36°C</td>
<td>+20</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>+60</td>
</tr>
<tr>
<td>Arterial oxygen saturation ≥90%</td>
<td>+20</td>
</tr>
</tbody>
</table>

A total point score for a given patient is obtained by summing the patient’s age in years and the points for each applicable predictor. Points assignments correspond with the following risk classes:
- ≤65 class I; 66–85 class II; 86–105 class III; 106–125 class IV and
- > 125 class V. Patients in risk classes I and II are defined as low-risk. *Assessed with or without the administration of supplemental oxygen. †Defined as confusion, disorientation, or somnolence.

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Results

Overall, 357 patients had objectively confirmed PE, defined by a positive multi-detector spiral CT (n=299) or pulmonary angiography (n=4), a high-probability ventilation/perfusion lung scan (n=1), or proximal DVT (n=53). The mean age of the patients was 64 years and 44% were men; 32% had a history of venous thromboembolism, 9% had a history of cancer, and 4% had a systolic blood pressure of less than 100 mm Hg at the time of presentation (Table 2). Overall, 186 patients (52%) were classified in risk classes I and II, 91 (25%) in class III, 41 (11%) in class IV, and 39 (11%) in class V. Eight patients (2%) received thrombolytic treatment.

No patient was lost to follow-up. Twenty-one patients (5.9%) died. Of these, nine (43%) died from definite or possible PE. No patient died in risk class I, two (0.2%) in class II, seven (7.7%) in class III, five (12.2%) in class IV, and seven (17.9%) in class V (Table 3). The mortality among low-risk (risk classes I and II) and higher-risk (classes III-V) patients was 1.1% (2/186; 95% confidence interval [CI]: 0.1–3.8%) and 11.1% (19/171; 95% CI: 6.8–16.8%), respectively. Among the two low-risk patients who died during follow-up, both died from definite or possible PE. Only one low-risk patient (0.5%, 95% CI: 0–3.0%) and six higher-risk patients (3.5%, 95% CI: 1.3–7.5%) died within seven days of presentation. The cumulative survival difference between low-risk and higher-risk patients was statistically significant (p<0.001, log-rank test) (Fig. 1).

When dichotomized as low risk versus higher risk, the PESI had a negative predictive value of 99% (95% confidence interval [CI]: 96–100%) and a negative likelihood ratio of 0.2 (95% CI: 0–0.70) for predicting mortality (Table 4). Because this cutpoint was specifically chosen to identify low-risk patients with PE, the positive predictive value (11%, 95% CI: 7–17%) and the positive likelihood ratio (2.0, 95% CI: 1.7–2.4) for predicting mortality were low. The area under the ROC curve of the PESI was 0.78, (95% CI: 0.70–0.86), indicating a good discriminatory power.

Overall, the frequency of missing values was very low: one patient (0.3%) had missing values for systolic blood pressure, 25 (7%) for respiratory rate, 12 (3%) for temperature, and 13 (4%) for arterial oxygen saturation.

Discussion

In this prospective validation study, the PESI classified more than half of patients with PE as low-risk and these low-risk patients had a very low overall mortality at seven (0.5%) and 90 days (1.1%) following presentation. The negative predictive value for overall mortality of the PESI was high and reached 99%. These results are consistent with the original derivation and prior validation studies in which overall short-term mortality rates ranged from 0% to 2.6% among low-risk patients (13, 14, 20, 21). Compared to the original derivation study, the PESI’s discriminative power for mortality, expressed as the area under the ROC curve, remained stable in this validation study (0.78 in both studies) (13). Overall, the accuracy and the generalizability of the PESI are now supported by the validation in over 7,000 patients from over 300 teaching and non-teaching hospitals in the United States and Europe. Risk stratification based on the PESI is reliable and accurately identifies patients at low-risk of death when evaluated over periods of follow-up ranging from 7–90 days, demonstrating the PESI’s excellent follow-up transportability. Given its validation in a wide variety of patients and settings, the PESI currently represents the second highest level (2) on the hierarchy of evidence for clinical prediction rules (22). While level 2 rules can be used in various settings with confidence in their accuracy, their potential for changing physician behavior and improving quality of care must be demonstrated in a formal impact analysis (level 1, highest level on the hierarchy of evidence) before their utilization can be generally recom-
mended (22). Thus, whether the utilization of the PESI increases the frequency of PE outpatient treatment without compromising patient safety, must be further examined before its implementation into practice guidelines or decision algorithms can be justified.

Despite earlier recommendations to treat clinically stable patients with nonmassive PE in the outpatient setting (23, 24), most patients with non-massive PE continue to be hospitalized (25). The potential economic benefit of the PESI can be estimated using data from a recent cost-effectiveness analysis comparing inpatient treatment with unfractionated heparin versus LMWH in patients with PE. Assuming a cost difference of $4,500 between inpatient and outpatient treatment of PE (10) and an annual PE incidence of 122,000 cases in the United States (1), up to $275 million per year could be saved if 50% of patients were treated as outpatients. However, at the initial site of treatment decision for patients with PE, it is important for physicians also to consider psychosocial contraindications to outpatient care (e.g. lack of treatment adherence). Other potential barriers to outpatient treatment are the lack of outpatient systems of health care and the absence of insurance coverage for more costly LMWH. Moreover, there are other clinical predictors of adverse outcome following PE, for example, immobilization for neurologic disease or renal failure (26, 27). These factors should also be taken into consideration before a patient with PE is treated as an outpatient.

The diagnostic accuracy of the PESI compares well to another clinical prognostic rule, the Wicki score (28, 29). The Wicki score assesses six clinical, laboratory, and ultrasonographic variables to identify patients with a low risk of adverse outcomes. In a study by Jimenez et al. enrolling almost 600 consecutive outpatients with PE (20), PESI low-risk patients had a significantly lower short-term mortality compared to low-risk patients based on the Wicki score (0.9% vs. 5.6%, p < 0.0001).

### Table 3: Pulmonary Severity Index risk class-specific mortality at 90 days (N=357).

<table>
<thead>
<tr>
<th>Risk class</th>
<th>Number (percent, 95% CI)</th>
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<tbody>
<tr>
<td>Class I</td>
<td>0 (0.0–4.1)</td>
</tr>
<tr>
<td>Class II</td>
<td>2 (2.0, 0.2–7.1)</td>
</tr>
<tr>
<td>Class I and II combined</td>
<td>2 (1.1, 0.1–3.8)</td>
</tr>
<tr>
<td>Class III</td>
<td>7 (7.7, 3.1–15.2)</td>
</tr>
<tr>
<td>Class IV</td>
<td>5 (12.2, 4.1–26.2)</td>
</tr>
<tr>
<td>Class V</td>
<td>7 (17.9, 7.5–33.5)</td>
</tr>
<tr>
<td>Class III, IV, and V combined</td>
<td>19 (11.1, 6.8–16.8)</td>
</tr>
</tbody>
</table>

Figure 1: Cumulative survival among low-risk (risk classes I and II) versus higher-risk patients (risk classes III-V) based on the Pulmonary Embolism Severity Index.
What is known about this topic?
– The Pulmonary Embolism Severity Index (PESI) stratifies patients in five classes (I-V) of increasing risk of short-term mortality.
– Patients in PESI risk classes I and II have a low risk of death and may be potential candidates for outpatient care.

What does this paper add?
– In our patient sample, patients in PESI risk classes I or II had a three-month mortality of 1.1%, corresponding to a negative predictive value of 99% for mortality.
– The PESI accurately identifies a substantial proportion of patients with PE who are at low risk of mortality and who are potential candidates for outpatient treatment.

When dichotomized as low (classes I and II) versus higher-risk (classes III–V), the negative predictive value of the PESI for mortality is comparable to other prognostic tests for PE such as echocardiography and ventricular measurements on computed tomography (30, 31). Prognostic tools based on radiographic procedures are expensive, require specialized personnel for performance and interpretation, and may not be available 24 hours a day. Although cardiac biomarkers such as troponins and brain natriuretic peptides are available at most hospital EDs and have a high negative predictive value (> 93%) for mortality in patients with PE (32), use of such biomarkers to identify low-risk patients is limited by their lack of standardized testing methods (e.g. troponin I vs. T) and variable cutoff points to define abnormal results.

To date, studies directly comparing the prognostic accuracy of clinical prognostic models and radiographic procedures or cardiac biomarkers are lacking. A potential advantage of cardiac biomarkers over the PESI is their greater simplicity. In contrast, the PESI is comprised of 11 clinical parameters and may require the use of pocket cards, electronic handheld devices, or internet support systems to facilitate its application in clinical practice.

Our study has limitations. First, the study used to validate the PESI prospectively was not originally designed for this task and patients with severe renal failure or a terminal illness with an expected survival of less than three months (i.e. patients with a terminal cancer) were excluded (16). Thus, these patients groups are underrepresented in our study sample, and we cannot exclude the possibility that the PESI would have performed differently in these patient groups. Second, we could not estimate the potential impact of treatments (e.g. quality of oral anticoagulation) on patient outcomes, because this information was not consistently available.

In conclusion, the PESI accurately identifies a substantial proportion of patients with PE who are at low-risk of mortality and who are potential candidates for outpatient treatment or an abbreviated hospital stay. Whether utilization of the PESI can change physician behavior and safely increase the proportion of outpatient treatment for non-massive PE must be assessed in a formal impact analysis.

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References


