

Derivation and Validation of a Prognostic Model for Pulmonary Embolism

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ABSTRACT

Rationale: An objective and simple prognostic model for patients with pulmonary embolism could be helpful in guiding initial intensity of treatment.

Objectives: To develop a clinical prediction rule that accurately classifies patients with pulmonary embolism into categories of increasing risk of mortality and other adverse medical outcomes.

Methods: We randomly allocated 15,531 inpatient discharges with pulmonary embolism from 186 Pennsylvania hospitals to derivation (67%) and internal validation (33%) samples. We derived our prediction rule using logistic regression with 30-day mortality as the primary outcome, and patient demographic and clinical data routinely available at presentation as potential predictor variables. We externally validated the rule in 221 inpatients with pulmonary embolism from Switzerland and France.

Measurements: We compared mortality and nonfatal adverse medical outcomes across the derivation and 2 validation samples.

Main Results: The prediction rule is based on 11 simple patient characteristics that were independently associated with mortality and stratifies patients with pulmonary embolism into 5 severity classes, with 30-day mortality rates of 0-1.6% in class I, 1.7-3.5% in class II, 3.2-7.1% in class III, 4.0-11.4% in class IV, and 10.0-24.5% in class V across the derivation and validation samples. Inpatient death and nonfatal complications were $\leq 1.1\%$ among patients in class I and $\leq 1.9\%$ among patients in class II.

Conclusions: Our rule accurately classifies patients with pulmonary embolism into classes of increasing risk of mortality and other adverse medical outcomes. Further

validation of the rule is important prior to its implementation as a decision aid to guide the initial management of patients with pulmonary embolism.

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INTRODUCTION

Acute pulmonary embolism (PE) is a major health problem, with an estimated incidence of 23 to 69 cases per 100,000 persons annually (1, 2). Data from the National Hospital Discharge Survey show that in the year 2002, 101,000 patients were hospitalized in acute care hospitals with a primary diagnosis of PE in the US, resulting in 676,700 inpatient days (3). The short-term mortality of this illness varies widely, ranging from <2% in many patients with non-massive PE to >95% in patients who experience cardiorespiratory arrest (4-6).

Despite this broad variability in short-term mortality, models for the risk stratification during admission for PE are not well established. An accurate, objective, and simple clinical prediction rule may be helpful in guiding medical decision making. For example, patients estimated to be at low risk could be discharged early or managed entirely as outpatients using low-molecular-weight heparin (7), whereas patients estimated at high-risk may benefit from a more intensive surveillance in an intensive care setting. Previous models of risk stratification for PE were limited by their reliance on arterial blood gas values at room air and leg vein ultrasound (8, 9) or by their ability to identify only low-risk patients with PE (10). We therefore sought to develop a practical clinical prediction rule for patients with PE that quantifies the risk of mortality and other adverse medical outcomes across the full spectrum of risk and that relies only on readily available clinical parameters.

METHODS (Word Count: 500)

Patient Identification and Eligibility

We identified patients with PE from 1/2000 to 11/2002 using the Pennsylvania Health Care Cost Containment Council (PHC4) database (11) We included inpatients age ≥ 18 years who were discharged with a primary ICD-9-CM diagnosis of PE or a secondary diagnosis for PE and one of the following primary diagnosis that represent complications or treatments of PE: respiratory failure, cardiogenic shock, cardiac arrest, secondary pulmonary hypertension, syncope, thrombolysis, and intubation/mechanical ventilation. A detailed description of the methods is available as an online supplement.

Baseline Predictor Variables and Outcome Measures

The baseline clinical variables used to derive our prediction rule were obtained by linking all eligible patients identified using PHC4 to the MediQual Atlas database (11). To derive our prediction rule, we used clinical variables routinely available at presentation that were previously shown to be associated with mortality in patients with PE or other acute diseases. These variables included demographics (12-15), comorbid conditions (8, 12-14, 16), physical examination findings (8, 14, 15, 17, 18), and laboratory and chest x-ray findings (8, 14, 16, 19-24).

The study outcome used to derive our prediction rule was death from all causes within 30 days of hospitalization based on mortality data from the National Death Index (NDI) (25). We also assessed whether patients developed severe nonfatal outcomes (cardiogenic shock/cardiorespiratory arrest) during hospitalization.

Derivation and Internal Validation of the Prediction Rule

The study cohort was comprised of 15,531 discharges with PE treated at 186 hospitals. We randomly selected 10,354 discharges (67%) for the derivation and 5177 (33%) for the internal validation sample. We derived our prediction rule using stepwise logistic regression, with 30-day mortality as the outcome and the demographic and clinical variables previously described as predictors. In a first step, we constructed our logistic regression model excluding laboratory variables. To quantify the impact of including laboratory tests on model performance, we also estimated a model that included baseline laboratory tests. Based on the beta-coefficients of the model, we generated a point score that divides patients into 5 risk classes for 30-day mortality (class I-very low-risk; class II-low-risk; class III-intermediate-risk; class IV-high-risk; and class V-very high-risk).

External Validation of the Prediction Rule

We validated our rule in an independent patient population using data from 221 inpatients prospectively diagnosed with PE using spiral computed tomography at 3 emergency departments at 2 university hospitals in Switzerland and 1 in France (26). Patients who had a contraindication to computed tomography or were severely ill were not eligible for this study. Follow-up information about mortality, recurrent venous thromboembolism, and major bleeding was obtained by phone interviews of patients, family members, and/or primary care physicians, and hospital chart review.

Statistical Analyses

We compared risk-class-specific mortality and rates of nonfatal adverse medical outcomes in the derivation sample to each validation sample using logistic

regression with a robust variance estimator or exact chi-square tests. To assess the discriminatory power of our rule to predict 30-day mortality, we also compared the area under the receiver operating characteristic (ROC) curves of the prediction rule (27).

RESULTS

Patients in the external validation sample had a lower prevalence of most comorbid illnesses and fewer abnormal findings on physical examination compared to those in the derivation and internal validation samples. This reflects the exclusion of more severely ill patients from the external validation sample (Table 1). Thirty-day mortality rates in the derivation, internal and external validation samples were 9.2%, 9.5%, and 2.7%, respectively.

Derivation of the Prediction Rule

The 11 patient factors independently associated with 30-day mortality included 2 demographic characteristics (age, male sex), 3 comorbid illnesses (cancer, heart failure, chronic lung disease), and 6 clinical findings (pulse ≥ 110 per minute, systolic blood pressure < 100 mm Hg, respiratory rate ≥ 30 per minute, temperature $< 36^\circ\text{C}$, altered mental status, and oxygen saturation < 90 mm Hg) (Table 2). The scoring system shown in Table 2 was used to quantify the magnitude of the association of each of these 11 factors with mortality. These associations changed only minimally if the 5.5% of discharges with recurrent PE during the study period or the 1.8% who were identified using primary ICD-9-CM codes for PE complications or treatments were excluded from the analysis. In the derivation sample, risk-class-specific 30-day mortality was 1.1% in

risk class I, 3.1% in risk class II, 6.5% in risk class III, 10.4% in risk class IV, and 24.5% in risk class V.

When laboratory variables also were assessed as potential predictors in the logistic regression model, all of the demographic and clinical variables in the simpler model except heart failure remained independently associated with 30-day mortality. In addition, 7 laboratory variables (hemoglobin <12 g/dL, white blood cell count <4000 or >12,000 per mm³, platelets <100,000 per mm³, sodium <130 or >150 mmol/L, blood urea nitrogen ≥11 mmol/L [30 mg/dL], arterial pH <7.25, and arterial pCO₂ <25 or >55 mm Hg) were independently associated with mortality. Although this more complex, 17 variable model had a higher discriminatory power than the 11 variable model without laboratory variables (area under the ROC curve 0.82 vs. 0.78, *P*<0.001), the risk-class-specific 30-day mortality rates for the more complex model (0.8% in risk class I; 2.5% in class II; 4.3% in class III; 9.9% in class IV; and 27.1%) were similar to those for the simpler model.

Validation of the Prediction Rule

The prediction rule classified similar proportions of patients in each of the 5 risk classes across the derivation and internal validation samples (Table 3). In the external validation sample, a higher proportion of patients was classified in risk classes I-III and a lower proportion was classified in risk classes IV and V, reflecting the exclusion of severely ill patients from this sample. Thirty-day mortality rates in each risk class were not significantly different between the derivation and the validation samples; in the internal validation sample, these rates ranged from 1.6% in the very low-risk, class I patients to 23.9% in the very high-risk, class V patients (Table 4). The 30-day mortality

was lower overall in the external validation sample and ranged from 0% among patients in risk class I to 10.0% among patients in class V. The rule's discriminatory power for 30-day mortality was nearly identical in the derivation and internal and external validation samples, with an area under the ROC curve of 0.78, 0.77, and 0.79, respectively (Figure 1).

Inpatient mortality rates in risk class I (where comparable data were available) were similar across the 3 study samples (Table 4). The rates of nonfatal cardiogenic shock or cardiorespiratory arrest in each risk class in the derivation and internal validation samples also were similar, and ranged from 0.6-1.0% in class I to 4.6-5.3% in class V.

In the external validation sample, no patients in class I or II had nonfatal recurrent venous thromboembolism or major bleeding at 30 days after presentation. Overall, 6 patients died during follow-up in the external validation sample (3 died from PE, 1 died from possible PE, and 1 from major bleeding). The rates of nonfatal recurrent venous thromboembolism were 1.6% in class III, 0 % in class IV, and 0% in class V. The rates of nonfatal major bleeding were 1.6% in class III, 8.0% in class IV, and 0% in class V.

DISCUSSION

In this study to develop a clinical prediction rule for prognosis of PE, we identified 11 clinical findings from the history and physical examination that classify patients into 5 risk classes of increasing risk of death and other adverse medical outcomes. When validated in a retrospectively identified internal validation sample and a prospectively

identified external validation sample, the performance of the rule was highly reliable. In all 3 study samples, mortality increased in a step-wise fashion with increasing risk class and no significant differences in risk class specific mortality were observed across risk classes I-V.

Our rule accurately identifies patients who are at low-risk of fatal and nonfatal medical outcomes: class I and class II patients had a 30-day mortality of $\leq 1.6\%$ and $\leq 3.5\%$, respectively. Nonfatal cardiogenic shock or cardiorespiratory arrest occurred in $\leq 1.0\%$ of patients in class I and $\leq 1.3\%$ in class II, and no patient in these 2 risk classes had nonfatal major bleeding or recurrent venous thromboembolism. Recent evidence suggests that many patients with non-massive PE can be safely treated entirely as outpatients using low-molecular-weight heparins or discharged early (28-32). Based on this evidence, the British Thoracic Society recommends outpatient treatment for clinically stable patients with PE (7). Thus, our rule provides clinicians an explicit tool for identifying very low-risk (class I) and low-risk (class II) patients with PE that may be potential candidates for outpatient treatment or early hospital discharge. If applied on a health system or national level, outpatient treatment or early discharge of only a small proportion of patients with PE is likely to result in substantial cost-savings (33). However, it is important to note that our rule is intended to supplement, not replace clinical judgment. The initial site of treatment decision for patients with PE must also consider psychosocial contraindications to outpatient care (e.g., frailty, lack of treatment adherence due to psychiatric or substance abuse problems) or the availability of outpatient systems of health care. Likewise, physicians would be unlikely to discharge a previously healthy 40-year-old woman who has severe hypoxemia and no additional

pertinent prognostic factors, even if she was classified as very low-risk (class I) by the rule.

Our rule also accurately identifies patients who are at higher-risk of short-term death and other adverse medical outcomes. Patients in class V had 30-day mortality rates of up to 24.5% and rates of nonfatal cardiogenic shock or cardiorespiratory arrest of up to 5.3%. Whether these high-risk patients with PE could potentially benefit from more intensive forms of surveillance and care (e.g., in an intensive care unit setting) remains to be shown.

Our prediction rule has several distinctive strengths compared to a prior model of prognosis following PE (8, 9). First, it consists of clearly defined, routinely available predictors and does not require any laboratory tests or radiographic procedures not routinely performed in the management of PE. Second, the accuracy and generalizability of the rule are supported by its derivation (US patients only) and validation in 15,752 patients from 189 hospitals in the USA, Switzerland, and France. Third, our study samples represent a broad disease spectrum, ranging from non-massive PE to PE with cardiorespiratory arrest.

Our study also has potential limitations. First, patients in our derivation and internal validation samples were identified using ICD-9-CM codes for PE rather than standardized radiographic criteria, and therefore, patient eligibility may be subject to study selection biases due to hospital coding procedures. However, 2 prior studies demonstrated that up to 96% of patients with specific ICD-9-CM codes for PE had objectively documented disease based on chart review criteria (34-36). Furthermore, we cannot rule out the possibility that patients who were identified using a secondary

ICD-9-CM code for PE with a primary diagnosis of possible PE complications (e.g., cardiogenic shock) actually developed PE as a consequence of one of these other conditions. Yet the performance of our rule did not change when these patients were excluded from our analyses. Second, the study used to externally validate our rule was not originally designed for this task and information about mental status was not explicitly recorded (26). Although it is very unlikely that more than a few patients had an altered mental status in the external validation sample, we cannot exclude the possibility that disease severity may have been underestimated in these patients. The external validation sample also excluded more severely ill patients (e.g., those who were hemodynamically unstable). As a result, there were fewer higher-risk patients in this sample and the 95% confidence interval for risk-class-specific mortality was relatively wide among patients in risk classes IV and V. Finally, we could not assess the occurrence of recurrent venous thromboembolism and major bleeding in the derivation and internal validation samples and cardiogenic shock or cardiorespiratory arrest in the external validation sample because these complications were not reliably documented in our databases.

In conclusion, we derived and validated a practical bedside tool for risk stratification that accurately classifies patients with PE at increasing risk of death and other adverse outcomes. Outpatient management or early hospital discharge of patients with PE identified as very low-risk (class I) and low-risk (class II) has the potential to result in large cost-savings without added risk to patients. However, before this rule can be implemented into clinical practice, its clinical usefulness should be tested in a prospective study.

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FIGURE 1 LEGEND

Receiver Operating Characteristic Curves for 30-Day Mortality in the Derivation and Validation Samples

The area under the receiver operating characteristic curves were 0.78 (95% confidence interval [CI]: 0.77-0.80) in the derivation sample, 0.77 (95% CI: 0.75-0.79) in the internal validation sample, and 0.79 (95% CI: 0.65-0.93) in the external validation sample (derivation vs. internal validation sample, $P=0.35$; derivation vs. external validation sample, $P=0.93$).

Table 1. Comparison of Baseline Patient Characteristics in the Derivation and Validation Samples

Patient Characteristics*	Derivation Sample (n=10,354)	Internal Validation Sample (n=5177)	External Validation Sample (n=221)
	Percent		
Demographic factors			
Age >65 years	52.8	53.1	59.3
Male sex	39.6	41.1	45.2
Comorbid illnesses			
Cancer	19.9	19.0	15.8
Heart failure	16.1	15.3	11.8
Chronic lung disease	18.2	19.1	8.6
Chronic renal disease	4.4	4.2	4.5
Cerebrovascular disease [†]	8.9	9.9	4.5
Clinical findings			
Temperature <36°C	16.7	16.4	3.6
Pulse ≥110 per minute	29.2	30.0	14.0
Systolic blood pressure <100 mm Hg	10.6	10.2	1.8
Respiratory rate ≥30 per minute	14.5	14.7	10.9
Altered mental status [‡]	6.9	8.1	0
Arterial oxygen saturation <90% [§]	8.0	7.8	5.9
Laboratory findings			
Hemoglobin <12 g/dL	30.4	29.9	Not available
White blood cell count <4000 or >12,000 per mm ³	27.6	28.3	Not available

Continued

Table 1 Continued

Patient Characteristics*	Derivation Sample (n=10,354)	Internal Validation Sample (n=5177)	External Validation Sample (n=221)
	Percent		
Platelets <100,000 per mm ³	3.0	2.5	Not available
Sodium <130 or >150 mmol/L	2.4	2.5	Not available
Blood urea nitrogen ≥11 mmol/L (30 mg/dL)	13.5	13.0	Not available
Creatinine >177 μmol/L (2.0 mg/dL)	4.7	4.6	0.9
Arterial pH <7.25	1.1	1.2	0.5
Arterial pCO ₂ <25 or >55 mm Hg	2.9	2.9	2.3

*In the derivation and internal validation sample, 1.9% of patients had unknown values for temperature, 1.7% for pulse, 1.4% for systolic blood pressure, 1.9% for respiratory rate, 64.6% for arterial oxygen saturation, 8.1% for hemoglobin, 8.4% for white blood cell count, 9.2% for platelet count, 11.6% for sodium, blood urea nitrogen, and creatinine, 62.0% for arterial pH, and 62.5 for pCO₂. Comorbid conditions were coded as present versus unknown. In the external validation sample, 4.5% of patients had unknown values for temperature, 3.2% for respiratory rate, 45.2% for oxygen saturation, 0.5% for creatinine, 59.7% for pH, and 1.4% for pCO₂. Chronic renal disease and cerebrovascular disease were coded as present versus unknown. For calculating the frequency of baseline patient characteristics, unknown values were assumed to be normal and were included in the denominator.

†Defined as transient ischemic attack or stroke.

‡Defined as disorientation, lethargy, stupor, or coma. Information about mental status was not recorded in the external validation sample. Because patients with cognitive impairment were excluded from the study, mental status was assumed to be normal in all patients in this sample.

§With and without administration of supplemental oxygen.

Table 2. Independent Predictors of 30-day Mortality in the Derivation Sample and Points Assigned to the Risk Score

Predictors	β -Coefficients (95% Confidence Interval)	Points Assigned
Demographic characteristics		
Age, per year	0.03 (0.02-0.03)	Age, in years
Male sex	0.17 (0.02-0.32)	+10
Comorbid illnesses		
Cancer	0.87 (0.71-1.03)	+30
Heart failure	0.31 (0.14-0.49)	+10
Chronic lung disease	0.30 (0.12-0.47)	+10
Clinical findings		
Pulse \geq 110 per minute	0.60 (0.44-0.76)	+20
Systolic blood pressure <100 mm Hg	0.86 (0.67-1.04)	+30
Respiratory rate \geq 30 per minute	0.41 (0.23-0.58)	+20
Temperature <36°C	0.42 (0.25-0.59)	+20
Altered mental status*	1.50 (1.30-1.69)	+60
Arterial oxygen saturation <90 % [†]	0.58 (0.37-0.79)	+20

A total point score for a given patient is obtained by summing the patient's age in years and the points for each applicable characteristic. Points assignments correspond with the following risk classes: \leq 65 class I - very low-risk; 66-85 class II - low-risk; 86-105 class III - intermediate-risk; 106-125 class IV - high-risk; >125 class V - very high-risk.

*Defined as disorientation, lethargy, stupor, or coma.

[†]With and without the administration of supplemental oxygen.

Table 3. Risk Class Distributions in the Derivation and Validation Samples

Risk Class	Derivation Sample (n=10,354)	Internal Validation Sample (n=5177)	External Validation Sample (n=221)
	Percent (95% Confidence Interval)		
Class I - very low-risk	19.4 (18.7-20.2)	19.6 (18.5-20.7)	24.4 (18.9-30.7)
Class II - low-risk	21.5 (20.7-22.3)	21.2 (20.1-22.4)	27.1 (21.4-33.5)
Class III - intermediate-risk	21.7 (20.9-22.5)	22.2 (21.0-23.3)	28.1 (22.2-34.5)
Class IV - high-risk	16.4 (15.7-17.1)	15.8 (14.8-16.8)	11.3 (7.5-16.2)
Class V - very high-risk	21.0 (20.3-21.8)	21.3 (20.2-22.4)	9.0 (5.6-13.6)

Table 4. Risk-Class Specific Medical Outcomes in the Derivation and Validation Samples

Medical Outcomes	Derivation Sample (n=10,354)	Internal Validation Sample (n=5177)	External Validation Sample (n=221)	<i>P</i> Value*	<i>P</i> Value†
Percent (95% Confidence Interval)					
30-day mortality					
Class I	1.1 (0.7-1.7)	1.6 (0.9-2.6)	0 (0-6.6)	0.32	0.66
Class II	3.1 (2.5-4.0)	3.5 (2.5-4.7)	1.7 (0-8.9)	0.63	0.72
Class III	6.5 (5.5-7.6)	7.1 (5.7-8.7)	3.2 (0.4-11.2)	0.51	0.43
Class IV	10.4 (9.0-11.9)	11.4 (9.3-13.8)	4.0 (0.1-20.4)	0.44	0.36
Class V	24.5 (22.7-26.4)	23.9 (21.4-26.5)	10.0 (1.2-31.7)	0.69	0.19
Inpatient mortality‡					
Class I	0.8 (0.5-1.3)	1.1 (0.5-1.9)	0 (0-6.6)	0.42	1.00
Class II	1.8 (1.3-2.4)	1.9 (1.2-2.9)	Not available [§]	0.75	---
Class III	4.2 (3.4-5.1)	4.7 (3.6-6.1)	Not available [§]	0.49	---
Class IV	5.9 (4.8-7.1)	7.0 (5.3-9.0)	Not available [§]	0.31	---
Class V	15.8 (14.3-17.4)	17.2 (15.1-19.6)	Not available [§]	0.29	---

Continued

Table 4 Continued

Medical Outcomes	Derivation Sample (n=10,354)	Internal Validation Sample (n=5177)	External Validation Sample (n=221)	<i>P</i> Value*	<i>P</i> Value†
Percent (95% Confidence Interval)					
Nonfatal cardiogenic shock or cardiorespiratory arrest					
Class I	0.6 (0.3-1.0)	1.0 (0.5-1.8)	Not available [§]	0.24	---
Class II	1.3 (0.9-1.9)	1.2 (0.6-2.0)	Not available [§]	0.77	---
Class III	2.1 (1.6-2.8)	2.0 (1.3-3.0)	Not available [§]	0.86	---
Class IV	1.9 (1.3-2.7)	2.1 (1.2-3.3)	Not available [§]	0.82	---
Class V	4.6 (3.8-5.6)	5.3 (4.0-6.8)	Not available [§]	0.40	---

*For comparisons of outcomes in the derivation and internal validation samples.

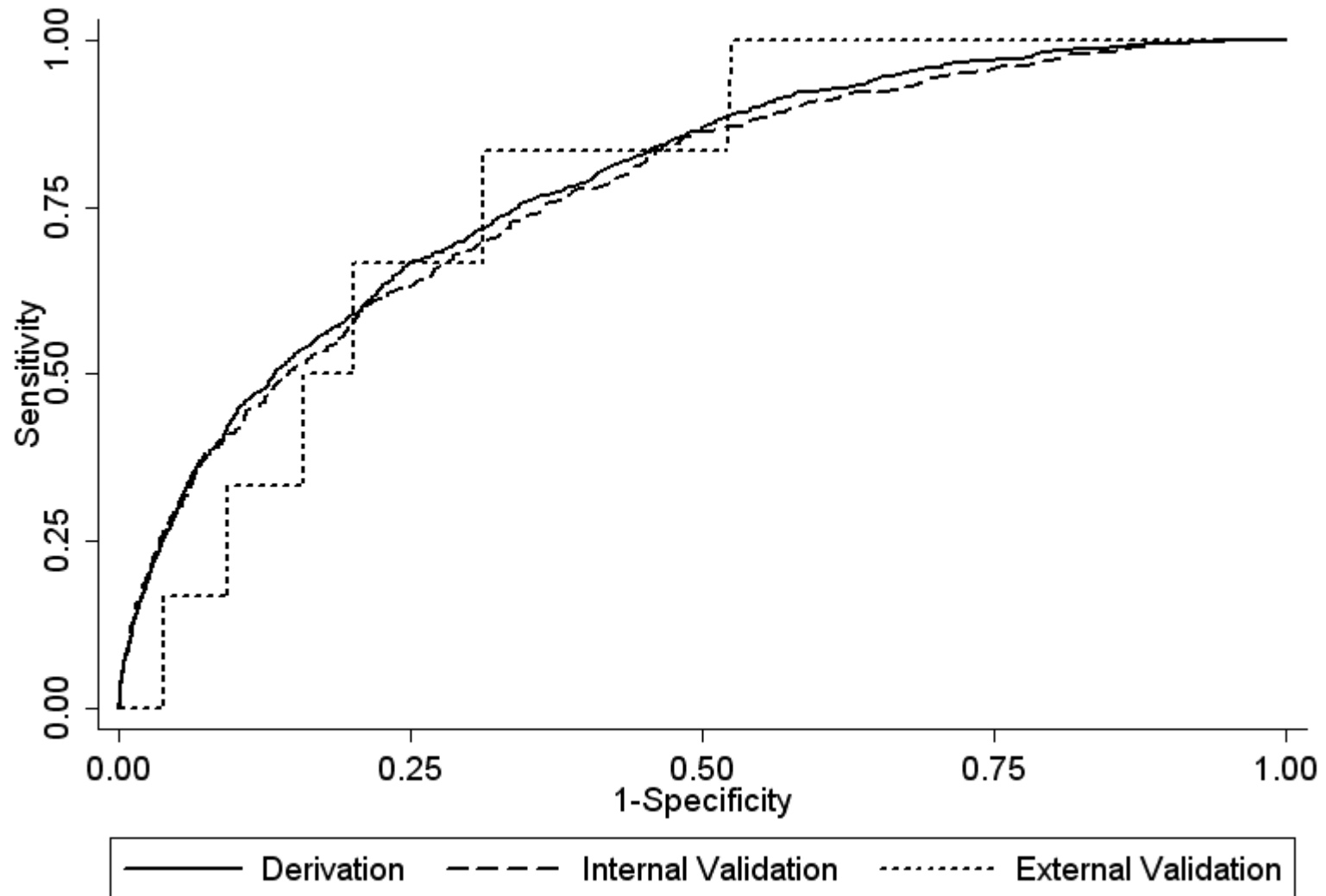
† For comparisons of outcomes in the derivation and external validation samples.

‡Patients who remained in the hospital for >30 days were censored at 30 days.

§Inpatient complications such as death, cardiogenic shock, and cardiorespiratory arrest were not explicitly recorded in the external validation sample.

||During the initial hospital stay only.

FIGURE 1



ONLINE SUPPLEMENT

Derivation and Validation of a Prognostic Model for Pulmonary

Embolism

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DETAILED METHODS SECTION

This project used existing data for patients with PE treated at 186 Pennsylvania hospitals to derive and internally validate a clinical prediction rule to classify patients into categories of increasing risk of mortality and adverse medical outcomes. This rule was then externally validated in patients with objectively confirmed PE from 3 hospitals in Switzerland and France. The project adhered to methodological standards for the development of prediction rules that recommend use of objective predictor and outcome variables, appropriate derivation techniques, and assessment of the accuracy of the rule by validation in an independent patient population (E1-4). The Institutional Review Board of the University of Pittsburgh approved the project.

Patient Identification and Eligibility

We identified patients with PE from 1/2000 to 11/2002 using the Pennsylvania Health Care Cost Containment Council (PHC4) database (E5). This database contains information on demographic characteristics, source of admission, International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) discharge diagnosis and procedure codes, admission and discharge dates, and inpatient mortality data for all patients admitted to non-governmental acute care hospitals in Pennsylvania.

We included inpatients age 18 or older who were discharged with a primary diagnosis of PE based on the following ICD-9-CM codes: 415.1, 415.11, 415.19, and 673.20-24. To ensure that we identified the most severely ill patients with PE as the primary reason for hospitalization, we also included inpatients with or a secondary

diagnosis code for PE and one of the following primary codes that may represent complications or treatments of this condition: respiratory failure (518.81), cardiogenic shock (785.51), cardiac arrest (427.5), secondary pulmonary hypertension (416.8), syncope (780.2), thrombolysis (99.10), and intubation/mechanical ventilation (96.04, 96.05, 96.70-96.72). Because patients with recurrent PE may have a higher mortality than patients with a first episode (E6, E7) to avoid potential selection bias, we assessed all hospitalizations at the study sites of PE for these patients within the study period.

We excluded patients who only had a secondary ICD-9-CM code for PE and/or those that were transferred from another health care facility, because such patients are more likely to have PE as a complication of hospitalization. We also excluded patients without identifiers allowing linkage to the necessary clinical data and those for whom mortality information was not available.

Baseline Predictor Variables

The baseline clinical variables used to derive our prediction rule were obtained by linking all eligible patients identified using PHC4 to the Atlas Database (MediQual, Malborough, MA), which includes detailed clinical findings for all inpatients treated at non-governmental acute care hospitals in Pennsylvania (E5). Atlas data is compiled from patient medical records using standardized data collection procedures. Trained reviewers are required to achieve 95% inter-rater agreement with data abstracted by an Atlas instructor. Atlas abstracts data on more than 400 clinical variables relating to history, physical examination, coexisting illnesses, laboratory results, radiographic findings, and inpatient mortality. Atlas collects vital signs measured in the emergency department and all clinical variables

on the first two days of hospitalization. The recorded data represent the most abnormal value on a given calendar day.

For the development of our prediction rule, we used clinical variables obtained as close to the time of hospital presentation as possible. For all patients admitted through the emergency department we used vital signs measured in the emergency department; all other variables were recorded from the day of hospital admission. For patients admitted from other sources (e.g., directly from a physician's office), we abstracted all clinical variables from the day of admission. To derive our prediction rule, we used clinical variables routinely available at presentation that were previously shown to be associated with short-term mortality in patients with PE or other acute cardiopulmonary conditions. These variables included demographic characteristics (age, sex) (E7-10), comorbid conditions (cancer, heart failure, ischemic heart disease, chronic lung disease, chronic renal disease, cerebrovascular disease, severe neurological disease [defined as limb paresis], and smoking status) (E7-9, E11, E12), physical examination findings (body temperature, pulse, systolic blood pressure, respiratory rate, mental status) (E7, E10, E12-14), laboratory findings (hemoglobin, white blood cell count, platelets, serum glucose, troponins, sodium, blood urea nitrogen, arterial blood gas values measured with or without the administration of supplemental oxygen [pH, partial pressure of oxygen and CO₂, oxygen saturation]) (E7, E11, E12, E15-20), and radiographic findings on chest x-ray (pleural effusion, cardiomegaly) (E7). We did not consider several potential predictors such as echocardiographic right ventricular dysfunction, mean pulmonary arterial pressure, or concomitant deep vein thrombosis shown by sonography because these conditions are not routinely assessed in patients

diagnosed with PE and were not uniformly available in the Atlas database (E8, E12, E21). All clinical variables were linked and downloaded into the project database using unique patient identifiers common to the PHC4 and Atlas databases.

Outcome Measures

The study outcome used to derive our prediction rule was death from all causes within 30 days of hospitalization. All cause, 30-day mortality is objective and clinically relevant, and a widely used outcome of prognostic models for other acute diseases or medical interventions (E22-24). The majority of deaths due to PE occur within this time frame (E25). We obtained mortality data from the National Death Index (NDI) (E26). Patients identified in the PHC4 database were linked to the NDI using patient identifiers with proven accuracy for patient matching including social security number, full name, full date of birth, and sex (E27, E28). Using inpatient mortality rates obtained from the PHC4 and Atlas databases for all eligible patients as a reference standard, the NDI had a positive predictive value of 98% and a negative predictive value of 100% for mortality.

Because mortality is not the only medical outcome of interest to clinicians, we used the Atlas database and ICD-9-CM discharge codes from the PHC4 database to assess whether patients classified as low-risk by our rule developed severe adverse medical outcomes. These nonfatal outcomes were cardiogenic shock (785.51) or cardiorespiratory arrest, defined as cardiac arrest [427.5], resuscitation [99.60, 99.63, 37.91], intubation [96.04, 96.05], or mechanical ventilation [96.70-72] during the admission for PE.

Derivation and Internal Validation of the Prediction Rule

Of the 16,468 patient discharges that met all eligibility criteria, we excluded 867 that were missing patient identifiers and 70 that could not be linked to the NDI. The study cohort was comprised of 15,531 patient discharges with PE treated at 186 Pennsylvania hospitals. These discharges represented 14,672 individual patients with PE; 859 discharges (5.5%) were recurrent PE episodes that occurred during the study period. We randomly selected 10,354 discharges (67%) for the derivation sample and 5177 discharges (33%) for the internal validation sample.

We derived our prediction rule using stepwise logistic regression, with 30-day mortality as the outcome and the demographic and clinical variables previously described as predictors. Because our objective was to derive a prediction rule based on simple clinical measures, we initially constructed our initial logistic regression model excluding laboratory variables. To quantify the impact of including laboratory tests on model performance, we also estimated a model that included baseline laboratory tests. With the exception of age, we dichotomized continuous variables using clinically meaningful cutpoints. Unknown values were assumed to be normal, a strategy successfully employed in the derivation and validation of a widely used prognostic model for pneumonia (E22). Only predictors with a *P* value of <0.05 were retained in the final model.

To generate a simple-integer point score, the beta-coefficients for all parameters retained in the model were divided by the coefficient for age, and rounded to the nearest multiple of 10. A prognostic score for each patient was computed by adding the age in years and all additional points for the documented

predictor variables. These scores were then divided into approximate quintiles, with each quintile representing a distinct risk class for 30-day mortality (class I-very low-risk; class II-low-risk; class III-intermediate-risk; class IV-high-risk; and class V-very high-risk). To simplify the application of the rule, cutpoints between risk classes were rounded to the nearest multiple of 5.

We assessed the performance of our prediction rule in the internal validation sample by computing the proportion of patients classified within each risk group and the proportions of patients in each risk group who died within 30 days of presentation and during the hospital stay for PE. We also estimated the proportion of patients in both samples who experienced nonfatal cardiogenic shock or cardiorespiratory arrest.

External Validation of the Prediction Rule

We validated our rule in an independent patient population using data collected in a prospective cohort study of spiral computed tomography to diagnose PE (E29). This study enrolled patients with suspected PE from 3 emergency departments at the university hospitals of Geneva and Lausanne (Switzerland), and Angers (France) between 10/2000 and 6/2002. Patients who had a contraindication to spiral computed tomography (allergy to iodine contrast agents, creatinine clearance <30 ml/minute, pregnancy) or were severely ill (massive PE with shock, expected survival <3 months) or unable to sign informed consent (due to cognitive impairment) were excluded from this study. The criteria used to establish the diagnosis of PE in this cohort are described elsewhere (E29).

Baseline patient characteristics, including the predictors that comprise our rule, were collected in the emergency department. Three months after diagnosis, patients,

family members, and/or primary care physicians were contacted by phone and information about mortality, objectively confirmed recurrent venous thromboembolism, and major bleeding (defined as retroperitoneal, joint, or cerebral bleeding, or any bleeding requiring transfusion) and the dates of these adverse events were obtained. In addition, hospital charts were reviewed if a patient was admitted to the hospital during follow-up. Three independent experts adjudicated deaths as definitely caused by PE, possibly caused by PE, or definitely unrelated to PE (E29).

For our external validation, we used data from 221 of the 222 patients with objectively confirmed PE (E29). We excluded 1 patient who did not complete follow-up. We then classified patients into the 5 risk classes and estimated the proportion of patients in each class who died at 30 days after presentation. Within each risk class, we also assessed whether patients developed nonfatal recurrent venous thromboembolism or had an episode of major bleeding.

Statistical Analyses

We compared risk-class-specific mortality and rates of nonfatal adverse medical outcomes in the derivation sample to each validation sample using logistic regression with a robust variance estimator to account for the clustering of patients who were discharged more than once for PE during the study period. For comparisons involving observed zeros, we used exact chi-square tests. To assess the discriminatory power of our rule to predict 30-day mortality, we compared the area under the receiver operating characteristic (ROC) curves of the prediction rule across derivation and validation samples (E30). A two-sided P value of <0.05 was considered statistically

significant. Statistical analyses were performed using Stata 8.2 (Stata Corporation, College Station, Texas).

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