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 I-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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