Derivation and Validation of a Novel Prediction Model to Identify Low-Risk Patients With Acute Pulmonary Embolism

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Accurate identification of low-risk patients with acute pulmonary embolism (PE) who may be eligible for outpatient treatment or early discharge can have substantial cost-saving benefit. The purpose of this study was to derive and validate a prediction model to effectively identify patients with PE at low risk of short-term mortality, right ventricular dysfunction, and other nonfatal outcomes. This study analyzed data from 400 consecutive patients with acute PE. We derived and internally validated our prediction rule based on clinically significant variables that are routinely available at initial examination and that were categorized and weighted using coefficients in the multivariate logistic regression. The model was externally validated in an independent cohort of 82 patients. The final model (HOPPE score) consisted of 5 categorized patient variables (1, 2, or 3 points, respectively): systolic blood *p*ressure (>120, 100 to 119, <99 mm Hg), diastolic blood *p*ressure (>80, 65 to 79, <64 mm Hg), *h*eart rate (<80, 81 to 100, >101 beats/min), arterial partial pressure of *o*xygen (>80, 60 to 79, <59 mm Hg), and modified *e*lectrocardiographic score (<2, 2 to 4, >4). The 30-day mortality rates were 0% in low risk (0 to 6 points), 7.5% to 8.5% in intermediate risk (7 to 10), and 18.2% to 18.8% in high-risk patients (≥11) across the derivation and validation cohorts. In comparison with the previously validated PESI score, the HOPPE score had a higher discriminatory power (area under the curve 0.74 vs 0.85, p = 0.033) and significantly improved both the discrimination (integrated discrimination improvement, p = 0.002) and reclassification (net reclassification improvement, p = 0.003) of the model for short-term mortality. In conclusion, the HOPPE score accurately identifies acute patients with PE at low risk of short-term mortality, right ventricular dysfunction, and other nonfatal outcomes. Prospective validation of the prediction model is necessary before implementation in clinical practice. **(Am J Cardiol 2017;120:676−681)**

Prognostic assessment of patients with acute pulmonary embolism (PE) is crucial in guiding therapeutic decision making and helping clinicians determine the appropriateness of ambulatory treatment or early hospital discharge. There is increasing evidence supporting the use of low−molecular weight heparin in outpatient treatment of patients with low-risk PE.[1,2] Accurate identification of those patients who may be theoretically eligible for outpatient treatment or early discharge can have substantial cost-saving benefit.[3] Although several prognostic models have been derived and validated in patients with acute PE, they are over-dependent on co-morbidities, which represent a spectrum of disease and are clinically difficult to classify as binary parameters.[4−8] The purpose of this study was to derive and validate a clinical prediction rule (CPR) based on simple clinical information that is routinely collected in emergency departments to effectively identify patients with PE at low risk of short-term mortality, right ventricular dysfunction (RVD), and other nonfatal complications. In addition, this study wanted to compare the prognostic ability of this prediction model with the previously validated pulmonary embolism severity (PESI) score.

Methods

We retrospectively analyzed the data of all consecutive inpatients and outpatients with confirmed acute PE from January 2011 to March 2015 at a tertiary care hospital in Chennai, India. Eligibility for this study required patients to be >18 years of age and have acute PE confirmed by an intraluminal filling defect on CT pulmonary angiography. The study was approved by the institutional review board and ethics committee of our hospital.

The baseline clinical variables necessary to derive our prediction rule were abstracted using a standardized form from the hospital database. All patients had been

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See page 680 for disclosure information.

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Table 1
Demographic and clinical characteristics of the patients in the derivation and validation cohorts

Variables	Derivation Sample (N=300)	Internal Validation Sample (N=100)	External Validation Sample (N=82)	P value
Age (years)	54.2±12.2	53.8+11.9	55.1+9.7	0.53
Men	162 (54%)	56(56%)	45 (55%)	0.46
Deep Vein Thrombosis	85 (28.3%)	26 (26%)	21 (27%)	0.32
Surgery (<3months)	50 (16.7%)	14 (14%)	12 (15%)	0.21
Bone Fracture (<3months)	46 (15.3%)	14 (14%)	9 (11%)	0.33
Chronic Airway Disease	40 (13.3%)	15 (15%)	16 (20%)	0.26
Heart Failure	50 (16.7%)	18 (18%)	13 (16%)	0.43
Malignancy	45 (15.0%)	16 (16%)	12 (15%)	0.46
Systolic Blood Pressure (mmHg)	109.7±13.4	111.1±12.4	107.9±10.9	0.44
Diastolic Blood Pressure (mmHg)	73.5±9.5	72.3±8.6	75.2±10.4	0.42
Heart Rate (beats/minute)	97.6±9.9	101.5±11.3	100.4±93.4	0.18
Respiratory Rate (breaths/ minute)	27.8±4.1	26.6±3.8	26.0±4.0	0.63
PaO_2 (mmHg)	70.5±8.2	72.2±9.6	69.9±8.9	0.45
$PaCO_2$ (mmHg)	30.2±6.1	29.6±5.2	31.5±5.9	0.23
PAO_2-PaO_2 (mmHg)	35.7±4.6	39.8±5.1	38.7±6.1	0.20
Modified ECG Score	3.4±0.8	3.2±0.7	3.5±0.8	0.39

Continuous variables are represented as mean ± standard deviation.

PaO_2 = arterial partial pressure of oxygen; $PaCO_2$ = arterial partial pressure of carbon dioxide; PAO_2-PaO_2 = alveolar-arterial difference in partial pressure of oxygen.

examined in the emergency department and during hospitalization in the intensive care unit. Information was obtained regarding demographics, co-morbidities (malignancy, chronic lung disease, congestive heart failure), and recent events leading to PE (trauma, surgery). A modified electrocardiographic score with adjusted variables and point values was used (tachycardia = 2, incomplete right bundle branch block = 1, complete right bundle branch block = 3, T-wave inversion in V1 to V3 = 4, $S_1Q_3T_3$ = 4).[9,10] Two blinded investigators independently assess the electrocardiographic parameters, and discrepancies were resolved by consensus.

The patients were required to undergo transthoracic echocardiography within 24 hours after diagnosis of PE to assess the presence of RVD. RVD was defined in echocardiography as the presence of ≥2 of the following criteria: RV >30 mm or RV/LV end-diastolic ratio >1 (apical 4-chamber view), dyskinesia or hypokinesia of the right ventricular free wall, hypokinesia of the infundibular RV region with normal contraction of the RV apex, tricuspid annular plan systolic excursion <15 mm, and RV/atrial gradient >30 mm Hg.[11−13] Using the CT pulmonary angiogram, the pulmonary artery obstruction index (PAOI) was calculated according to the Qanadli score (0% to 100% obstruction), taking into consideration the number of occluded segmental arteries and estimated degree of occlusion of each vessel.[14]

The primary outcome used to derive and validate the prediction rule was all-cause 30-day mortality after diagnosis of acute PE. Secondary end points were (1) in-patient mortality, (2) RVD, diagnosed by echocardiography, and (3) nonfatal cardiogenic shock and aborted cardiorespiratory arrest. Outcomes were assessed using patient or proxy phone interviews and/or review of the hospital medical records.

Of the 400 patients who met our inclusion criterion, we randomly selected 300 (75%) for the derivation sample and 100 (25%) for the internal validation sample. To derive our prediction rule, we used variables that were readily accessible by an emergency physician and previously shown to be associated with short-term mortality in acute PE. We performed univariate analysis to select predictor variables for the multivariate model, using a cutoff of $p < 0.20$. Continuous variables that were statistically significant were then categorized, choosing the most discriminative cut-off points. We included variables that were statistically significant in a logistic regression model. After removing nonstatistically significant variables, a regression coefficient for each significant variable in the final model was calculated. Similar to previous studies, we explored candidate models in an attempt 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 <1%.[15−17] An external validation was performed in an independent patient population using data from 82 patients with acute PE at another tertiary care hospital. Follow-up information was obtained by medical records review and phone interview of patients.

A descriptive analysis was performed using relative frequencies for categorical variables and means (SD) for continuous variables. We used the chi-square or Fisher's exact test to compare categorical variables. The Mann-Whitney and Kruskal-Wallis tests were used for continuous parameters. Interobserver agreement between the electrocardiographic parameters of both blinded observers was assessed by the kappa statistic using Fleiss' agreement scale. We compared mortality rates in each of the 3 risk classes across the derivation and validation cohorts using chi-square statistics. We used a receiver-operating characteristic curve to estimate the discriminatory power of our rule to predict 30-day mortality across both the derivation