CHEST

Original Research

PULMONARY VASCULAR DISEASE

Acute Pulmonary Embolism

External Validation of an Integrated Risk Stratification Model

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Background: **In hemodynamically stable patients with acute pulmonary embolism, risk stratification is essential to drive clinical management. In these patients, risk stratification for in-hospital adverse outcomes based on markers of right ventricular dysfunction and injury has been proposed.**
Methods: **The aim of this study was to validate a model based on the incremental prognostic value of right ventricular dysfunction and injury in hemodynamically stable patients with acute pulmonary embolism. Patients from the prospective Italian Pulmonary Embolism Registry were included in the study. Study outcomes were in-hospital death and the composite of in-hospital death or clinical deterioration.**
Results: **Among 1,515 hemodynamically stable patients, 869 had both echocardiography and troponin assessments. The risk for in-hospital death or clinical deterioration was higher in patients with right ventricular dysfunction and elevated troponin level (8.8%; hazard ratio [HR], 14.2 [95% CI, 1.94-104.16]; $P < .01$) and with either right ventricular dysfunction or elevated troponin level (4.7%; HR, 7.9 [95% CI, 1.1-59.9]; $P < .05$) compared with patients without dysfunction and normal troponin levels. The negative predictive value of the model was 100% for in-hospital death and 99% for death or clinical deterioration. C statistics showed an improvement of the discriminatory power for in-hospital death or clinical deterioration by using the overall model (0.66; 95% CI, 0.60-0.73) over either echocardiography (0.59; 95% CI, 0.53-0.67) or troponin level (0.61; 95% CI, 0.53-0.69) alone.**
Conclusions: **A model that includes both dysfunction and injury of the right ventricle has an incremental prognostic value for risk stratification in hemodynamically stable patients with acute pulmonary embolism. Patients with no dysfunction or injury have a favorable outcome.**
Trial registry: **ClinicalTrials.gov; No.: NCT01604538; URL: www.clinicaltrials.gov**

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Abbreviations: HR = hazard ratio; IPER = Italian Pulmonary Embolism Registry; NPV = negative predictive value; PPV = positive predictive value

Acute pulmonary embolism is a life-threatening condition, being the third-leading cause of death among the cardiovascular diseases.[1] Pulmonary embolism has a wide range of clinical presentations that are associated with different clinical severity and risk for adverse short-term outcomes.[2-5] Clinical scores as well as imaging procedures and biomarkers have been proposed for risk stratification in patients with acute pulmonary embolism.[6] Risk stratification helps to drive clinician decisions on clinical management during the acute in-hospital phase. Patients with a high mortality risk should receive intensive care and more aggressive treatment, whereas patients with a low risk could be managed with a short hospital stay or even home treatment.[7]

Risk stratification models for in-hospital death have been proposed by the European Society of Cardiology and by the American Heart Association for patients with acute pulmonary embolism.[7,8] The models identify as high risk or massive pulmonary embolism for those hemodynamically unstable patients who present with shock or sustained hypotension. These patients have

an estimated risk of in-hospital death of ≥ 15%[8] and do not require further risk stratification. Hemodynamically stable patients should be further stratified according to the presence of right ventricular dysfunction or injury.[9] Incremental prognostic value of the association of markers of right ventricular dysfunction and injury over either alone has been suggested by observational studies.[10,11] However, although this incremental prognostic value is pathophysiologically plausible and clinically sound, it needs confirmation in large prospective studies. The incremental prognostic value of right ventricular dysfunction and injury has been evaluated in studies that included a limited number of patients[12,13] and, to our knowledge, has never been prospectively validated in a single study of hemodynamically stable patients. The aim of the present study is to validate a model for risk stratification built on the incremental prognostic value of right ventricular dysfunction and injury in hemodynamically stable patients with acute pulmonary embolism included in a multicenter prospective registry.

Materials and Methods

Study Design and Patient Population

The Italian Pulmonary Embolism Registry (IPER) is a prospective, Web-based registry comprising patients aged ≥18 years with objectively confirmed pulmonary embolism on admission to academic or community hospitals in Italy.[14] The list of participating centers is reported in the e-Appendix 1. Results of imaging studies and laboratory tests (D-dimer, troponin I or T, and natriuretic peptide levels) were reported according to local standards. Right ventricular dysfunction on echocardiography was defined in the presence of at least one of the following: (1) right-to-left ventricular/end-diastolic diameter ratio > 1 in apical four-chamber view, (2) right-to-left ventricular/end-diastolic diameter ratio > 0.6 in parasternal long-axis or subcostal four-chamber view, and (3) right ventricular-to-right atrial pressure gradient > 30 mm Hg.[14] Right ventricular dysfunction was not considered to be of acute onset in the presence of a right ventricular wall thickness of > 7 mm or documentation of right ventricular overload at previous examinations.

The protocol was approved by the institutional review board at the coordinating center (San Carlo Borromeo Hospital Ethical Committee; approval number 364; April 12, 2006). All patients gave informed consent before being included in the study.

In-hospital death and the composite of in-hospital death or clinical deterioration were the study outcomes. The cause of in-hospital death was adjudicated by the local investigator at each participating center. Pulmonary embolism was considered the cause of death if it was confirmed by autopsy or objectively or, in the case of sudden death, it could not be explained by a more compelling alternative diagnosis.[15] Clinical deterioration was adjudicated as clinical worsening from a stable to an unstable hemodynamic condition that required at least one of the following: (1) IV catecholamine infusion to maintain adequate tissue perfusion and prevent or treat cardiogenic shock, (2) endotracheal intubation, or (3) CPR.[16]

Study Analysis

Frequency data are presented as proportions with 95% CIs. Continuous data are shown as mean ± SD. Student *t* test and χ^2 or Fisher exact test were used for comparisons of continuous and nominal variables, respectively. The Cox proportional hazard model was used to calculate univariable and multivariable hazard ratios (HRs) of clinical predictors of death and death or clinical deterioration. For the purpose of this study, age, sex, hemodynamic status, increased troponin level, and right ventricular dysfunction on echocardiography were evaluated as univariate predictors of study outcomes. Multivariable analyses were constructed from the set of significant ($P < .05$) univariable predictors. A comparison of clinical features of between patients who received a complete stratification with both echocardiography and serum troponin assessment and those who did not receive it was also reported.

To assess the incremental prognostic value of right ventricular dysfunction and injury, hemodynamically stable patients with echocardiography performed within 48 h and troponin levels assessed within 12 h from diagnosis were selected. Class-specific risks for death and death or clinical deterioration were calculated with a Cox proportional hazard model. The ability of the integrated model to correctly classify hemodynamically stable patients into one risk category was assessed by the C statistic and the discrimination slope.[17] Positive predictive values (PPVs) and negative predictive values (NPVs) for risk groups are reported.

Results

Over a 48-month period, 1,716 patients were included in the IPER.[14] Demographic and clinical features as well as the distribution of risk factors and mortality rates in the IPER population have been reported elsewhere.[14] At presentation, 201 patients (11.7%) were hemodynamically unstable, and 1,515 were hemodynamically stable.

Clinical Course in Hemodynamically Stable Patients

Death occurred in 52 of the 1,515 hemodynamically stable patients (3.4%; 95% CI, 2.5%-4.3%) during the hospital stay. Twenty-one patients died of acute

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