CHEST™

# Prognostic Accuracy of Clinical Prediction Rules for Early Post-Pulmonary Embolism All-Cause Mortality

## A Bivariate Meta-analysis

*Christine G. Kohn, PharmD; Elizabeth S. Mearns, PharmD; Matthew W. Parker, MD; Adrian V. Hernandez, MD, PhD; and Craig I. Coleman, PharmD*

**BACKGROUND:** Studies suggest outpatient treatment or early discharge of patients with acute pulmonary embolism (aPE) is reasonable for those deemed to be at low risk of early mortality. We sought to determine clinical prediction rule accuracy for identifying patients with aPE at low risk for mortality.

**METHODS:** We performed a literature search of Medline and Embase from January 2000 to March 2014, along with a manual search of references. We included studies deriving/validating a clinical prediction rule for early post-aPE all-cause mortality and providing mortality data over at least the index aPE hospitalization but ≤ 90 days. A bivariate model was used to pool sensitivity and specificity estimates using a random-effects approach. Traditional random-effects meta-analysis was performed to estimate the weighted proportion of patients deemed at low risk for early mortality and their ORs for death compared with high-risk patients.

**RESULTS:** Forty studies (52 cohort-clinical prediction rule analyses) reporting on 11 clinical prediction rules were included. The highest sensitivities were observed with the Global Registry of Acute Coronary Events (0.99, 95% CI = 0.89-1.00), Aujesky 2006 (0.97, 95% CI = 0.95-0.99), simplified Pulmonary Embolism Severity Index (0.92, 95% CI = 0.89-0.94), Pulmonary Embolism Severity Index (0.89, 95% CI = 0.87-0.90), and European Society of Cardiology (0.88, 95% CI = 0.77-0.94) tools, with remaining clinical prediction rule sensitivities ranging from 0.41 to 0.82. Of these five clinical prediction rules with the highest sensitivities, none had a specificity > 0.48. They suggested anywhere from 22% to 45% of patients with aPE were at low risk and that low-risk patients had a 77% to 97% lower odds of death compared with those at high risk.

**CONCLUSIONS:** Numerous clinical prediction rules for prognosticating early mortality in patients with aPE are available, but not all demonstrate the high sensitivity needed to reassure clinicians.

CHEST 2015; 147(4):1043-1062

Manuscript received August 1, 2014; revision accepted September 16, 2014; originally published Online First October 9, 2014.

**ABBREVIATIONS:** aPE = acute pulmonary embolism; CCI = Charlson Comorbidity Index; DOR = diagnostic OR; ESC = European Society of Cardiology; GRACE = Global Registry of Acute Coronary Events; LR = likelihood ratio; LR-PED = Low-Risk Pulmonary Embolism Decision; PESI = Pulmonary Embolism Severity Index; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QUADAS = Quality Assessment of Diagnostic Accuracy Studies; ROC = receiver operator curve; sPESI = Simplified Pulmonary Embolism Severity Index; sROC = summary receiver operator curve; VKA = vitamin K antagonist

**AFFILIATIONS:** From the University of Saint Joseph School of Pharmacy (Dr Kohn), Hartford, CT; the University of Connecticut/Hartford Hospital Evidence-Based Practice Center (Drs Mearns and Coleman), Hartford, CT; the University of Connecticut School of Pharmacy (Drs Mearns and Coleman), Storrs, CT; the Departments of Critical Care Medicine and Cardiology (Dr Parker), Hartford Hospital, Hartford, CT; the Department of Quantitative Health Sciences (Dr Hernandez), Cleveland Clinic Lerner Research Institute, Cleveland, OH; and the Unidad de Análisis y Gestión de Evidencias en Salud Pública (Dr Hernandez), Instituto Nacional de Salud, Lima, Peru.

**FUNDING/SUPPORT:** This project was supported by a grant from Janssen Scientific Affairs, LLC, Raritan, NJ.

Acute pulmonary embolism (aPE) is common, with an estimated annual incidence of 69 cases per 100,000.[1-4] aPE often leads to hospitalization for monitoring and initiation of a parenteral anticoagulant as a bridge to vitamin K antagonist (VKA) therapy.[3,4] However, the management of aPE with a VKA carries the need for frequent laboratory monitoring and dosage adjustments, which can significantly delay hospital discharge.[5] The newer oral anticoagulants (chiefly rivaroxaban and apixaban, which do not require pretreatment with a heparin) provide the potential for cost-effective management of aPE by allowing for shorter aPE-related hospital stays or, in some patients, reducing the need for a hospital admission altogether.

Multiple studies[6] suggest outpatient treatment of symptomatic aPE is reasonable for patients at low risk of early post-aPE all-cause mortality. However, there is currently no consensus for what criteria or clinical prediction rules to use to categorize patients with aPE into lower- or higher-risk groups.[7-46] Thus, we performed a systematic review and meta-analysis to (1) identify published clinical prediction rules that use a combination of multiple prognostic factors for determining the risk of early all-cause mortality in patients suffering an aPE, (2) determine the proportion of patients with aPE deemed to be at low (generally regarded as suitable for outpatient treatment or early hospital discharge) or high risk of early mortality according to these prediction rules and the relative odds of early mortality between these groups, and (3) assess the prognostic accuracy of clinical prediction rules for identifying patients with aPE at low risk for early mortality and, thus, suitable for outpatient treatment or early hospital discharge.

## Materials and Methods

### *Study Selection*

We performed a systematic literature search of the Medline and Embase computerized bibliographic databases from January 1, 2000, through March 17, 2014. The searches began at the year 2000 to limit the identification of studies not using modern aPE diagnostic and treatment practices (ie, not following evidence-based guidelines for diagnosis, risk stratification, use of interventions, and duration of anticoagulation created after the performance of well-done heparin and VKA randomized trials).[47-49] For our search, we combined Medical Subject Heading terms and key words for aPE with previously validated search filters for prognostic studies.[50] Our Medline search strategy is provided in e-Appendix 1. Manual backward citation tracking of references from identified studies and review articles was also performed to identify additional relevant studies.

Two investigators (C. G. K., C. I. C.) independently scanned titles and abstracts for initial inclusion, with disagreements resolved by discussion. Potentially eligible articles were then reviewed in depth by two investigators (C. G. K., C. I. C.) for inclusion, with disagreements resolved by discussion. To be included in this analysis, studies had to meet the following inclusion criteria: (1) evaluate a cohort of patients experiencing an aPE, (2) be a prognostic study designed to derive and/or validate a clinical prediction rule consisting of a combination of multiple prognostic factors for early post-aPE all-cause mortality, (3) provide data on early all-cause mortality (the reference standard) over at least the index aPE hospital admission but not longer than at 90 days, and (4) be published in English language full text. Our base-case analysis only included studies enrolling patients with aPE regardless of hemodynamic stability at admission. However, we did identify studies limited to hemodynamically stable patients only and used these studies in sensitivity analysis.

**CORRESPONDENCE TO:** Craig I. Coleman, PharmD, University of Connecticut/Hartford Hospital, Evidence-Based Practice Center, 80 Seymour St, Hartford, CT 06102-5037; e-mail: craig.coleman@hhchealth.org



**DOI:** 10.1378/chest.14-1888

### *Validity Assessment*

Two investigators (C. G. K., C. I. C.) independently assessed validity for each included study. We adapted the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool, which assesses bias and applicability over multiple domains (eg, patient selection, index test [clinical prediction rule], reference test [early all-cause mortality], and flow and timing)[51] to assess the quality of each cohort-clinical prediction rule analysis as having low, high, or unclear risk of bias and concerns regarding applicability (e-Table 1). In addition, we used the Hierarchy of Evidence for Clinical Decision (Prediction) Rules described by McGinn and colleagues[52] to classify the overall body of evidence for each clinical prediction rule into one of four levels (level 1 = one or more prospective validation in a different population and one impact analysis demonstrating change in clinician behavior with beneficial consequences; level 2 = demonstrated accuracy in either one large prospective study including a broad spectrum of patients and clinicians or validated in several smaller settings that differ from one another; level 3 = validated in only one narrow prospective sample; level 4 = derived but not validated or validated only in split samples, large retrospective databases, or by statistical techniques).

### *Data Extraction*

Two investigators (C. G. K., E. S. M.), through the use of a standardized tool, independently extracted all data, with disagreements resolved by a third investigator (C. I. C.). Data collected included: study/cohort identifier and year of publication; geographic location; sample size; study design (prospective vs retrospective); study inclusion/exclusion criteria; sampling technique (consecutive patients, random, or convenience sample); patient characteristics (age, proportion of patients with cancer), methods for diagnosing aPE (clinical signs and symptoms, pulmonary angiography, CT scan, ventilation-perfusion lung scan, medical records, billing codes); hemodynamic status of patients at admission; loss to follow-up, method of mortality determination, clinical prediction rule scoring, and patient-level $2 \times 2$ data (proportions dying in both the low- and high-risk groups) needed to calculate true and false positives and negatives for the occurrence of early all-cause mortality (the latter used to calculate sensitivity, specificity, and other accuracy statistics for clinical prediction rule prognostication). Some studies reported all-cause mortality data at various time points. For the purposes of this meta-analysis we preferentially used 30-day mortality data, followed by 90-day, 7-day, and, finally, in-hospital data. In cases of missing $2 \times 2$ data, we attempted to contact the corresponding authors by e-mail. If we did not receive an answer after sending a reminder, we excluded