Diagnostic Accuracy of Pulmonary Embolism Rule-Out Criteria: A Systematic Review and Meta-analysis

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Study objective: To perform a systematic review and meta-analysis to define the diagnostic performance of pulmonary embolism rule-out criteria (PERC) in deferring the need for D-dimer testing to rule out pulmonary embolism in the emergency department (ED).

Methods: We searched EMBASE, MEDLINE, Scopus, Web of Knowledge, and all the evidence-based medicine reviews that included the Cochrane Database of Systematic Reviews through August 14, 2011, and hand searched references in potentially eligible articles and conference proceedings of major emergency medicine organizations for the previous 2 years. We selected studies that reported diagnostic performance of PERC, reported original research, and were conducted in the ED, with no language restrictions. Two investigators independently identified eligible studies and extracted data. We used contingency tables to calculate sensitivity, specificity, and likelihood ratios.

Results: We found 12 qualifying cohorts (studying 13,885 patients with 1,391 pulmonary embolism diagnoses), 10 prospective and 2 retrospective, from 6 countries. Pooled sensitivity, specificity, positive likelihood ratios, and negative likelihood ratios for 10 included studies were 0.97 (95% confidence interval [CI] 0.96 to 0.98), 0.23 (95% CI 0.22 to 0.24), 1.24 (95% CI 1.18 to 1.30), and 0.17 (95% CI 0.13 to 0.23), respectively. Significant heterogeneity was observed in specificity ($\text{I}^2=97.2\%$) and positive likelihood ratio ($\text{I}^2=84.2\%$).

Conclusion: The existing literature suggests consistently high sensitivity and low but acceptable specificity of the PERC to rule out pulmonary embolism in patients with low pretest probability. [Ann Emerg Med. 2012;59:517-520.]

Please see page 518 for the Editor’s Capsule Summary of this article.

SEE EDITORIAL, P. 524.

INTRODUCTION

Pulmonary embolism often has a nonspecific clinical presentation. Emergency physicians have been increasing their use of diagnostic testing in an attempt to avoid missing this potentially life-threatening diagnosis, increasing both cost and use of medical resources.

To try to limit such diagnostic testing, Kline et al developed a clinical decision rule (pulmonary embolism rule-out criteria [PERC]) from parameters available at initial emergency department (ED) assessment. Patients meeting all 8 PERC (younger than 50 years, pulse rate $<100$ beats/min, $\text{SpO}_2 >94\%$, no unilateral leg swelling, no hemoptysis, no surgery or trauma within 4 weeks, no deep venous thrombosis or pulmonary embolism, and no oral hormone use) would appear to have a pretest probability low enough to defer D-dimer testing, thus removing any possibility of subsequent imaging. However, a recent systematic review of clinical decision rules for pulmonary embolism did not include PERC. Therefore, we performed a systematic review and meta-analysis to summarize the diagnostic accuracy of PERC.

MATERIALS AND METHODS

Data Collection and Processing

We performed a comprehensive search of the following biomedical databases through August 14, 2011: EMBASE, MEDLINE, SCOPUS, Web of Knowledge, and all the EBM reviews that included the Cochrane Database of Systematic Reviews. The search strategy is detailed in Appendix E1, available online at http://www.annemergmed.com. We hand searched references cited in potentially eligible articles and the previous 2 years’
Editor’s Capsule Summary

What is already known on this topic
The pulmonary embolism rule-out criteria (PERC) are commonly used to identify patients for whom D-dimer or other testing can be deferred.

What question this study addressed
Are the PERC reliable?

What this study adds to our knowledge
In this meta-analysis of 11 studies from 6 countries, the PERC were highly sensitive (97%) in excluding pulmonary embolism but were nonspecific (23%).

How this is relevant to clinical practice
This pooled analysis strongly corroborates the safety of using PERC to defer D-dimer testing.

Conference proceedings of major emergency medicine organizations (Society for Academic Emergency Medicine and American College of Emergency Physicians, Canadian Association of Emergency Physicians). We performed PubMed searches of authors of identified abstracts to locate full articles otherwise missed.

Two investigators (B.S. and A.K.P.) independently screened first titles and abstracts and then full texts of potentially eligible articles. With no language restrictions, we selected studies that reported diagnostic performance of PERC to rule out pulmonary embolism, reported original research, and were conducted in the ED setting. We assessed interobserver agreement for study selection with Cohen’s weighted \( \kappa \). Disagreements were resolved by consensus in the presence of third investigator (S.C.).

Because there is no single well-validated and widely accepted quality assessment tool for assessing the study methodology of clinical decision rule studies, we adopted a previously used checklist, which was developed after reviewing the QUADAS tool, recommendations by Laupacis et al, and recommendations by Stiell et al, among others. The checklist included 7 criteria: (1) patients selected in an unbiased fashion (consecutive or random sample); (2) the study sample included a wide-spectrum pulmonary embolism pretest probability for which PERC was designed; (3) predictor variables were assessed without knowledge of the outcome; (4) outcomes were assessed without knowledge of the predictor variables; (5) outcomes were accurately defined; (6) loss-to-follow-up rate of less than 10%; and (7) explicit interpretation of the risk score by clinicians in practice without knowledge of the outcome.

Responses for each criterion were dichotomized to yes and no/unclear. Two investigators (B.S., A.K.P.) independently graded study methodology quality with this checklist as yes and no/unclear. Interreviewer agreement was assessed and disagreements were resolved as above for study selection.

Two reviewers (B.S. and S.C.) then independently extracted data from the included articles, using a predesigned form, and assessed the reported quality of the methods. Data points were study characteristics (author, country, publication year, number of patients, study settings, study design, description of study participants, and duration of follow-up), subject selection (inclusion and exclusion criteria), PERC classification, outcome definition and measurement, outcomes in PERC positives and negatives, and follow-up. We determined the number of outcomes as reported by the study or calculated from reported sensitivity and specificity and cohort size. If a study reported more than 1 cohort, each cohort was included separately. Our primary outcome of interest was the diagnosis of pulmonary embolism or venous thromboembolism or death caused by venous thromboembolism within 90 days of initial ED evaluation. All the disagreements in data extraction were resolved by consensus in the presence of third investigator (S.C.). We excluded studies reported in abstract form only and those scoring less than 50% on the methodology checklist from quantitative data synthesis.

Primary Data Analysis
We describe continuous variables with either means with SD or medians with interquartile range as reported in the included studies. Categorical variables are expressed as frequency of occurrence and proportions. We used contingency tables to calculate the pooled sensitivity and specificity. A random-effects model was used to calculate pooled likelihood ratios and diagnostic odds ratios. We quantified the statistical heterogeneity between the studies with \( I^2 \) statistic, which indicates the proportion of variability in study estimate.

Because PERC was originally developed for patients with low clinical suspicion of pulmonary embolism, we performed a subgroup analysis based on pulmonary embolism prevalence. We further performed meta-regression with a generalization of Littenberg and Moses linear model to determine association between pulmonary embolism prevalence and PERC diagnostic accuracy. All analyses were performed with Meta-DiSc software.
RESULTS

The results of study search and screening are displayed in Figure 1. Investigator agreement for screening study abstracts and then full text was excellent ($\kappa=0.94$ and 0.80, respectively).

The 11 final studies (Table E1, available online at http://www.annemergmed.com) included 12 cohorts comprising 13,885 patients from 6 countries (United States, United Kingdom, Switzerland, France, Belgium, and New Zealand). Two cohorts were derived retrospectively, with the rest prospective. Included patients were 56% women, with a mean age of 52.9 years (SD 8.5 years). Follow-up ranged from 14 to 90 days. Results of the methodological quality checklist are shown in Table E2 (available online at http://www.annemergmed.com), with an investigator agreement $\kappa$ of 0.66. Study populations appeared unbiased in all cohorts, and none had reported implementation of PERC in clinical practice.

Test performance of the included studies is shown in Figure 2. The pooled sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio were 0.97 (95% confidence interval [CI] 0.96 to 0.98), 0.23 (95% CI 0.22 to 0.24), 1.24 (95% CI 1.18 to 1.30), and 0.18 (95% CI 0.13 to 0.23), respectively. The overall proportion of missed pulmonary embolisms was 0.32% (95% CI 0.20% to 0.44%) (44 of 13,885 total cases). The pooled diagnostic odd ratio was 7.3 (95% CI 5.4% to 9.8%). Significant heterogeneity was observed in specificity ($I^2=97.2%$) and positive likelihood ratio ($I^2=84.2%$).

To perform the preplanned subset analysis, we divided studies into 2 groups according to pulmonary embolism prevalence above or below 10%. The pooled specificity was 0.16 (95% CI 0.14 to 0.17) in higher-prevalence group and 0.24 (95% CI 0.24 to 0.25) in lower-prevalence group.

We found no significant association between pulmonary embolism prevalence and PERC diagnostic performance on meta-regression analysis (coefficient of $-0.038 [SE 0.023]; P=.14$) or on relative diagnostic odds ratios (0.92; 95% CI 0.91 to 1.01).

LIMITATIONS

A major limitation of this meta-analysis is the small number of studies available for data synthesis. We could not assess the possibility of publication bias because the meta-analysis included fewer than 20 studies. Further, this analysis is limited by specificity heterogeneity.

DISCUSSION

We conducted a systematic review of the literature to assess the diagnostic performance of PERC in deferring the need for D-dimer when considering the diagnosis of pulmonary embolism in the ED. We found that when the pretest probability is low, PERC are highly sensitive in predicting pulmonary embolism, and D-dimer testing is thus unnecessary. These findings are at a confidence of what is considered “level 2 evidence,” ie, demonstrated accuracy in either 1 large prospective study including a broad spectrum of patients and clinicians or validated in several smaller settings that differed from one another.8

Our meta-analysis observed consistently high PERC sensitivity across cohorts from 6 countries and both rural and
urban settings. Use of PERC could thus avoid the frequent expensive diagnostic imaging that typically results when a D-dimer result is positive.

Application of a well-validated clinical decision rule such as PERC adds objectivity to the diagnostic evaluation of pulmonary embolism and should decrease the excessive testing that has resulted from physician fears of missing pulmonary embolism and of litigation. Our meta-analysis reports consistent high sensitivity and negative predictive value of PERC, with missed pulmonary embolism in just 0.5% of patients. Two of the included studies (Hugli et al12 and Righini et al13) report a higher frequency of missed pulmonary embolism and have raised concern about the reliability of PERC. However, their higher failure rate likely results from the higher pulmonary embolism prevalence observed in their European settings. The threshold for pulmonary embolism diagnostic imaging in the United States is substantially lower than that in Europe, presumably because of the higher litigation risk.14,19,20 The PERC rule was developed for use in low-probability settings.2,12,14

The PERC rule is limited by its low specificity. We did not find a significant difference in PERC performance based on pulmonary embolism prevalence. In summary, our meta-analysis has demonstrated high sensitivity for the PERC rule and evidence that the rule can be used in settings of low pretest probability with confidence. The major limitation of PERC is its low but acceptable specificity.

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**Author contributions:** AKP and BS contributed equally to the article and collected data. AKP, BS, and SC were responsible for study design. AKP, DA, AS, SSM, and SC analyzed the data. BS was responsible for study selection. All authors participated in writing the article. SC takes responsibility for the paper as a whole.

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**REFERENCES**

APPENDIX E1.

Search strategy.
Ovid MEDLINE(R) 1948 to August Week 2 2011 # Searches Results Search Type

1 *pulmonary embolism/di 3318 Advanced
2 venous thrombosis/ or venous thromboembolism/ 17149 Advanced
3 2 and ("pe" or (pulmonary adj embolism)).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] 4300 Advanced
4 1 or 3 7306 Advanced
5 4 and (perc or (rule adj “out”)).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] 124 Advanced
6 4 and (exp emergency medical services/ or triag*.mp. or emergencies.mp. or emergency medicine/) [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] 233 Advanced
7 4 and (decision support systems, clinical/ or diagnosis, differential/ or decision support techniques/ or diagnosis, computer assisted/ or algorithms/) 842 Advanced
8 7 and (risk factors/ or risk assessment/) 150 Advanced
9 5 or 6 or 8 399 Advanced
10 7 and ("sensitivity and specificity"/ or validat*.mp. or probability/ or likelihood*.mp. or low.mp.) [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] 293 Advanced
11 9 or 10 588 Advanced
12 exp case control study/ or exp case study/ or exp clinical trial/ or exp intervention study/ or exp longitudinal study/ or exp major clinical study/ or exp prospective study/ or exp retrospective study/ 2207353 Advanced
13 follow up/ 493436 Advanced
14 comparative study/ or systematic review/ or meta-analysis/ or cohort*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 744561 Advanced
15 11 and (12 or 13 or 14) 261 Advanced
16 11 and diagnostic accuracy/
WoS/Scopus

Topic=("pulmonary embolism*" AND (PERC OR “rule out” OR "clinical rule" OR “clinical predict* rule" OR “clinical probability" OR "low risk" OR "low probability" OR "no risk")) AND Topic=(ed OR emergenc* OR triage*)
Table E1. Characteristics of included cohorts.

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Country</th>
<th>N (% Women)</th>
<th>Age, Mean (SD) or Median (IQR)</th>
<th>Subject Selection</th>
<th>Outcome Definition</th>
<th>PE Prevalence</th>
<th>Duration of Follow-up, days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolf 2008</td>
<td>United States</td>
<td>134 (54.0)</td>
<td>58 (43–72)</td>
<td>Adults aged 18–85 y with clinically suspected PE, chest radiograph, and ECG included</td>
<td>Exclusion: pregnant, hemodynamically unstable, known D-dimer level in recent past</td>
<td>11.9</td>
<td>90</td>
</tr>
<tr>
<td>Hogg 2005</td>
<td>UK</td>
<td>425 (51.1)</td>
<td>38.3 (15.0)</td>
<td>Adults (&gt;18 y) presenting to ED with pleuritic chest pain</td>
<td>Exclusion: pneumothorax, ECG changes of myocardial infarction, ischemia or pericarditis, pregnancy or trauma within 4 wk</td>
<td>5.4</td>
<td>90</td>
</tr>
<tr>
<td>Kline 2004</td>
<td>United States,</td>
<td>1,427 (60.0)</td>
<td>47 (17)</td>
<td>Adults (&gt;18 y) with clinical suspicion for PE whom emergency physicians believed were at low risk to justify exclusion of PE on the basis of a negative D-dimer result</td>
<td>Combination of: CT angiography CT angiography-venography V/Q scan (followed by duplex ultrasonography of the extremities)</td>
<td>8.0</td>
<td>90</td>
</tr>
<tr>
<td>Kline 2004</td>
<td>United States,</td>
<td>382 (56.0)</td>
<td>56 (18)</td>
<td>Adults (&gt;18 y) presenting with shortness of breath but emergency physician stated pulmonary embolism not the most likely diagnosis</td>
<td>Combination of: CT angiography CT angiography-venography V/Q scan (followed by duplex ultrasonography of the extremities)</td>
<td>2.4</td>
<td>90</td>
</tr>
<tr>
<td>Dachs 2010</td>
<td>United States</td>
<td>213</td>
<td></td>
<td>All the ED patients who underwent a CT scan to rule out PE</td>
<td>CT chest</td>
<td>8.5</td>
<td>90</td>
</tr>
<tr>
<td>Hugli 2011</td>
<td>Switzerland,</td>
<td>1,675 (56.7)</td>
<td>61 (45–76)</td>
<td>Adult outpatients treated in the ED, with a clinical suspicion of PE.</td>
<td>Exclusion: contraindication to multidetector CT MDCT (ie, allergy to iodine contrast agents, creatinine clearance &lt;30 mL/min, or pregnancy), a terminal illness with an expected survival of &lt;3 mo, a previous documented diagnosis of PE or were receiving anticoagulant therapy at presentation.</td>
<td>21.3</td>
<td>90</td>
</tr>
<tr>
<td>Author Year Country</td>
<td>N (% Women)</td>
<td>Age, Mean (SD) or Median (IQR)</td>
<td>Subject Selection</td>
<td>Outcome Definition</td>
<td>PE Prevalence</td>
<td>Duration of Follow-up, days</td>
<td></td>
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<tr>
<td>Beam 2007 United States</td>
<td>189</td>
<td>18 y</td>
<td>Adults (&gt;18 y) with clinical suspicion for PE for whom emergency physicians considered formal PE evaluation necessary</td>
<td>Combination of: CT scan and V/Q scan</td>
<td>4.2</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Righini 2005 Switzerland</td>
<td>762 (58.0)</td>
<td>61 (19)</td>
<td>Consecutive outpatients suspected of having PE</td>
<td>Combination of: Clinical probability assessment D-dimer measurement Venous ultrasonography Helical CT Pulmonary angiogram</td>
<td>25.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kline 2008 United States, New Zealand</td>
<td>8,138 (67.0)</td>
<td>49.1</td>
<td>Adults (&gt;18 f) with clinical suspicion for PE on emergency physician’s evaluation. Exclusion: (1) positive pulmonary vascular imaging study result in last 7 days, (2) patient indicated that the enrollment hospital was not his or her choice for follow-up, (3) patient would be lost to follow-up (eg, homeless, psychiatric disorders, international travelers, person arrested for felonies)</td>
<td>Combination of: A high-probability V/Q scan CT angiogram Conventional pulmonary angiogram PE on autopsy</td>
<td>7.7</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Kline 2010 United States</td>
<td>115</td>
<td></td>
<td>ED patients (&gt;17 y) admitted with chief complaints: chest pain, shortness of breath, respiratory distress, syncope, hypotension, palpitations, cough, altered mental status, or syntax indicating that the patient was sent from outside facility for PE evaluation</td>
<td>Combination of: D-Dimer Pulmonary vasculature imaging Venous ultrasonography</td>
<td>1.74</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Courtney 2006 United States</td>
<td>315</td>
<td></td>
<td>ED patients with any testing (V/Q scan, CT scan or D-dimer test) to evaluate for PE</td>
<td>Combination of: V/Q scan, CT scan, D-dimer test</td>
<td>4.44</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Crichtlow 2011 United States</td>
<td>110 (74)</td>
<td>46.4 (30.8–62.0)</td>
<td>Patients who received CT pulmonary angiography or lower-extremity duplex ultrasonography</td>
<td>Combination of: CT pulmonary angiography Lower-extremity duplex ultrasonography</td>
<td>5.26</td>
<td>90</td>
<td></td>
</tr>
</tbody>
</table>

IQR, Interquartile range; PE, pulmonary embolism; V/Q, ventilation-perfusion scan; CT, computed tomography; VTE, venous thromboembolism; LR, low risk; VLR, very low risk.
Table E2. Quality assessment study methodology score obtained by each study on the checklist.*

<table>
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</thead>
<tbody>
<tr>
<td>1) Were the patients selected in an unbiased fashion (consecutive or random sampling)?</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2) Do they represent a spectrum of pretest probability the PERC is used for?</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0/1†</td>
<td>1</td>
</tr>
<tr>
<td>3) Were the predictor variables assessed without knowledge of the outcome?</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4) Were the outcomes assessed without knowledge of the predictor variables?</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5) Were the outcomes defined accurately (especially PE)?</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>6) Was follow-up adequate (&lt;10% lost to follow-up)?</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>7) Was there an explicit interpretation of PERC by clinicians in practice without knowledge of the outcome?</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Yes=1, no=0.
†The study had 2 cohorts.
‡Scores represent the score for the low-risk and very low-risk cohort, respectively.