

# Critical Review Form

## Diagnostic Test

Clinical Features from the History and Physical Examinations that Predict The Presence or Evidence of PE in Symptomatic ED Patients: Results of a Prospective, Multicenter Study, *Ann Emerg Med* 2010; 55:307-315

**Objectives:** “To compute and compare the adjusted odds ratios (OR) for 13 predefined implicit variables, (assumed to be predictive but not part of existing pretest probability or scoring systems) that are commonly taught and used as rationale to initiate, delay, or obviate testing for pulmonary embolism versus 12 explicit predictor variables (with origin in published prediction rules for pulmonary embolism).” (p. 308)

**Methods:** A prospective observational trial in 12 (9 teaching, 3 community) U.S. EDs from July 2003 until November 2006. Eligible patients had to present to an ED with signs or symptoms interpreted by the treating physician as sufficient to warrant testing (D-dimer, CT angiogram, or V/Q scan) for PE. Exclusion criteria included current treatment for VTE, diagnostic DVT or PE imaging (CT, V/Q or venous Dopplers) in the preceding 30 days, critical illness (circulatory shock, respiratory failure, or comorbid illness with death likely in the next few days), or social circumstances precluding reliable follow-up (homeless, imprisoned). Patients who were only evaluated for DVT were not included.

Research assistants at each site monitored PE test ordering during randomly assigned shifts. The method to test for PE was not standardized but each site was provided a recommended protocol level upon pretest probability assessment followed by selective D-dimer testing and imaging. All patients with VTE at enrollment were followed up (telephone interview, medical record review or social security Death index) using previously validated techniques.

Explicit predictor variables were obtained from 4 CDR's: [Well's](#), [Geneva](#), [Charlotte](#), and [PERC](#). Variables that are not included in these models, but commonly referenced in teaching modules and textbooks were labeled as “implicit” predictor variables. Data for each predictor variable were recorded prior to criterion standard testing at the ED point-of-care by research assistants or clinicians using a web-based data collection instrument with preformed fields, and drop-down menus to prevent

**mistyped or missing data. Users could not upload the form until all elements were populated.**

Categorization and definition of predictor variables

	Probability System
<b>Explicit predictor variables</b>	
<b>Unilateral leg swelling</b>	W,G,C,P
<b>Surgery</b> within the previous 4 weeks (requiring general anesthesia)	W,G,C,P
<b>Trauma</b> within the previous 4 weeks (requiring hospitalization)	W,P
<b>Immobilization</b> (any of the following: generalized body immobility for 48 hours in the prior 2 days Bedridden status, paralysis/paresis, or limb in cast/external fixator)	W
<b>Hemoptysis</b>	W,G,C,P
<b>Patient history of VTE</b>	W,G,P
<b>Pulse &gt;94*</b>	G
<b>Active malignancy:</b> (current chemotherapy, radiation therapy, or palliative care)	W,G
<b>Shock index &gt;1.0</b> (SI-pulse divided by systolic blood pressure)	C
<b>Age &gt; 50 years</b>	C,P
<b>Hypoxemia</b> (oxygen saturation <95% on pulse oximetry)	C,P
<b>Estrogen:</b> (current use)	P

**Implicit predictor variables**

Female gender

**Pregnancy or post partum state**

**Thrombophilic condition (non-cancer related):** any of the following known in the ED: Factor V Leiden mutation, protein C or S deficiency, prothrombin mutation, anti-phospholipid antibody syndrome, or sickle cell disease (SS or SC)

**Smoking** tobacco currently

**Sudden onset** of symptoms

**Sub-sternal chest pain** (located behind the sternum)

**Pleuritic chest pain** (between clavicles & costal margin, that changes with respiration)

**Dyspnea:** (patient perception of shortness of breath or difficulty breathing)

**Inactive malignancy** (not being treated with chemotherapy, radiation, or palliative care)

**Obesity** (body mass index-BMI  $\geq$  30)

**Fever** (temperature  $\geq$  38.0° C)

**Tachypnea** (respiratory rate  $>$ 24 breaths/minute)

**Family history of VTE**

W, Wells score; G, Geneva score; C, Charlotte rule; P, PERC rule.

\*tachycardia was also part of the PERC rule ( $>$ 99 beats per minute) and the Wells score ( $>$ 100 beats per minute).

**The primary outcome was PE or DVT diagnosed at the ED visit or hospitalization or during the 45-day long follow-up. Diagnosis of PE required attending radiologist positive PA filling defect on CT, high probability V/Q scan, or autopsy PE. DVT of arm or leg required a positive venous Duplex Doppler with resulting treatment. The 25 implicit and explicit variables were entered into a logistic regression equation to yield adjusted odd ratios (OR) with 95% CI. Based upon 568 patients with VTE, the regression equation ratio of subjects with outcome of interest to candidate variables 20:1 would permit at least 25 candidate variables to be assessed.**

Guide		Comments																																																																																	
<b>I.</b>	<b>Are the results valid?</b>																																																																																		
<b>A.</b>	<b>Did clinicians face diagnostic uncertainty?</b>	Yes, "All clinical data, including signs, symptoms, and variables, were entered before results of final pulmonary embolism testing while patients were in the ED." (p. 310)																																																																																	
<b>B.</b>	<b>Was there a blind comparison with an independent gold standard applied similarly to the treatment group and to the control group?</b>  <b>(Confirmation Bias)</b>	Yes, although the specific proportions of criterion standard tests used is not detailed by the authors. "All subjects enrolled had to have testing with at least 1 of the following: D-dimer blood test, CT angiography of the pulmonary arteries, or ventilation-perfusion scan." (p. 309) Also, the authors do not mention whether radiologists were blinded to the test variables.																																																																																	
<b>C.</b>	<b>Did the results of the test being evaluated influence the decision to perform the gold standard?</b>  <b>(Ascertainment Bias)</b>	No, "All decisions about admission, further evaluation, and anticoagulation were made by treating physicians independent of the study protocol." (p. 310)																																																																																	
<b>II.</b>	<b>What are the results?</b>																																																																																		
<b>A.</b>	<b>What likelihood ratios were associated with the range of possible test results?</b>	<ul style="list-style-type: none"> <li>After exclusion of 5% who refused to consent and 39% due to poor follow-up potential 7940 ED patients evaluated by 477 unique emergency physicians were enrolled with a median age of 47 years, 67% female and predominately Caucasian (57%) or African-American (34%) race. Most presented with chest pain (71%) and had Well's score &lt; 4 (84%).</li> <li>568/7940 (7.2%, 95%, CI 6.6-7.7%) had VTE by day 45, most (552/568) were diagnosed at the initial ED visit.</li> <li>In multivariate analysis 8 implicit and 9 explicit variables were significant (defined as OR not crossing unity) noted in red at left.</li> </ul>																																																																																	
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<b>III.</b>	<b>How can I apply the results to patient care?</b>	
<b>A.</b>	<b>Will the reproducibility of the test result and its interpretation be satisfactory in my clinical setting?</b>	Yes. “In contrast to the strict qualifying process required for a management study or a clinical trial, the present work was designed to collect a large, relatively unbiased sample of patients with heterogeneous clinical characteristics known to clinicians when they ordered a test for pulmonary embolism in the ED; we believe our findings represent actual, current acute care practice in the United States.” (p. 313)
<b>B.</b>	<b>Are the results applicable to the patients in my practice?</b>	Probably – see above.
<b>C.</b>	<b>Will the results change my management strategy?</b>	Yes, by recognizing the relative importance for the diagnosis of PE amongst variables not included in current PE CDR’s: thrombophilia, pleuritic chest pain, family history, and substernal chest pain. The authors hedge regarding the reduced diagnostic risk (for the variables of female gender and smoking: “we strongly urge that this observation not be interpreted as evidence that women are at lower risk for pulmonary embolism. They are not.” (p. 314) instead, the authors suggest that “One possible explanation of this finding is that it is a function of over testing for pulmonary embolism among women and smokers.” (p. 313)
<b>D.</b>	<b>Will patients be better off as a result of the test?</b>	No patient-centric outcomes were evaluated or discussed. However, “Practitioners may wish to document these significant predictors when considering whether or not to test for PE and may wish to add them as standard elements to chief-complaint-based template charting systems. Researchers may consider testing the predictors we found to be significant in a new decision rule or management algorithm.” (p. 314)



## **Limitations**

- 1) The pragmatic trial design. Improving external validity usually means compromising internal validity. These investigators did not use a standardized PE testing protocol which may have lowered internal validity, but certainly enhances external validity.**
- 2) No assessment of inter-observer agreement, although “implicit variables are either objective data elements or are relatively clear binary elements from the history.” (p. 313)**
- 3) No assessment of or hypothesis about the results’ effects on patient-centric outcomes.**
- 4) No description of the final diagnosis for the 93% without PE (what did they have?).**

## **Bottom Line**

**The most important variables to heighten or reduce the ED suspicion for PE amongst patients with dyspnea and chest pain continue to be more confidently defined. Adding to current clinical decision rules to reliably establish pretest probability for PE, clinicians can use other risk factors to increase (thrombophilia, pleuritic pain, family history of VTE) or decrease (substernal pain, current smoker) the probability even further in contemplating test-treat thresholds.**