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## Prospective Study of the Diagnostic Accuracy of the Simplify D-dimer Assay for Pulmonary Embolism in Emergency Department Patients\*

Jeffrey A. Kline, MD; Michael S. Runyon, MD; William B. Webb, BSPH; Alan E. Jones, MD; and Alice M. Mitchell, MD

**Objective:** To determine if a d-dimer assay (Simplify D-dimer; Agen Biomedical; Brisbane, Australia) can reliably exclude pulmonary embolism (PE) by producing a posttest probability of PE < 1% in low-risk, symptomatic emergency department (ED) patients.

**Methods:** Hemodynamically stable patients were evaluated for PE using a structured d-dimer-centered protocol; d-dimer testing was performed prior to imaging. Prior to testing, physicians completed an electronic data form that included their unstructured clinical estimate for the pretest probability of PE (< 15%, 15 to 40%, or > 40%) and the elements of the Charlotte rule and Canadian score for PE. Criterion standard was selective use of pulmonary vascular imaging and 90-day follow-up.

**Results:** We enrolled 2,302 patients (mean age, 45 ± 16 years [± SD]; 31% male); 108 patients received a diagnosis of PE (4.7%; 95% confidence interval [CI], 3.6 to 5.6%). The overall sensitivity and specificity of the d-dimer assay were 80.6% (95% CI, 71.8 to 87.5%) and 72.5% (95% CI, 70.6 to 74.4%), respectively. The negative likelihood ratio and negative predictive value were 0.27 (95% CI, 0.18 to 0.39) and 98.7% (95% CI, 98.0 to 99.1%), respectively. The posttest prevalence of PE among low-risk patients with negative d-dimer results was 0.7% (95% CI, 0.3 to 1.4%) for the unstructured estimate, 1.2% (95% CI, 0.7 to 2.0%) for the Canadian score, and 1.1% (95% CI, 0.6 to 1.7%) for the Charlotte rule.

**Conclusions:** The Simplify D-dimer assay had moderate sensitivity and relatively high specificity for PE in low-risk ED patients. The combination of a physician's unstructured estimate of pretest probability of PE of < 15% and a negative d-dimer result produced a posttest probability of PE of 0.7% (95% CI, 0.3 to 1.4%).  
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**Key words:** d-dimer; diagnosis; pulmonary embolism; sensitivity and specificity; thromboembolism

**Abbreviations:** CI = confidence interval; DVT = deep venous thrombosis; ED = emergency department; PE = pulmonary embolism; PE+ = pulmonary embolism positive; PE- = pulmonary embolism negative.

The ideal screening strategy to exclude pulmonary embolism (PE) in the emergency department (ED) setting would be, fast, cheap, accurate, and easy to use. The d-dimer assay (Simplify D-dimer; Agen Biomedical; Brisbane, Australia) is a single-use,

individually packaged immunofiltration cartridge assay. The kits and the reagents can be stored at room temperature. The user adds a drop of whole blood to a well, followed by a few drops of buffer. The test result is read in 10 min at the bedside. The test has an acquisition cost of < \$20. However, to ensure patient safety and to maintain a defensible standard of care, any PE screening strategy must have sufficiently high sensitivity and specificity to reliably

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produce a posttest probability  $< 1.0\%$ .<sup>1,2</sup> Very few published studies have addressed the sensitivity and specificity of the Simplify D-dimer assay for the diagnosis of PE.<sup>3</sup> Researchers<sup>2,3</sup> remain concerned that qualitative d-dimer assays may demonstrate lower diagnostic sensitivity compared with quantitative d-dimer assays, which are becoming more widely

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used in EDs to rule out the diagnosis of PE. In the present report, we test the hypothesis that the Simplify D-dimer assay can produce a posttest probability of PE  $< 1.0\%$  in certain low-risk, symptomatic ED patients. The specific aims were as follows: (1) to report the clinical characteristics of ED patients tested with the Simplify D-dimer assay; (2) to measure the diagnostic sensitivity, specificity, and negative likelihood ratio for the d-dimer assay, and examine the posttest probability of PE in low risk-patients with a negative d-dimer result; and (3) to test if spectrum bias affected the diagnostic indexes.

## MATERIALS AND METHODS

This protocol was approved by the Carolinas Medical Center Institutional Review Board. Carolinas Medical Center is an urban teaching hospital with a residency in emergency medicine and a 2002 census of 107,000. Research participants were ED patients of all ages who were selected by a board-certified emergency physician to undergo a structured PE rule-out protocol, using methods we have described previously.<sup>2</sup> Typical indications for the PE rule-out protocol included symptoms of dyspnea, chest pain, or syncope, or physical signs such as a rapid pulse or low pulse oximetry reading that could not be explained by another disease process. Exclusions were hemodynamic instability (clinical signs of shock as described by Jones et al<sup>4</sup>), inability to obtain a blood sample for the d-dimer assay, or patient unwillingness to participate. Prior to diagnostic testing, physicians completed a Web-based electronic data collection form that contained  $> 70$  data fields. The contents and methodology of this Web-based form have been published.<sup>5</sup> The form first asks the clinician to provide his or her own three-tiered, unstructured pretest probability (low,  $< 15\%$ ; moderate, 15 to 40%; high,  $> 40\%$ ),<sup>6</sup> and later parts of the data form contained elements required to compute the Canadian score<sup>7</sup> and the Charlotte rule.<sup>8</sup> The Charlotte rule, when negative, predicts a low-enough pretest probability to allow PE to be ruled out safely using either a quantitative d-dimer<sup>9</sup> or a qualitative d-dimer in conjunction with a normal alveolar dead space measurement.<sup>10</sup> The Charlotte rule has not yet been tested or validated to allow PE to be ruled out with a qualitative d-dimer alone. D-dimer results were obtained prior to any pulmonary vascular imaging, and all patients with positive d-dimer assay results underwent imaging. Imaging was performed in a minority of patients with negative d-dimer results at the discretion of the attending emergency physician. Our institutionally approved PE rule-out protocol required that clinicians order pulmonary vascular imaging in patients with either a positive Charlotte rule or a high unstructured pretest probability.<sup>6,8</sup> However, in these higher-risk patients, physicians were free to simultaneously order the Simplify D-dimer assay in addition to performing pulmonary vascular imaging.

## D-dimer Testing

Arterial blood was used with the Simplify D-dimer assay. Blood was drawn by qualified respiratory therapists, usually from the radial artery;  $> 1$  mL was collected in an arterial blood gas syringe containing lithium-heparin. The d-dimer assay was then performed in the ED by the respiratory therapist using a written protocol in accordance with manufacturer recommendations.<sup>10</sup> All therapists underwent a structured training process overseen by the principle investigator, which included a semiannual quality assurance evaluation as required by government agencies.

## Criterion Standard

Imaging was performed according to a flow diagram posted in the ED.<sup>10</sup> The primary pulmonary vascular imaging study was CT angiography of the chest and venography of the legs, performed and interpreted as we have previously described.<sup>11</sup> Patients who were allergic to iodinated contrast or had a serum creatinine measurement  $> 1.5$  mg/dL underwent ventilation-perfusion scintillation lung scanning, interpreted by board-certified radiologists with specialty training in nuclear medicine in accordance with Prospective Investigation of Pulmonary Embolism Diagnosis study criteria.<sup>12</sup> Lower-extremity venous ultrasound was ordered at the discretion of the attending emergency physician. Radiologists who interpreted images were unaware of the of the d-dimer result. Patients with negative d-dimer results did not necessarily undergo pulmonary vascular imaging. For all patients, the criterion standard was the result of 90-day follow-up, using a structured combination of telephone and medical record follow-up as we have previously described.<sup>10,13</sup> The diagnosis of PE included patient-verified and medical record-verified evidence of a new diagnosis of PE or deep venous thrombosis (DVT) requiring treatment, or death from PE within 90 days after testing with the d-dimer assay. The details of the methodology of defining PE or DVT discovered on follow-up have been published.<sup>13</sup> Briefly, this required that two independent physicians agree that the patient had image- or autopsy-proven PE or DVT diagnosed within the follow-up period, and that treatment (either anticoagulation, vena caval interruption, or both) was initiated in living patients. Patients with either PE or DVT or both were considered PE positive (PE+). Patients who were alive and had no diagnosis of PE or DVT after 90 days were considered PE negative (PE-).

## Statistical Analysis

Data are presented in accordance with the Standards for Reporting of Diagnostic Accuracy initiative.<sup>14</sup> Primary analyses are from  $2 \times 2$  diagnostic tables, and all analyses were performed using statistical software (version 2.2.4; StatsDirect; Cheshire, UK). Diagnostic indexes and 95% confidence intervals (CIs) were calculated by the exact (Clopper-Pearson) method. To examine for spectrum bias, we used first-order regression analysis and Pearson correlation coefficient ( $R$ ) to examine the plots of sensitivity, specificity, and negative likelihood ratio as a function of prevalence of PE. An unpaired  $t$  test was applied to the slope of the regression lines to test for a significant correlation with  $p < 0.05$  considered significant.

## RESULTS

The d-dimer assay was performed on 2,302 patients enrolled from October 1, 2001, until June 30, 2004. Clinical characteristics of the study population

are shown in Table 1. PE was diagnosed in 108 patients (4.7%; 95% CI, 3.6 to 5.6%). Figure 1 shows the flow diagram of diagnostic imaging relevant to PE. One thousand two hundred sixty-two patients with negative d-dimer results had no imaging performed, so the results of 90-day follow-up served as the criterion standard.

The distributions of pretest probability estimates from the unstructured approach, the Canadian score, and the Charlotte criteria are shown in Figure 2, which demonstrates that patients categorized as low risk for PE, either by the unstructured method < 15%, or by the Canadian score < 2, had a very low observed frequency of PE, at 2.7% (95% CI, 1.9 to 3.6%) and 2.9% (95% CI, 2.2 to 3.9%), respectively. When the Charlotte rule was negative, the frequency of PE was 3.9% (95% CI, 3.1 To 4.8%).

Table 2 shows the diagnostic 2 × 2 table results for the d-dimer assay in the entire cohort, for patients categorized as low risk by the unstructured method and the Canadian score, and for patients with a negative Charlotte rule. The sensitivity and specificity for the d-dimer assay in the entire cohort were 80.6% and 72.5%, respectively. These values did not change significantly when patients were selected on the basis of the three different pretest

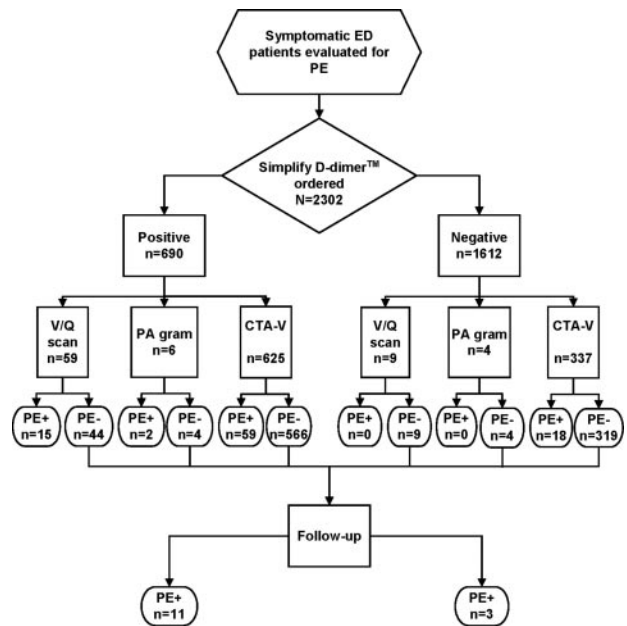


FIGURE 1. Flow diagram of diagnostic imaging performed in all patients. V/Q = ventilation/perfusion; PA gram = pulmonary angiogram; CTA-V = CT angiography-venography.

**Table 1—Clinical Characteristics of the Study Cohort (n = 2,302)\***

Characteristics	Data
Vital signs	
Age, yr	44.7 ± 15.8
Respiratory rate, breaths/min	21.1 ± 5.5
Pulse rate, beats/min	91.7 ± 19.6
Systolic BP, mm Hg	136.0 ± 25.1
Room air arterial oxygen saturation, %	97.3 ± 3.6
Body temperature, °C	36.7 ± 1.1
Male gender	703 (31)
Symptoms	
Pleuritic chest pain	1,290 (56)
Dyspnea	1,510 (66)
Substernal chest pain	976 (42)
Syncope	142 (6)
Cough	749 (33)
Hemoptysis	65 (3)
Risk factors and other conditions	
Surgery within prior 4 weeks	105 (5)
Immobility†	198 (9)
Prior DVT or PE	171 (7)
Active malignancy	179 (8)
Exogenous hormone use	232 (10)
Pregnancy or postpartum within 4 wk	100 (4)
History of coronary artery disease	221 (10)
Congestive heart failure	155 (7)
Asthma or COPD	307 (13)
Current smoker	862 (37)

\*Data are presented as mean ± SD or No. (%).

†Total body > 48 h or limb immobility by cast or external fixation device.

probability systems. If pretest probability was not considered, 1,612 patients in the entire cohort had negative d-dimer results, of whom 21 patients (1.3%; 95% CI, 0.8 to 2.0%) had PE. If we examine the effect of first stratifying for a low pretest probability, only one combination resulted in a posttest probability of PE < 1.0%: a low (< 15%) unstructured pretest probability estimate, plus a negative d-dimer result, which yielded a posttest probability of 0.7% (95% CI, 0.3 to 1.4%).

To examine for possible spectrum bias, we plotted the sensitivity, specificity, and negative likelihood ratio as a function of the prevalence of PE that was observed in each of the eight different pretest probability strata: three each for the unstructured estimate and Canadian score, and two for the Charlotte rule. None of the regression plots demonstrated significant correlation. Figure 3 shows the plot of the likelihood ratio as a function of prevalence ( $R^2 = 0.006$  with  $t$  test on slope yielding  $p = 0.85$ ; power to detect a significant correlation of 29%). The Pearson correlation coefficient observed for the plot of sensitivity vs prevalence yielded  $R^2 = 0.20$ , with  $p = 0.27$  from the  $t$  test on the slope; the plot of specificity vs prevalence yielded  $R^2 = 0.38$  with  $p = 0.10$ , and power of 36% (plots not shown). These regression analyses suggest the absence of a significant spectrum bias for either the pretest probability estimate or the underlying prevalence of PE on the

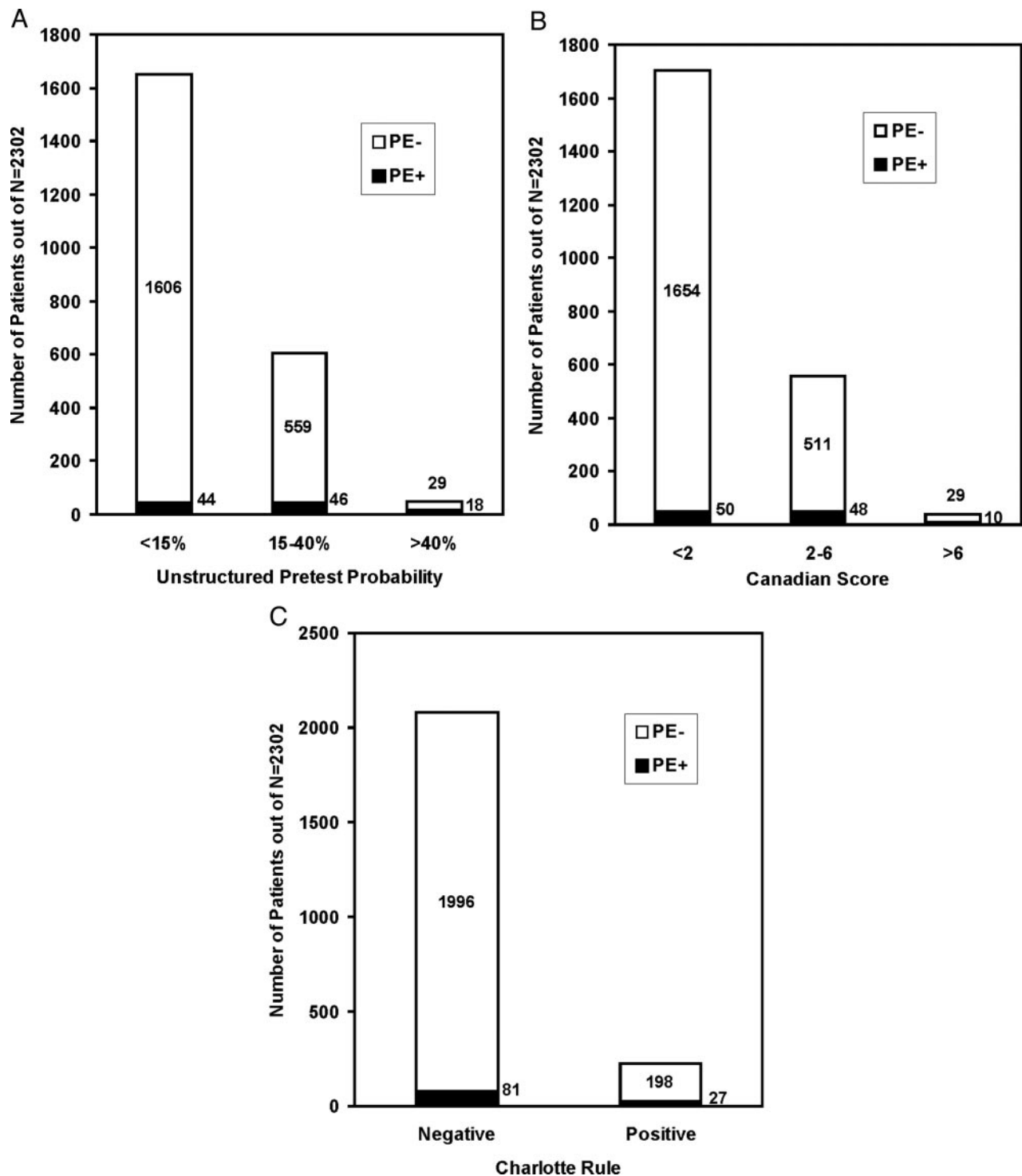


FIGURE 2. Distribution of pretest probability estimates derived the unstructured approach (top left, A), the Canadian Score (top right, B), and the Charlotte rule (bottom, C). The stacked bars show the total number of patients in each subcategory classified into patients without PE (open area) and patients with PE (filled area).

diagnostic accuracy of the d-dimer assay. These computations do not address the possibility of spectrum effect, and the power to detect a significant relationship was small for each regression.<sup>15</sup>

## DISCUSSION

This large, single-center study measured the diagnostic accuracy of a rapid, point-of-care, qualitative

**Table 2—Diagnostic Performance of the Simplify D-dimer Assay\***

Assay Results	Criterion Standard Results†							
	Entire Cohort (n = 2,302)		Unstructured Estimate < 15% (n = 1,650)		Canadian Score < 2 (n = 1,704)		Charlotte Rule Negative (n = 2,077)	
	PE+	PE–	PE+	PE–	PE+	PE–	PE+	PE–
Positive	87	603	35	376	35	428	65	501
Negative	21	1,591	9	1,230	15	1,226	16	1,495
Sensitivity	80.6 (71.8–87.5)		79.6 (64.7–90.2)		70.0 (55.4–82.1)		80.3 (69.9–88.2)	
Specificity	72.5 (70.6–74.4)		76.6 (74.4–78.6)		74.1 (71.9–76.2)		74.9 (72.9–76.8)	
Negative likelihood ratio	0.27 (0.18–0.39)		0.27 (0.15–0.45)		0.40 (0.26–0.59)		0.26 (0.17–0.40)	
Negative predictive value	98.7 (98.0–99.1)		99.3 (98.6–99.6)		98.8 (98.0–99.3)		98.9 (98.3–99.4)	
Negative posttest probability	1.3 (0.8–2.0)		0.7 (0.3–1.4)		1.2 (0.7–2.0)		1.1 (0.6–1.7)	

\*Data are shown as % (95% CI) unless otherwise indicated.

†Shown for the entire cohort and three low-risk subgroups, estimated using three different methods of pretest probability assessment.

d-dimer assay in the ED setting. In a cohort of 2,302 patients, we found a moderate sensitivity of 80.5% and a relatively high specificity of 72.5%, leading to a negative likelihood ratio of 0.27. These findings are remarkably similar to the 81.8% sensitivity, 74.2% specificity, and negative likelihood ratio of 0.24 for the Simplify D-dimer assay recently reported by Hogg et al,<sup>3</sup> who studied 417 adult ED patients in the United Kingdom who met an explicit definition of pleuritic chest pain. The criterion standard for the diagnosis of PE used by Hogg et al<sup>3</sup> was very similar to ours. It therefore appears almost certain that the diagnostic accuracy of the Simplify D-dimer for PE differs significantly from the diagnostic accuracy of quantitative d-dimer assays used in ED populations with similar criterion standards. Systematic analyses have found the sensitivity and negative likelihood ratio of quantitative d-dimer tests at a cutoff of 500 ng/mL (either immunoturbidimetric or enzyme-linked immunoassay) to be approximately 93 to 94% and 0.12 to 0.15, respectively, when used to evaluate for PE in ED populations.<sup>16,17</sup> We examined the test

characteristics of the Simplify D-dimer assay in an unselected, consecutive, nonconvenience sample of ED patients suspected of having PE. This fact and the lack of correlation between test performance vs stratification by pretest probability suggest that the relatively modest diagnostic performance of the Simplify D-dimer assay was probably not a result of spectrum bias.

We and others<sup>1,2</sup> have stated the position that a safe d-dimer–based screening strategy to rule out PE in the ED should afford a posttest probability of PE < 1.0%. If the negative likelihood ratio of the Simplify D-dimer assay is very close to 0.27, then a negative d-dimer result could theoretically produce a posttest probability < 1.0% in any population with a pretest probability below (approximately) 3.5%. However, this may not occur in real practice. For example, in the present study, although the Canadian score < 2 produced a pretest probability of 2.9%, the actual measured posttest probability of PE was 1.2% (95% CI, 0.8 to 2.0%). In our population, the < 1.0% posttest probability objective was met only when a negative Simplify D-dimer result occurred when the physician's unstructured pretest probability estimate was < 15%, which yielded a population with only a 2.7% prevalence of PE. With this combination, the actual measured posttest probability of PE was 0.7% (95% CI, 0.3 to 1.4%). We emphasize that these results are from one ED that appears to test for PE at a very low threshold.

Several factors could limit the external validity of this study. The upper limit of the 95% CI for the 0.7% post-test probability for PE after an unstructured estimate of PE < 15% plus a negative Simplify D-dimer result was 1.4%. Patients deemed low risk by clinicians were drawn from a cohort of urban ED patients with an overall 4.7% prevalence of PE. Researchers<sup>18,19</sup> in Europe have found the preva-

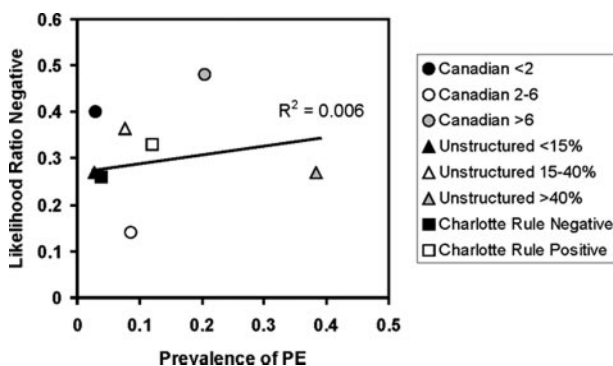


FIGURE 3. Plot of the negative likelihood ratio as a function of prevalence of PE for eight different categories of pretest probability assessment.

lence of PE to be > 20% in patients referred from the ED; however, we submit that the threshold at which clinicians decide to order a d-dimer assay to rule out PE in the ED has decreased remarkably in the past 10 years, and continues to drop in the United States and also in Canada.<sup>18,20</sup> The accuracy and reliability of unstructured estimation of pretest probability assessment has been questioned.<sup>21</sup> We previously found good interobserver agreement (Cohen  $\kappa = 0.60$ ) for the unstructured method of pretest probability assessment, and that this finding was independent of training level.<sup>6</sup> These results have not yet been reproduced at other EDs, and the interobserver variation for the interpretation of the Simplify D-dimer assay used at the point of care in an ED has not been examined.<sup>22</sup> Our ongoing research efforts may make our practitioners likely to remember the components of published decision rules, which might enhance their unstructured estimates. Fewer than one half of the patients received pulmonary vascular imaging as part of the criterion standard diagnosis. We use what we believe to be very thorough, explicit, and meticulous follow-up methodology.<sup>13</sup> It remains possible that a patient who had PE could have been discharged after a false-negative d-dimer result did not seek additional medical care and reported better health at the 90-day follow-up. This effect could have resulted in an underestimate of false-negative Simplify D-dimer results. However, we also considered a patient with DVT diagnosed 89 days after study enrollment as tantamount to the diagnosis of acute PE on the day of enrollment. This effect may have resulted in an overestimate of false-negative Simplify D-dimer results.

When interpreted together with the data from Hogg et al,<sup>3</sup> and systematic analyses,<sup>16,23</sup> we believe that our data allow the definitive conclusion that the Simplify D-dimer assay has a higher negative likelihood ratio than the quantitative d-dimer at a 500 ng/mL cutoff. We also conclude that the Simplify D-dimer assay must be used in a very-low-risk population to produce a posttest probability < 1.0%. Future work will directly compare the diagnostic accuracy and operational performance of the point-of-care Simplify D-dimer assay to the laboratory-based quantitative d-dimer.

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