

# D-Dimer for the Exclusion of Acute Venous Thrombosis and Pulmonary Embolism

## A Systematic Review

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**Background:** Despite extensive literature, the diagnostic role of D-dimer for deep venous thrombosis (DVT) or pulmonary embolism (PE) remains unclear, reflecting multiple D-dimer assays and concerns about differing sensitivities and variability.

**Purpose:** To systematically review trials that assessed sensitivity, specificity, likelihood ratios, and variability among D-dimer assays.

**Data Sources:** Studies in all languages were identified by searching PubMed from 1983 to January 2003 and EMBASE from 1988 to January 2003.

**Study Selection:** The researchers selected prospective studies that compared D-dimer with a reference standard. Studies of high methodologic quality were included in the primary analyses; sensitivity analysis included additional weaker studies.

**Data Extraction:** Two authors collected data on study-level factors: D-dimer assay used, cutoff value, and whether patients had suspected DVT or PE.

**Data Synthesis:** For DVT, the enzyme-linked immunosorbent assay (ELISA) and quantitative rapid ELISA dominate the rank order for these values: sensitivity, 0.96 (95% confidence limit [CL], 0.91 to 1.00), and negative likelihood ratio, 0.12 (CL, 0.04 to

0.33); and sensitivity, 0.96 (CL, 0.90 to 1.00), and negative likelihood ratio, 0.09 (CL, 0.02 to 0.41), respectively. For PE, the ELISA and quantitative rapid ELISA also dominate the rank order for these values: sensitivity, 0.95 (CL, 0.85 to 1.00), and negative likelihood ratio, 0.13 (CL, 0.03 to 0.58); and sensitivity, 0.95 (CL, 0.83 to 1.00), and negative likelihood ratio, 0.13 (CL, 0.02 to 0.84), respectively. The ELISA and quantitative rapid ELISA have negative likelihood ratios that yield a high certainty for excluding DVT or PE. The positive likelihood values, which are in the general range of 1.5 to 2.5, do not greatly increase the certainty of diagnosis. Sensitivity analyses do not affect these findings.

**Limitations:** Although many studies evaluated multiple D-dimer assays, findings are based largely on indirect comparisons of test performance characteristics across studies.

**Conclusion:** The ELISAs in general dominate the comparative ranking among the D-dimer assays for sensitivity and negative likelihood ratio. For excluding PE or DVT, a negative result on quantitative rapid ELISA is as diagnostically useful as a normal lung scan or negative duplex ultrasonography finding.

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Tests for D-dimer to exclude venous thromboembolic disease have been available since the 1980s (1). Hundreds of original studies, reviews, commentaries, and technical notes related to D-dimer as a diagnostic aid have been published. Even with this extensive literature, the role of D-dimer in the diagnosis of deep venous thrombosis (DVT) or pulmonary embolism (PE) remains unclear. This lack of clarity is due in part to the multiple D-dimer assays that are available (Appendix Table 1, available at [www.annals.org](http://www.annals.org)), availability of central laboratory and point-of-care testing, and concerns about differing sensitivities and variability of the assays (1).

In 1998, the American College of Chest Physicians Consensus Panel on Pulmonary Embolism called for more evaluation of the utility of D-dimer (2). In 1999, a Clinical Practice Guideline of the American Thoracic Society also called for additional outcome studies to further define the role of rapid bedside assays of D-dimer (3). As recently as 2000, investigators argued that the whole-blood agglutination test with D-dimer is not validated for clinical use for the exclusion of DVT (4). Although several useful reviews of the topic exist (1, 3, 5), none in recent years have comprehensively reviewed the world literature in an effort to summarize the accumulated published experience with D-dimer testing. Given continuing uncertainty about

D-dimer testing, we performed a systematic review of the literature to assess the sensitivity and specificity of the D-dimer assays and the variability of those measures among studies for diagnosing DVT and PE. The comparative findings among the differing D-dimer assays provide both the laboratory pathologist and clinician with a practical pathway for translating clinical research into practice.

## METHODS

We used several sources to guide our review processes, including recommendations by Lijmer and colleagues concerning avoidance of bias in studies of diagnostic tests (6), the Standards for Reporting Diagnostic Accuracy (STARD) statement (7, 8), and guidelines for meta-analyses of observational studies in epidemiology (9).

## Study Identification

We attempted to identify all published trials in all languages that used D-dimer to exclude PE or DVT on the basis of objective diagnostic tests. Studies were identified by searching PubMed from 1983 to January 2003 and EMBASE from 1988 to January 2003. All searches used the key words *D-dimer*, *PE*, and *DVT*. We augmented our searches by manually reviewing the reference lists of all

**Context**

Clinicians may not know which D-dimer assay is best for diagnosing deep venous thrombosis (DVT) or pulmonary embolism (PE).

**Contribution**

This meta-analysis summarizes data from 78 prospective studies that compared results of different D-dimer assays with findings of objective tests (for example, compression ultrasonography, venography, lung scanning) in patients with suspected DVT or PE. Enzyme-linked immunosorbent assays (ELISAs) had the best sensitivity (about 95%) and negative likelihood ratios (about 0.1) for excluding DVT and PE. None of the assays had positive likelihood values that greatly increased the certainty of diagnosis.

**Implications**

Negative ELISA results are strong evidence against DVT or PE.

—The Editors

original articles and all review articles. This was done by 2 of the authors working together. Abstracts were excluded.

**Study Eligibility**

At least 2 authors evaluated each study for inclusion. Any disagreements were resolved by discussion. Authors were not blinded to journal, author, or institution. Studies were included if they met all of the following criteria: 1) A specific statement was made about whether PE or DVT (not the inclusive term “thromboembolic disease”) was being diagnosed; 2) the diagnosis of PE or DVT was based on objective tests; 3) studies were performed prospectively; 4) participants were recruited consecutively; 5) the population studied included a broad spectrum of patients; 6) results of D-dimer and the diagnostic tests for PE and DVT were interpreted independently; 7) the participants studied were suspected of having PE or DVT, and all studies included patients with and without disease; 8) the decision to perform the reference diagnostic test was made independently of the D-dimer result; 9) test descriptions were sufficiently detailed to permit replication; 10) the cutoff value for a negative D-dimer test result was stated unless qualitative tests were used; and 11) sensitivity and specificity or the raw data for these calculations were presented.

We labeled studies that did not meet the third, fourth, or tenth inclusion criteria as tier 3 studies and included them in sensitivity analyses. We categorized studies that met all inclusion criteria into 2 tiers. Tier 1 included studies that compared an enzyme-linked immunosorbent assay (ELISA) and at least one other D-dimer assay. Tier 2 included the tier 1 studies and all other studies that met all inclusion criteria.

**Data Extraction**

Two authors collected data on the following study-level factors: 1) the D-dimer assay used in the study, 2) the cutoff value below which disease was considered to be absent, and 3) whether D-dimer was used to exclude PE or DVT. At least 2 authors confirmed the values for sensitivity and specificity.

**Statistical Analysis**

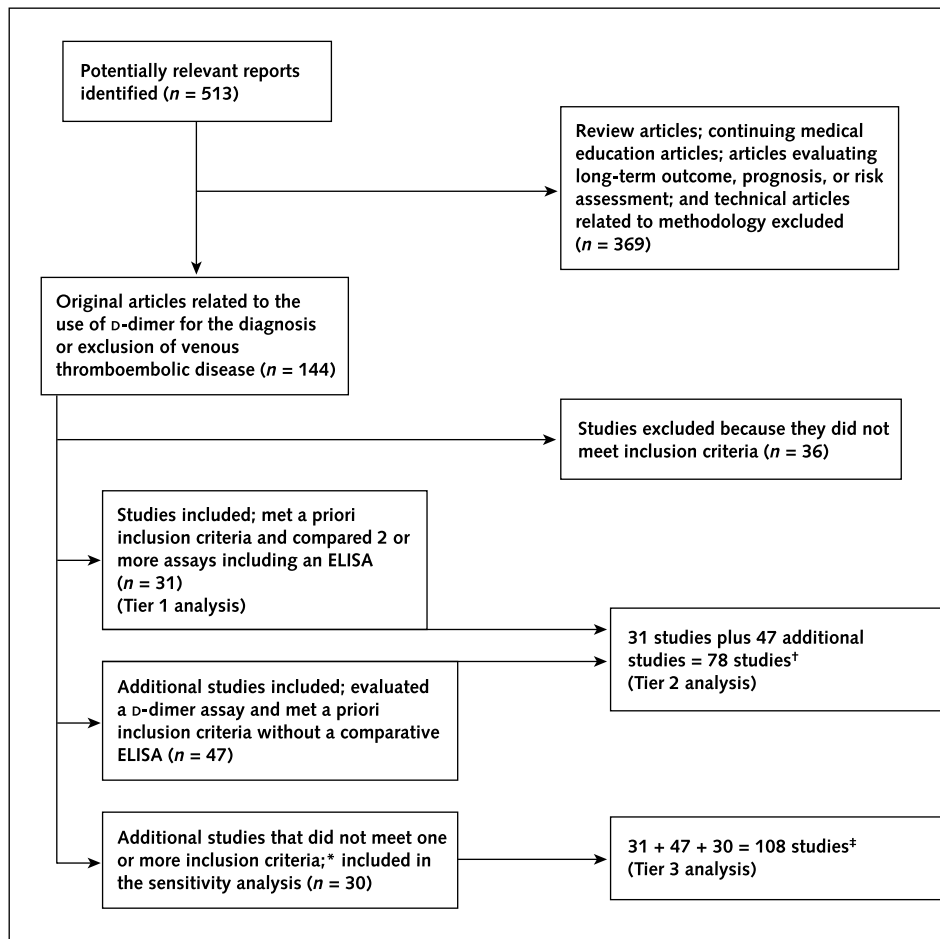
Sensitivities reflect the proportion of patients with disease who had a positive D-dimer result, while specificities reflect the proportion of patients without disease who had a negative D-dimer result, depending on cutoff level. Values for the likelihood ratio (the multiplicative factor for converting pretest to post-test disease probabilities) associated with positive test results were obtained by the following formula: sensitivity/(1 – corresponding specificity). This formula provided likelihood ratios arising from negative test results. Primary analysis was restricted to the 500-ng/mL cutoff because that was the most commonly used value.

On the basis of the varying array of assays examined in individual studies and our anticipation of important between-study heterogeneity, we applied a linear mixed-model approach (10) to jointly analyze the proportions of positive test results in the disease and nondisease samples (that is, true-positive and false-positive rates). Similar models have been applied to Bayesian meta-analysis of receiver-operating characteristic curves (11).

The main explanatory term in the model was a fixed effect reflecting distinct positive response rates for each combination of assay and population. To allow for variability in assay performance that might arise from idiosyncratic features of patient samples, such as spectrum of disease severity, and other aspects of study context, such as laboratory procedure, we incorporated 3 random-effects terms corresponding to assay nested within patient group (disease/nondisease) nested within study. Residual variances were assumed to follow the standard binomial form depending on underlying proportion and sample size. Applying restricted maximum likelihood, we obtained population average estimates for sensitivity and specificity, which were later combined to provide estimated likelihood ratios. Overall, the estimates did not differ substantially from conventional sample-size weighted averages, although the associated standard errors were increased, reflecting underlying between-study heterogeneity.

The joint statistical significance of overall differences was assessed by using likelihood-based Wald tests. Pairwise differences between estimates were assessed on the basis of the model-based standard errors without adjustment for multiple comparisons. Significant pairwise differences should be interpreted with caution when the Wald test is not significant. Confidence limits are derived from asymptotic standard errors; asymmetric intervals for likelihood ratios reflect the application of likelihood theory to loga-

Figure 1. Reports evaluated for inclusion in the review.



\* Studies that did not meet the third, fourth, or tenth inclusion criteria were labeled as tier 3 studies and were included in sensitivity analyses. † 49 studies of deep venous thrombosis (DVT), 31 studies of pulmonary embolism (PE); of these studies, 2 reported both DVT and PE as separate cohorts. ‡ 70 studies of DVT, 41 studies of PE; of these studies, 3 reported both DVT and PE. ELISA = enzyme-linked immunosorbent assay.

rhythmically transformed estimates. Values for the sensitivity and specificity for the different studies and test types were examined graphically by use of boxplots. The range between the upper and lower quartiles of the values for each assay provides a measure of between-study variability associated with the assay. Sensitivity analyses were conducted by adding the 30 studies that did not meet one or more of the 3 inclusion criteria previously mentioned (tier 3 analysis) and by analyzing sensitivity and specificity at the 250-ng/mL and 1000-ng/mL cutoffs.

All analyses were conducted by using S-PLUS, version 6.1.2, 2002 (Insightful Corp., Seattle, Washington) (12).

## DATA SYNTHESIS

Figure 1 summarizes our search. We initially identified 513 potentially relevant reports. Thirty-one studies (13–43) were included; they met a priori inclusion criteria and compared 2 or more assays, including an ELISA (tier 1 analysis). An additional 47 studies (44–90) were also included; they did not have a comparative ELISA but met

the a priori inclusion criteria evaluating a D-dimer assay. The 47 studies combined with the 31 studies provided a study sample of 78 studies (tier 2 analysis). Thirty additional studies (91–120) that did not meet one or more inclusion criteria were included in the sensitivity, or tier 3, analysis, which also included the 78 studies in the tier 2 analysis.

Appendix Tables 2 and 3 (available at [www.annals.org](http://www.annals.org)) list the D-dimer assays that were evaluated, patient characteristics, and the objective diagnostic reference test that was used for patients with clinically suspected DVT (49 studies) and clinically suspected PE (31 studies). All studies met the 11 criteria for inclusion listed in the Methods section. There was a total of 78 studies (2 studies [60, 71] gave data for patients with PE and DVT separately in the same article).

In the various studies, prevalence of DVT ranged from 20% to 78% (overall prevalence, 36%), and the prevalence of PE ranged from 8% to 62% (overall prevalence, 25%). Sixteen studies of DVT used compression ultrasonography

as a reference standard; 19 used venography, and 11 used both ultrasonography and venography. In addition, 2 studies used impedance plethysmography; 1 study used plethysmography, ultrasonography, and venography; and 1 study used impedance plethysmography, ultrasonography, and venography. Among the studies of PE, 2 used pulmonary angiography alone, and 14 used ventilation–perfusion lung scanning alone. In addition, 12 studies used both pulmonary angiography and ventilation–perfusion lung scanning; 1 used impedance plethysmography, pulmonary angiography, and ventilation–perfusion lung scanning; and 1 used perfusion lung scanning alone.

These studies included patients with clinically suspected DVT or PE who also had miscellaneous medical conditions, including connective tissue disease, coronary artery disease, systemic infections, history of DVT or PE, and pregnancy. The studies also included postpartum as well as surgical and trauma patients.

### Deep Venous Thrombosis

#### Sensitivity, Specificity, and Likelihood Ratios

*Tier 1 (20 Studies).* Clinical and statistical superiority for sensitivity was observed for the ELISA compared with the quantitative latex agglutination and semi-quantitative latex agglutination assays, for the quantitative rapid ELISA over the quantitative latex agglutination and semi-quantitative latex agglutination assays, and for the qualitative rapid ELISA over the semi-quantitative latex agglutination assay. Clinical and statistical superiority for specificity was observed for the quantitative latex agglutination, semi-quantitative latex agglutination, and whole-blood agglutination assays over the ELISA, quantitative ELISA, semi-quantitative ELISA, and qualitative ELISA (Table 1).

The ELISA and quantitative rapid ELISA have negative likelihood ratios of 0.12 and 0.09, which are values that give a high certainty for a negative diagnosis. The estimated positive likelihood ratios for all but one of the D-dimer assays range between 1.47 and 2.49, which are values that do not greatly increase the certainty of a positive diagnosis (Table 1).

*Tier 2 (49 Studies).* Clinical and statistical superiority for sensitivity was observed for the ELISA over the quantitative latex agglutination, semi-quantitative latex agglutination, and whole-blood agglutination assays; quantitative rapid ELISA over the quantitative latex agglutination, semi-quantitative latex agglutination, and whole-blood agglutination assays; and the qualitative rapid ELISA over the semi-quantitative latex agglutination assay. Clinical and statistical superiority for specificity was observed for the quantitative latex agglutination, semi-quantitative latex agglutination, and whole-blood agglutination assays over the ELISA, quantitative rapid ELISA, semi-quantitative rapid ELISA, and qualitative rapid ELISA. The ELISA and quantitative rapid ELISA had negative likelihood ratios of 0.12 and 0.10, and the estimated positive likelihood ra-

tios among the D-dimer assays ranged from 1.48 to 2.62 (Table 1).

#### Boxplots

The sensitivity and specificity for the different studies of DVT and test types were examined graphically by use of boxplots for the 500-ng/mL cutoff level (Figure 2). The range between the upper and lower quartiles of the values for each assay provides a measure of between-study variability associated with the assay. In patients with DVT, the least variability for sensitivity was seen with the ELISA, qualitative rapid ELISA, and quantitative rapid ELISA.

### Pulmonary Embolism

#### Sensitivity, Specificity, and Likelihood Ratios

*Tier 1 (11 Studies).* Clinical and statistical superiority for sensitivity was observed for the ELISA, quantitative rapid ELISA, and semi-quantitative rapid ELISA over the whole-blood agglutination assay. Clinical and statistical superiority for specificity was observed for the whole-blood agglutination assay over the ELISA, quantitative rapid ELISA, semi-quantitative rapid ELISA, quantitative latex agglutination assay, and semi-quantitative latex agglutination assay; and clinical and statistical superiority for specificity was observed for the qualitative rapid ELISA over the ELISA, the quantitative rapid ELISA, semi-quantitative rapid ELISA, quantitative latex agglutination assay, and semi-quantitative latex agglutination assay (Table 1).

The ELISA, quantitative rapid ELISA, and qualitative rapid ELISA have negative likelihood ratios of 0.13, 0.13, and 0.11, respectively. The estimated positive likelihood ratio values among the D-dimer assays range from 1.45 to 2.93 (Table 1).

*Tier 2 (31 Studies).* Clinical and statistical superiority for sensitivity was observed for the ELISA and the quantitative rapid ELISA over the semi-quantitative latex agglutination and whole-blood agglutination assays. Clinical and statistical superiority for specificity was observed for the whole-blood agglutination assay over the ELISA, quantitative rapid ELISA, semi-quantitative rapid ELISA, and quantitative latex agglutination assay; and clinical and statistical superiority for specificity was observed for the qualitative rapid ELISA over the quantitative rapid ELISA, semi-quantitative rapid ELISA, and quantitative latex agglutination assay (Table 1).

The ELISA and quantitative rapid ELISA had negative likelihood ratios of 0.08 and 0.07, and the positive likelihood ratios among the D-dimer assays ranged from 1.55 to 3.01 (Table 1).

#### Boxplots

The sensitivity and specificity for the different studies of PE and test types were examined graphically by use of boxplots for the 500-ng/mL cutoff level (Figure 3). In pa-

Table 1. Data Synthesis\*

| Test                          | Deep Venous Thrombosis    |                           |                                    |                                    | Pulmonary Embolism        |                           |                                    |                                    |
|-------------------------------|---------------------------|---------------------------|------------------------------------|------------------------------------|---------------------------|---------------------------|------------------------------------|------------------------------------|
|                               | Sensitivity (95% CL)      | Specificity (95% CL)      | Positive Likelihood Ratio (95% CL) | Negative Likelihood Ratio (95% CL) | Sensitivity (95% CL)      | Specificity (95% CL)      | Positive Likelihood Ratio (95% CL) | Negative Likelihood Ratio (95% CL) |
| <b>Tier 1 analysis†</b>       |                           |                           |                                    |                                    |                           |                           |                                    |                                    |
| ELISA                         | <b>0.96† (0.91–1.00)</b>  | 0.38 (0.28–0.48)          | 1.55 (1.32–1.81)                   | <b>0.12§ (0.04–0.33)</b>           | <b>0.95   (0.85–1.00)</b> | 0.44 (0.34–0.54)          | 1.68 (1.44–1.95)                   | <b>0.13§ (0.03–0.58)</b>           |
| Quantitative rapid ELISA      | <b>0.96† (0.90–1.00)</b>  | 0.44 (0.32–0.55)          | 1.70 (1.39–2.09)                   | <b>0.09¶ (0.02–0.41)</b>           | <b>0.95   (0.83–1.00)</b> | 0.39 (0.28–0.51)          | 1.56 (1.32–1.83)                   | <b>0.13§ (0.02–0.84)</b>           |
| Semi-quantitative rapid ELISA | 0.89 (0.81–0.98)          | 0.39 (0.28–0.50)          | 1.47 (1.21–1.78)                   | 0.27 (0.12–0.60)                   | <b>0.93   (0.79–1.00)</b> | 0.36 (0.23–0.50)          | 1.45 (1.20–1.76)                   | <b>0.20§ (0.04–0.96)</b>           |
| Qualitative rapid ELISA       | <b>0.93† (0.84–1.00)</b>  | 0.47 (0.30–0.63)          | 1.75 (1.28–2.39)                   | <b>0.15§ (0.04–0.56)</b>           | 0.93 (0.74–1.00)          | <b>0.68   (0.50–0.87)</b> | 2.92 (1.77–4.79)                   | <b>0.11§ (0.01–0.93)</b>           |
| Quantitative latex            | 0.85 (0.74–0.95)          | <b>0.66† (0.55–0.78)</b>  | 2.49 (1.77–3.51)                   | 0.24 (0.12–0.45)                   | 0.89 (0.81–0.98)          | 0.45 (0.36–0.53)          | 1.62 (1.43–1.84)                   | 0.24 (0.13–0.45)                   |
| Semi-quantitative latex       | 0.78 (0.67–0.89)          | <b>0.66† (0.56–0.76)</b>  | 2.30 (1.69–3.13)                   | 0.33 (0.21–0.54)                   | 0.92 (0.79–1.00)          | 0.45 (0.31–0.59)          | 1.68 (1.35–2.09)                   | <b>0.17§ (0.04–0.78)</b>           |
| Whole-blood                   | 0.87 (0.68–1.00)          | <b>0.83† (0.65–1.00)</b>  | 4.97 (1.84–13.42)                  | <b>0.16§ (0.04–0.65)</b>           | 0.78 (0.64–0.92)          | <b>0.74   (0.60–0.88)</b> | 2.93 (1.89–4.52)                   | 0.31 (0.18–0.51)                   |
| <b>Tier 2 analysis**</b>      |                           |                           |                                    |                                    |                           |                           |                                    |                                    |
| ELISA                         | <b>0.95†† (0.91–0.99)</b> | 0.40 (0.32–0.49)          | 1.60 (1.39–1.83)                   | <b>0.12§ (0.05–0.29)</b>           | <b>0.96†† (0.88–1.00)</b> | 0.51 (0.44–0.59)          | 1.97 (1.72–2.26)                   | <b>0.08¶ (0.01–0.43)</b>           |
| Quantitative rapid ELISA      | <b>0.96†† (0.90–1.00)</b> | 0.44 (0.34–0.54)          | 1.71 (1.43–2.05)                   | <b>0.10§ (0.03–0.36)</b>           | <b>0.97†† (0.87–1.00)</b> | 0.41 (0.30–0.51)          | 1.64 (1.40–1.91)                   | <b>0.07¶ (0.00–1.55)</b>           |
| Semi-quantitative rapid ELISA | 0.90 (0.83–0.98)          | 0.39 (0.29–0.50)          | 1.48 (1.24–1.78)                   | 0.25 (0.12–0.55)                   | 0.93 (0.79–1.00)          | 0.40 (0.27–0.54)          | 1.55 (1.25–1.93)                   | <b>0.18§ (0.04–0.94)</b>           |
| Qualitative rapid ELISA       | <b>0.93†† (0.87–0.99)</b> | 0.46 (0.35–0.57)          | 1.73 (1.40–2.13)                   | <b>0.15§ (0.07–0.37)</b>           | 0.91 (0.68–1.00)          | <b>0.70†† (0.47–0.93)</b> | 3.01 (1.52–5.96)                   | <b>0.13§ (0.01–1.28)</b>           |
| Quantitative latex            | 0.86 (0.78–0.94)          | <b>0.61†† (0.51–0.71)</b> | 2.20 (1.70–2.84)                   | 0.23 (0.13–0.41)                   | 0.89 (0.80–0.99)          | 0.47 (0.38–0.57)          | 1.69 (1.44–1.99)                   | 0.23 (0.11–0.48)                   |
| Semi-quantitative latex       | 0.79 (0.69–0.88)          | <b>0.66†† (0.57–0.75)</b> | 2.33 (1.75–3.11)                   | 0.32 (0.20–0.51)                   | 0.80 (0.65–0.94)          | 0.56 (0.42–0.70)          | 1.81 (1.35–2.42)                   | 0.36 (0.20–0.67)                   |
| Whole-blood                   | 0.86 (0.80–0.93)          | <b>0.67†† (0.61–0.73)</b> | 2.62 (2.17–3.16)                   | <b>0.20§ (0.13–0.32)</b>           | 0.83 (0.74–0.92)          | <b>0.64†† (0.55–0.73)</b> | 2.32 (1.87–2.88)                   | 0.27 (0.17–0.42)                   |

\* All values in boldface represent statistically superior values. CL = confidence limit; ELISA = enzyme-linked immunosorbent assay.  
 † Deep venous thrombosis: Overall differences in sensitivity and specificity:  $P = 0.020$  and  $P < 0.001$ , respectively (Wald test). Pulmonary embolism: Overall differences in sensitivity and specificity:  $P > 0.2$  and  $P < 0.001$ , respectively (Wald test).  
 ‡ Deep venous thrombosis: Tier 1—*Sensitivity*: The ELISA is superior to the quantitative latex agglutination and semi-quantitative latex agglutination assays ( $P = 0.039$  and  $P = 0.002$ , respectively), the quantitative rapid ELISA is superior to the quantitative latex agglutination and semi-quantitative latex agglutination assays ( $P = 0.039$  and  $P = 0.002$ , respectively), and the qualitative rapid ELISA is superior to the semi-quantitative latex agglutination assay ( $P = 0.026$ ). *Specificity*: The quantitative latex agglutination, semi-quantitative latex agglutination, and whole-blood agglutination assays are superior to the ELISA ( $P < 0.001$ ,  $P < 0.001$ , and  $P < 0.001$ , respectively), quantitative rapid ELISA ( $P = 0.004$ ,  $P = 0.002$ , and  $P < 0.001$ , respectively), semi-quantitative rapid ELISA ( $P = 0.0040$ ,  $P < 0.001$ , and  $P < 0.001$ , respectively), and qualitative rapid ELISA ( $P = 0.048$ ,  $P = 0.038$ , and  $P = 0.003$ , respectively).  
 § Negative likelihood ratios of 0.1 to 0.2 generate moderate shifts in pretest to post-test probability.  
 || Pulmonary embolism: Tier 1—*Sensitivity*: The ELISA, quantitative rapid ELISA, and semi-quantitative rapid ELISA are superior to the whole-blood agglutination assay ( $P = 0.020$ ,  $P = 0.016$ , and  $P = 0.047$ , respectively). *Specificity*: The qualitative rapid ELISA is superior to the ELISA, quantitative rapid ELISA, semi-quantitative rapid ELISA, quantitative latex agglutination assay, and semi-quantitative latex agglutination assay ( $P = 0.004$ ,  $P = 0.002$ ,  $P = 0.001$ ,  $P = 0.005$ , and  $P = 0.019$ , respectively); the whole-blood agglutination assay is superior to the ELISA, quantitative rapid ELISA, semi-quantitative rapid ELISA, quantitative latex agglutination assay, and semi-quantitative latex agglutination assay ( $P < 0.001$ ,  $P < 0.001$ ,  $P < 0.001$ , and  $P = 0.001$ , respectively).  
 ¶ Negative likelihood ratios less than 0.1 generate large and often conclusive changes from pretest to post-test probability.  
 \*\* Deep venous thrombosis: Overall differences in sensitivity and specificity:  $P = 0.005$  and  $P < 0.001$ , respectively (Wald test). Pulmonary embolism: Overall differences in sensitivity and specificity:  $P = 0.071$  and  $P < 0.001$ , respectively (Wald test).  
 †† Deep venous thrombosis: Tier 2—*Sensitivity*: The ELISA is superior to the quantitative latex, semi-quantitative latex, and whole-blood agglutination assays ( $P = 0.040$ ,  $P = 0.001$ , and  $P = 0.020$ , respectively); the quantitative rapid ELISA is superior to the quantitative latex agglutination, semi-quantitative latex agglutination, and whole-blood agglutination assays ( $P = 0.037$ ,  $P = 0.001$ , and  $P = 0.022$ , respectively); and the qualitative rapid ELISA is superior to the semi-quantitative latex agglutination assay ( $P = 0.010$ ). *Specificity*: The quantitative latex agglutination, semi-quantitative latex agglutination, and whole-blood agglutination assays are superior to the ELISA ( $P = 0.001$ ,  $P < 0.001$ , and  $P < 0.001$ , respectively); quantitative rapid ELISA ( $P = 0.012$ ,  $P = 0.001$ , and  $P < 0.001$ , respectively); semi-quantitative rapid ELISA ( $P = 0.002$ ,  $P = 0.002$ , and  $P < 0.001$ , respectively); and qualitative rapid ELISA ( $P = 0.047$ ,  $P = 0.004$ , and  $P = 0.001$ , respectively).  
 ‡‡ Pulmonary embolism: Tier 2—*Sensitivity*: The ELISA and quantitative rapid ELISA are superior to the semi-quantitative latex agglutination assay ( $P = 0.024$  and  $P = 0.031$ , respectively) and whole-blood agglutination assay ( $P = 0.016$  and  $P = 0.021$ , respectively). *Specificity*: The quantitative rapid ELISA is superior to the quantitative rapid ELISA, semi-quantitative rapid ELISA, and quantitative latex agglutination assay ( $P = 0.012$ ,  $P = 0.015$ ,  $P = 0.040$ , respectively); the whole-blood agglutination assay is superior to the ELISA, quantitative rapid ELISA, semi-quantitative rapid ELISA, and quantitative latex agglutination assay ( $P = 0.018$ ,  $P < 0.001$ ,  $P = 0.001$ , and  $P = 0.004$ , respectively).

tients with PE, the least variability for sensitivity was seen among the ELISAs.

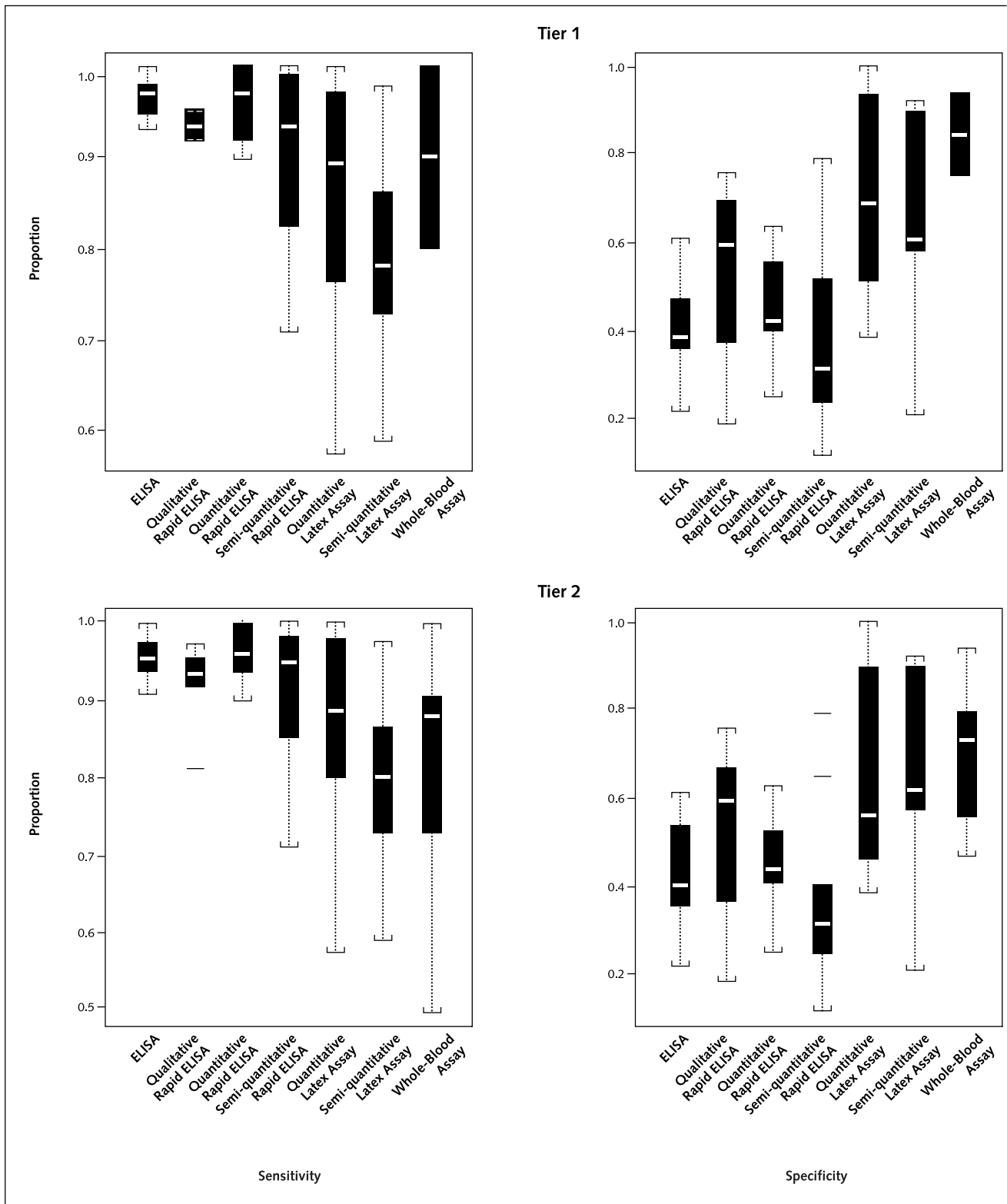
**Sensitivity Analysis**

**Deep Venous Thrombosis**

*Tier 3: 70 Studies; D-Dimer Cutoff Level, 500 ng/mL.* The 70 studies evaluated included 21 weaker methodologic studies: ELISA ( $n = 7$ ), qualitative rapid ELISA ( $n = 1$ ),

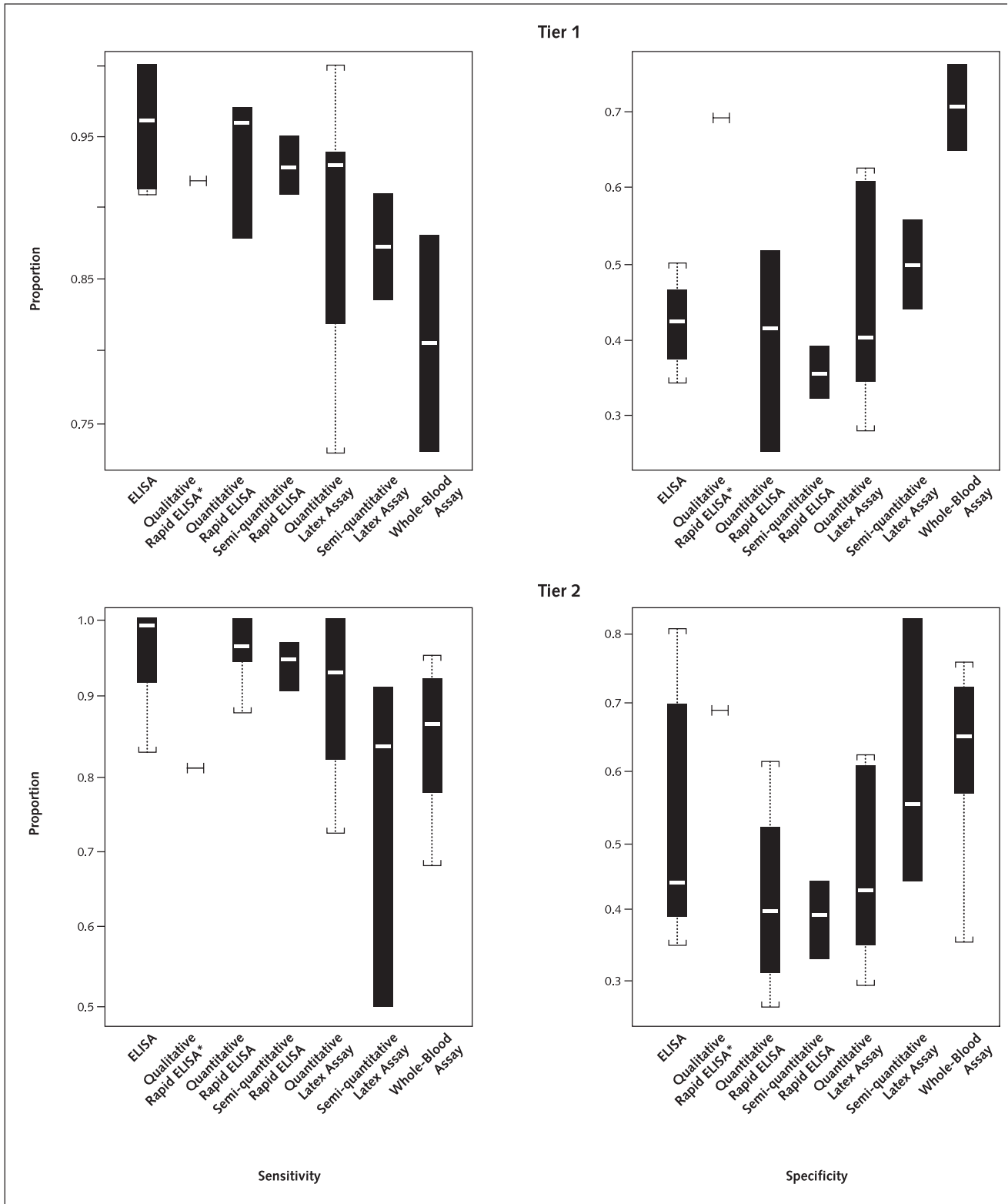
quantitative rapid ELISA ( $n = 1$ ), semi-quantitative ELISA ( $n = 4$ ), quantitative latex agglutination assay ( $n = 1$ ), semi-quantitative latex agglutination assay ( $n = 2$ ), and whole-blood agglutination assay ( $n = 6$ ). Table 2 shows the findings for sensitivity, specificity, and likelihood ratios. The values for these variables and their ranking are consistent with the primary analysis.

Figure 2. Boxplots of the findings for sensitivity and specificity among the D-dimer assays for patients with suspected deep venous thrombosis.



The top and bottom of each box represent the upper and lower quartiles of the values for the sample, and the white bars represent the medians. Bars extend above and below each box to the maximal and minimal value in the sample or, if there are extreme data points, to limits based on the interquartile range, defined as the distance from the lower quartile to the upper quartile. Outliers beyond these limits are plotted separately. ELISA = enzyme-linked immunosorbent assay; Quantitative latex assay = quantitative latex agglutination assay; semi-quantitative latex assay = semi-quantitative latex agglutination assay; whole-blood assay = whole-blood agglutination assay.

Figure 3. Boxplots of the findings for sensitivity and specificity among the D-dimer assays for patients with suspected pulmonary embolism.



The top and bottom of each box represent the upper and lower quartiles of the values for the sample, and the white bars represent the medians. Bars extend above and below each box to the maximal and minimal value in the sample or, if there are extreme data points, to limits based on the interquartile range, defined as the distance from the lower quartile to the upper quartile. Outliers beyond these limits are plotted separately. \* One study only. ELISA = enzyme-linked immunosorbent assay; Quantitative latex assay = quantitative latex agglutination assay; semi-quantitative latex assay = semi-quantitative latex agglutination assay; whole-blood assay = whole-blood agglutination assay.

Table 2. Sensitivity Analysis\*

|  | Deep Venous Thrombosis   |                      |                                    |                                    | Pulmonary Embolism   |                          |                                    |                                    |
|--|--------------------------|----------------------|------------------------------------|------------------------------------|----------------------|--------------------------|------------------------------------|------------------------------------|
|  | Sensitivity (95% CL)     | Specificity (95% CL) | Positive Likelihood Ratio (95% CL) | Negative Likelihood Ratio (95% CL) | Sensitivity (95% CL) | Specificity (95% CL)     | Positive Likelihood Ratio (95% CL) | Negative Likelihood Ratio (95% CL) |
| <b>Cutoff 500 ng/mL: Tier 3 analysis (all data)†</b>             |                          |                      |                                    |                                    |                      |                          |                                    |                                    |
| ELISA  | <b>0.94‡ (0.89–0.98)</b> | 0.43 (0.36–0.50)     | 1.65 (1.46–1.87)                   | <b>0.15§ (0.07–0.30)</b>           | 0.95 (0.88–1.00)     | 0.45 (0.38–0.53)         | 1.74 (1.55–1.96)                   | <b>0.11§ (0.03–0.39)</b>           |
| Quantitative rapid ELISA   | <b>0.97‡ (0.92–1.00)</b> | 0.42 (0.32–0.52)     | 1.67 (1.42–1.97)                   | <b>0.08   (0.02–0.38)</b>          | 0.98 (0.88–1.00)     | 0.40 (0.29–0.50)         | 1.62 (1.38–1.91)                   | <b>0.05   (0.00–4.15)</b>          |
| Semi-quantitative rapid ELISA                                    | <b>0.91‡ (0.85–0.98)</b> | 0.43 (0.34–0.52)     | 1.60 (1.37–1.88)                   | 0.21 (0.10–0.42)                   | 0.94 (0.81–1.00)     | 0.39 (0.26–0.52)         | 1.55 (1.24–1.92)                   | <b>0.15§ (0.02–1.13)</b>           |
| Qualitative rapid ELISA  | <b>0.93‡ (0.87–0.99)</b> | 0.53 (0.43–0.64)     | 1.99 (1.60–2.48)                   | <b>0.13§ (0.06–0.32)</b>           | 0.92 (0.71–1.00)     | 0.68 (0.46–0.90)         | 2.92 (1.52–5.61)                   | <b>0.11§ (0.01–1.45)</b>           |
| Quantitative latex   | 0.88 (0.80–0.95)         | 0.59 (0.49–0.69)     | 2.14 (1.68–2.73)                   | 0.21 (0.12–0.38)                   | 0.90 (0.81–1.00)     | <b>0.46¶ (0.37–0.56)</b> | 1.68 (1.42–1.98)                   | 0.21 (0.09–0.49)                   |
| Semi-quantitative latex  | 0.78 (0.69–0.87)         | 0.70 (0.62–0.78)     | 2.60 (1.95–3.46)                   | 0.31 (0.21–0.47)                   | 0.86 (0.74–0.97)     | <b>0.51¶ (0.39–0.62)</b> | 1.73 (1.39–2.16)                   | 0.29 (0.14–0.58)                   |
| Whole-blood  | 0.82 (0.76–0.89)         | 0.70 (0.64–0.76)     | 2.77 (2.27–3.38)                   | 0.25 (0.18–0.36)                   | 0.82 (0.74–0.91)     | <b>0.63¶ (0.54–0.71)</b> | 2.21 (1.81–2.70)                   | 0.28 (0.18–0.43)                   |
| <b>Cutoff 250 ng/mL: All studies meeting inclusion criteria</b>  |                          |                      |                                    |                                    |                      |                          |                                    |                                    |
| ELISA  | NA                       | NA                   | NA                                 | NA                                 | 0.96                 | 0.55                     | 2.13                               | 0.07                               |
| Quantitative rapid ELISA   | 0.98                     | 0.39                 | 1.58                               | 0.07                               | NA                   | NA                       | NA                                 | NA                                 |
| Semi-quantitative rapid ELISA                                    | 0.92                     | 0.56                 | 2.10                               | 0.14                               | NA                   | NA                       | NA                                 | NA                                 |
| Qualitative rapid ELISA  | NA                       | NA                   | NA                                 | NA                                 | NA                   | NA                       | NA                                 | NA                                 |
| Quantitative latex assay   | 0.91                     | 0.53                 | 1.96                               | 0.16                               | 0.94                 | 0.44                     | 1.69                               | 0.14                               |
| Semi-quantitative latex  | 0.91                     | 0.47                 | 1.73                               | 0.19                               | 0.90                 | 0.63                     | 2.39                               | 0.17                               |
| Whole-blood  | 0.88                     | 0.66                 | 2.57                               | 0.18                               | 0.84                 | 0.62                     | 2.22                               | 0.26                               |
| <b>Cutoff 1000 ng/mL: All studies meeting inclusion criteria</b> |                          |                      |                                    |                                    |                      |                          |                                    |                                    |
| ELISA  | 0.90                     | 0.72                 | 3.21                               | 0.14                               | NA                   | NA                       | NA                                 | NA                                 |
| Quantitative rapid ELISA   | 0.93                     | 0.58                 | 2.23                               | 0.13                               | NA                   | NA                       | NA                                 | NA                                 |
| Semi-quantitative rapid ELISA                                    | 0.94                     | 0.57                 | 2.19                               | 0.11                               | 0.74                 | 0.75                     | 2.96                               | 0.35                               |
| Qualitative rapid ELISA  | NA                       | NA                   | NA                                 | NA                                 | NA                   | NA                       | NA                                 | NA                                 |
| Quantitative latex   | 0.81                     | 0.70                 | 2.73                               | 0.27                               | NA                   | NA                       | NA                                 | NA                                 |
| Semi-quantitative latex  | 0.73                     | 0.78                 | 3.35                               | 0.34                               | NA                   | NA                       | NA                                 | NA                                 |
| Whole-blood  | 0.88                     | 0.66                 | 2.57                               | 0.18                               | 0.84                 | 0.62                     | 2.22                               | 0.26                               |

\* Values in boldface represent statistically superior values. CL = confidence limit; ELISA = enzyme-linked immunosorbent assay; NA = not applicable because of missing data.

† Deep venous thrombosis: Overall differences in sensitivity and specificity:  $P < 0.001$  and  $P < 0.001$ , respectively (Wald test). Pulmonary embolism: Overall differences in sensitivity and specificity:  $P = 0.063$  and  $P < 0.001$ , respectively (Wald test).

‡ The unadjusted pairwise comparisons of sensitivity showed the superiority of the quantitative rapid ELISA over the quantitative latex agglutination, semi-quantitative latex agglutination, and whole-blood agglutination assays ( $P = 0.018$ ,  $P < 0.001$ , and  $P < 0.001$ , respectively) and the superiority of the ELISA, qualitative rapid ELISA, and semi-quantitative rapid ELISA over the semi-quantitative latex agglutination assay ( $P = 0.001$ ,  $P = 0.003$ , and  $P = 0.010$ , respectively) and whole-blood agglutination assay ( $P = 0.001$ ,  $P = 0.017$ , and  $P = 0.046$ , respectively).

§ Negative likelihood ratios of 0.1 to 0.2 generate moderate shifts in pretest to post-test probability (121).

|| Negative likelihood ratios less than 0.1 generate large and often conclusive changes from pretest to post-test probability (121).

¶ The unadjusted pairwise comparisons of specificity showed the superiority of the quantitative latex agglutination, semi-quantitative latex agglutination, and whole-blood agglutination assays over the ELISA ( $P = 0.006$ ,  $P < 0.001$ , and  $P < 0.001$ , respectively); quantitative rapid ELISA ( $P = 0.008$ ,  $P < 0.001$ , and  $P < 0.001$ , respectively); and semi-quantitative rapid ELISA ( $P = 0.013$ ,  $P < 0.001$ , and  $P < 0.001$ , respectively) and the superiority of the whole-blood agglutination assay over the quantitative latex agglutination assay ( $P = 0.048$ ).

### Pulmonary Embolism

*Tier 3: 41 Studies; D-Dimer Cutoff Level, 500 ng/mL.*  
The 41 studies evaluated included 10 weaker methodologic studies: ELISA ( $n = 3$ ), semi-quantitative latex agglutination assay ( $n = 6$ ), and whole-blood agglutination assay ( $n = 2$ ). Table 2 shows the findings for sensitivity, specificity, and likelihood ratios. The values for these variables and their ranking are consistent with the primary analysis.

### D-Dimer Cutoff Values (250 ng/mL and 1000 ng/mL)

Most studies reported D-dimer assay findings using a 500-ng/mL cutoff (Appendix Tables 2 and 3, available at [www.annals.org](http://www.annals.org)). Limited data for sensitivity, specificity, and likelihood ratios (Table 2) were available for cutoff values of 250 ng/mL and 1000 ng/mL (for number of studies, see Appendix Tables 2 and 3) for some but not all of the D-dimer assays. For most assays, 5 or fewer studies

were available, which limited the ability to make valid inferences.

Multivariable models provide no indication that choice of reference standard (venography or ultrasonography), severity of patient spectrum, or DVT or PE prevalence is associated with sensitivity estimate. The differences among negative likelihood ratios are not statistically significant, largely because of the effect of the inverse ranking of the specificity values, which dilutes the comparative statistical analyses. The sensitivity analysis generally confirms the findings of the tier 1 and tier 2 analyses. Of note, the sensitivity analyses confirm that the negative likelihood ratios are lowest for the quantitative rapid ELISA (Table 2).

## DISCUSSION

The D-dimer assays differ in sensitivity, specificity, likelihood ratios, and variability among patients with suspected DVT or PE. In ranking the D-dimer assays according to the sensitivity values and likelihood of increasing certainty for ruling out DVT or PE, the ELISA and quantitative rapid ELISA D-dimer in general show dominant (most clinically useful) values. In particular, values for sensitivity for the ELISA or quantitative rapid ELISA are clinically and statistically significantly superior to those for the quantitative latex agglutination, semi-quantitative agglutination latex, and whole-blood agglutination assays in patients with suspected DVT. In patients with suspected PE, the values for sensitivity for the ELISA or quantitative rapid ELISA are significantly superior to those for the semi-quantitative latex agglutination and whole-blood agglutination assays. The variability of the sensitivity values is generally less for the ELISAs as a group (Figures 2 and 3), probably reflecting assay reproducibility given the large database in this systematic review. The sensitivity values for the quantitative latex agglutination assay differ among patients with suspected DVT or PE; in patients with suspected DVT, the ELISA and quantitative rapid ELISA are significantly superior.

Likelihood ratios greater than 10 or less than 0.1 result in large and often conclusive changes from pre- to post-test probability, whereas likelihood ratios of 1 to 2 and 0.5 to 1.0 alter probability in small and probably unimportant amounts (121). The ELISA and quantitative rapid ELISA have negative likelihood ratios (Table 1) that would usually generate conclusive changes from pre-test to post-test probability and provide high certainty for excluding DVT and PE. In patients with suspected PE, the low negative likelihood ratio values for the ELISA and quantitative rapid ELISA compare favorably with the negative likelihood ratio value of 0.10 for a normal to near-normal lung scan (121). Similarly, in patients with suspected DVT, the low negative likelihood ratio values for these ELISAs are similar to those found with a negative lower-extremity duplex ultrasonography finding (122, 123, 124) (negative likelihood ratio, 0.07).

The values for specificity and positive likelihood ratio differed among the assays, but all were within a range considered to be of little clinical value in altering probability of disease. Thus, the D-dimer finding is unidirectional; a negative result is used in the diagnostic pathway to exclude DVT or PE. The values for specificity vary inversely across D-dimer assays relative to those for sensitivity. Accordingly, the highly sensitive assays are less specific, whereas assays with better specificity are relatively insensitive. This paradox somewhat limits the clinical utility of the D-dimer assay. It is likely that some patients with DVT were analyzed as part of the study sample without DVT because Doppler ultrasonography did not detect DVT in the calf. This limitation, although affecting the absolute values for specificity, is unlikely to affect the ranking of specificity findings among the D-dimer assays.

This review included 70 studies that evaluated patients with suspected DVT and 41 studies that evaluated patients with suspected PE (3 studies evaluated both DVT and PE). The summary findings are based largely on indirect comparisons of test performance characteristics across studies. However, many studies evaluated multiple D-dimer assays, including an ELISA, which allowed within-study comparisons. We presented these studies in a separate analysis (tier 1) because observed differences between test performance found in head-to-head comparisons within studies may be influenced less often by such factors as disease severity, work-up variability, and variability in reference standards than are differences observed across studies conducted in different settings with different protocols.

Our observations and synthesis increase the database of knowledge for judging the accuracy of D-dimer for excluding PE or DVT. Several points seem clear. The D-dimer assays have a range of values that differ importantly for sensitivity, negative likelihood ratio, and variability. Patient samples in studies involve a broad spectrum of patients, including the elderly and outpatients. The clinical utility of the D-dimer assays is limited by the nonspecificity of a positive result because of such factors as inflammation, trauma, and surgery. The clinical utility differs among patient samples and may be higher in outpatients as a result of a lower frequency of disorders leading to a positive result. The rapid turnaround assays yield results in minutes rather than hours. Assays performed at the point of care probably increase convenience for the clinician and patient, but central laboratory assays with a quick turnaround time remain attractive because of the likelihood of less variability.

As recently as 1998, authors posited that clinical practice had not changed substantially with the use of D-dimer testing (125). Although various algorithms, including D-dimer testing, could result in significant cost savings as a result of fewer imaging studies (125–127), some clinicians remain reluctant to use these algorithms. This may reflect the historical concern that physicians have regarding the certainty of a negative D-dimer test result (125). Identifying the optimal D-dimer assay requires a balanced consid-

eration of sensitivity and specificity. Any decrease in sensitivity is associated with false-negative results—a highly undesirable diagnostic test outcome given the risk that such diagnostic errors pose to the patients involved. Because of this latter point, we anticipate that most institutions will opt for a D-dimer assay that consistently yields high sensitivity and low variability, such as the quantitative rapid ELISA.

The diagnostic pathway used in patients with suspected DVT or PE may well be a critical factor for determining which D-dimer assay is selected for excluding DVT or PE. Our findings suggest that the quantitative rapid ELISA, which is more convenient than the conventional ELISA, provides a marked downward shift in probability of venous thromboembolic disease and thus high certainty for a negative diagnosis. Indeed, the quantitative rapid ELISA has negative likelihood ratios similar to those of a normal perfusion lung scan or a negative Doppler ultrasonography finding, suggesting that this assay may stand alone (126, 128) for excluding DVT and PE, particularly if on-site imaging is not available. Non-ELISA assays should not be used as stand-alone tests (129) given their inferior sensitivity and negative likelihood ratio values.

The certainty of a negative diagnosis for DVT or PE is enhanced if the negative D-dimer result is incorporated into a multibranch diagnostic pathway (130). Indeed, combining a negative rapid ELISA result with a low or moderate clinical probability for DVT or PE rules out these diagnoses. The non-ELISA assays, when combined with a low clinical probability for DVT or PE, also provide a reasonable certainty of ruling out these disorders (131–133). A negative ELISA finding substantially reduces the need for both initial and serial ultrasonography in patients with suspected DVT; this is also true for negative non-ELISA findings when combined with a low clinical probability (133–136).

In summary, the ELISAs (in particular the quantitative rapid ELISA) dominate the comparative ranking among the D-dimer assays for sensitivity and negative likelihood ratio. The quantitative rapid ELISA has negative likelihood ratios similar to those for a normal to near-normal lung scan or negative duplex ultrasonography finding in patients with suspected PE or DVT, respectively. Accordingly, a negative quantitative rapid ELISA result is as diagnostically useful as a normal lung scan or negative duplex ultrasonography finding for excluding these life-threatening conditions.

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## COMMENTARY

We published the article by Stein and colleagues because we thought that physicians are confused by the myriad tests for deep venous thrombosis (DVT). By giving reliable figures for the accuracy of the 6 major classes of tests for D-dimer, Stein and colleagues' article should reduce uncertainty about how to interpret the results of a D-dimer test. The first step is to ask the clinical laboratory technician which method the laboratory uses to measure D-dimer levels. The second step is to use the likelihood ratios in Stein and colleagues' tables to interpret the results. In this commentary, I discuss how to use this information.

The authors express test performance as the likelihood ratio. This number is the ratio of the probability of a test result in a patient with disease (for example, DVT) divided by its probability in a patient without the disease. According to Bayes theorem, the post-test odds equal the pretest odds multiplied by the likelihood ratio. Therefore, the likelihood ratio indicates how much the odds of disease change after a test result, a very useful way to express test performance.

The pretest odds reflect the physician's opinion, before testing for D-dimer, that the patient has DVT. To estimate the probability, the physician can simply make a clinically informed guess, perhaps using the overall prevalence of DVT in patients with suspected DVT (it was 10% in one recent study [1]) as a starting point and using clinical judgment to adjust the probability for the patient's clinical findings. A clinical prediction rule is a more precise method to estimate the pretest probability. According to one clinical prediction rule for DVT (1), the prevalence of DVT was 0.06, 0.09, and 0.28 in patients whose scores on the clinical prediction rule were 0 or less, 1 or 2, or greater than 2, respectively.

**Table. Probability of Deep Venous Thrombosis after a Negative Result on Rapid Enzyme-Linked Immunosorbent Assay for D-Dimer\***

| Probability  | Probability of DVT | Odds of DVT | Negative Likelihood Ratio for Rapid ELISA | Post-Test Probability of DVT after Negative Result on Rapid ELISA for D-Dimer |
|--------------|--------------------|-------------|---|---|
| Low          | 0.06               | 0.06        | 0.09                                      | 0.006   |
| Intermediate | 0.09               | 0.10        | 0.09                                      | 0.009   |
| High         | 0.28               | 0.39        | 0.09                                      | 0.03  |
| Very high    | 0.8                | 4.00        | 0.09                                      | 0.28  |

\*DVT = deep venous thrombosis; ELISA = enzyme-linked immunosorbent assay.

Stein and colleagues point out that the D-dimer tests are unidirectional: A negative result can be useful, but a positive result has little effect on the probability of DVT. I want to concentrate on the interpretation of a negative D-dimer result in patients with low and high pretest odds of disease. The Table shows the pretest odds for low, intermediate, and high probability of DVT, as obtained in a prospective study (1). The Table also shows the negative likelihood ratio for the rapid enzyme-linked immunosorbent assay (taken from Table 1 in Stein and colleagues' article) and the post-test probability of disease after a negative D-dimer result (obtained by multiplying the pretest odds by the likelihood ratio [0.09] and converting the post-test odds to a probability).

What does this table tell us? It confirms Stein and colleagues' assertion that a negative D-dimer result in a patient with a low or intermediate probability of DVT provides high certainty for excluding DVT (post-test probability < 0.01). The post-test probability is 0.03 after a negative D-dimer result in a patient with a high probability of DVT (a score > 2 in the clinical prediction rule). Is this probability low enough for the physician to forgo anticoagulation?

Finally, the Table warns us to be careful about interpreting a negative D-dimer result in a patient with many findings of DVT (which might correspond to a pretest probability of 0.80). The post-test probability after a negative D-dimer result is 0.26, which is probably too high to forgo anticoagulation in most patients. Most diagnostic algorithms would call for further testing in such a patient.

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Editor

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