The accuracy of the enzyme-linked immunosorbent assay D-dimer test in the diagnosis of pulmonary embolism: a meta-analysis

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Authors' objectives
The primary objective was to determine the accuracy of the enzyme-linked immunosorbent assay (ELISA) D-dimer test in the diagnosis of pulmonary embolism (PE) in adults in the hospital emergency department (ED). A secondary objective was to determine whether the test performance is affected by covariates such as age, co-morbidity and duration of symptoms.

Searching
MEDLINE (from January 1980 to January 1 2001) and EMBASE were searched; the search terms were reported. The reference lists of articles identified by the search, and those of previous systematic reviews, were also checked. The authors also contacted experts in the field of PE and manufacturers of ELISA D-dimer tests.

Study selection
Study designs of evaluations included in the review
Prospective diagnostic cohort studies were eligible for inclusion in the review.

Specific interventions included in the review
Clinical studies assessing the accuracy of the ELISA D-dimer test were eligible for inclusion. Studies of both standard and rapid ELISA tests were included. The diagnostic test thresholds in the included studies ranged from 250 to 500 ng/mL.

Reference standard test against which the new test was compared
A positive angiogram or autopsy result was taken as the primary reference standard for the presence of PE. Acceptable surrogate reference standards were a high probability ventilation-perfusion (V/Q) scan, a computed tomography scan positive for PE, or a positive lower extremity imaging result (e.g. ultrasonography, impedance plethysmography, or venogram). The primary reference standard for ruling out PE was a negative angiogram or autopsy result. A normal or very low probability V/Q scan, or clinical follow-up showing the absence of a thromboembolic event over at least 3 months, were acceptable surrogate reference standards for a negative diagnosis.

Participants included in the review
The participants were patients presenting with signs and symptoms suggestive of PE. The study populations were required to consist predominantly of out-patients (at least 80%), or to allow the sensitivity and specificity to be calculated for out-patients separately from in-patients. Only one of the included studies contained in-patients (20%). Where reported, the mean age of the participants ranged from 54 to 81 years and the percentage of men from 34 to 50%.

Outcomes assessed in the review
No inclusion criteria relating to the outcome measures were specified. The outcome measures used in the review were sensitivity and specificity.

How were decisions on the relevance of primary studies made?
Two reviewers decided independently on the relevance of the primary studies. Any disagreements were resolved by consensus.

Assessment of study quality
Studies were assessed for vulnerability to differential reference standard bias, spectrum bias and partial verification bias. In terms of reference standard, studies that used the same reference standard regardless of the result of the ELISA

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D-dimer test were graded A; studies using different reference standards depending on the result of the ELISA D-dimer test were graded B; and studies that were indeterminate, or did not meet the protocol definition of a reference standard, were graded C. In terms of patient spectrum, studies that included a consecutive or random sample of a typical outpatient population were graded A; those that selected only a subgroup of patients with suspected PE were graded B; and studies that were indeterminate, or did not meet the protocol definition of an appropriate patient spectrum, were graded C.

Only studies graded A or B on both criteria were included in the analysis. Any study that did not apply a reference standard to all patients was analysed on a worst-case basis (patients lost to follow-up were assumed to have the worst outcome). Studies were also graded by whether or not the radiologist performing the reference test was blind to the result of the ELISA D-dimer test.

Two reviewers independently assessed validity. Any disagreements were resolved by consensus.

Data extraction
Two reviewers extracted the data independently. Any discrepancies were resolved by consensus. Data were extracted on prevalence of PE, percentage of out-patients, mean age, percentage male, test threshold, and sensitivity and specificity. The authors calculated the sensitivity and specificity, along with their associated 95% confidence intervals (CIs), for each study.

Methods of synthesis
How were the studies combined?
An unweighted summary receiver operating characteristic (SROC) curve was constructed using single test thresholds and dichotomous results. If a study reported results for more than one test threshold, a value of 500 ng/mL was used for the analysis. Pooled sensitivity and specificity values were calculated using a random-effects model. Publication bias, defined as differences in effect size between smaller and larger studies, was investigated using a Galbraith plot.

How were differences between studies investigated?
A regression equation derived from the SROC analysis was used to calculate a measure of heterogeneity among studies. The effect of study quality (rating for reference standard, patient spectrum, completeness of reference standard allocation, and blinded or unblinded assessment of the index test) on the SROC curve was assessed in a sensitivity analysis. Pre-specified subgroup analyses examined studies that used traditional ELISA, traditional ELISA with a 500 ng/mL threshold, and rapid ELISA. Patient characteristics (mean age 70 years or more, absence of co-morbidity and duration of symptoms 4 days or more) were also examined in pre-specified subgroup analyses.

Results of the review
Eleven studies (n=2,126) were included in the review. Eight studies included a consecutive or random sample of patients with suspected PE, while three included only a selected subgroup of patients.

Only 2 studies were rated A for both reference standard and patient spectrum; 3 studies were graded A for reference standard only and 6 studies for patient spectrum only. In seven of the included studies, the radiologist performing the reference test was blind to the D-dimer test results.

The pooled summary estimate across all 11 studies gave a sensitivity of 0.95 (95% CI: 0.90, 0.98) and a specificity of 0.45 (95% CI: 0.38, 0.52). This pooled estimate showed statistically significant heterogeneity (beta 0.43, 95% CI: 0.004, 0.87). For studies rated A for reference standard, the pooled sensitivity estimate was 0.90 (95% CI: 0.83, 0.94) and the specificity 0.40 (95% CI: 0.26, 0.55); heterogeneity was not significant (beta 0.18, 95% CI: -0.52, 0.88). For studies rated A for patient spectrum, the pooled sensitivity was 0.97 (95% CI: 0.92, 0.99) and the specificity 0.48 (95% CI: 0.41, 0.56); statistically significant heterogeneity was present (beta 0.46, 95% CI: 0.10, 0.81). Studies with adequate blinding gave a pooled sensitivity of 0.92 (95% CI: 0.85, 0.96) and a specificity of 0.39 (95% CI: 0.30, 0.49) without statistically significant heterogeneity (beta 0.39, 95% CI: -0.16, 0.94).

The 9 studies that used a traditional rather than a rapid ELISA method gave a pooled sensitivity estimate of 0.94 (95%...
CI: 0.88, 0.97) and a sensitivity of 0.45 (95% CI: 0.36, 0.55). The value of beta for these studies was 0.32 (95% CI: -0.18, 0.82). The 2 studies that used a rapid ELISA method gave a pooled sensitivity estimate of 1.00 with a specificity of 0.44 (95% CI: 0.40, 0.48). The one study in which all patients were aged 70 years or older gave a sensitivity of 1.00, but specificity was only 0.14 (95% CI: 0.07, 0.21). Three studies involving patients without co-morbidity gave a lower pooled sensitivity (0.89, 95% CI: 0.75, 0.96) and higher specificity (0.55, 95% CI: 0.46, 0.64), compared with the overall analysis. Based on one study, duration of symptoms of 4 days or more was associated with a relatively low sensitivity (0.73, 95% CI: 0.59, 0.86) and specificity (0.33, 95% CI: 0.19, 0.48) for the ELISA D-dimer test.

The regression analysis showed no statistical evidence of publication bias.

**Authors’ conclusions**
The ELISA D-dimer test has high sensitivity, but only moderate specificity, for the detection of PE. The test might be useful for ruling out PE, especially when the pre-test probability of PE is low.

**CRD commentary**
The review addressed a clear question and the inclusion and exclusion criteria were clearly defined. The search was adequate, although the fact that the required index terms included 'sensitivity and specificity' meant that some relevant studies could have been missed. The authors attempted to assess publication bias, although the method used was not specifically designed for this purpose. Two reviewers independently selected the studies, assessed validity and extracted the data, thus minimising the risk of bias during the review process. The validity assessment addressed important aspects of bias (spectrum bias, differential verification bias and blinding) that were relevant to the test under review.

Adequate information on the included studies was provided, although the results were presented only in terms of sensitivity and specificity; further details of the reference standards would have been desirable. The pooled sensitivity and specificity estimates were affected by significant heterogeneity, probably reflecting clinical heterogeneity (e.g. prevalence of PE, participant age and diagnostic threshold) in the included studies. Hence, these estimates should be treated with caution. The authors highlighted that, with the exception of two, all of the included studies were susceptible to spectrum bias (which limits their generalisability) or differential verification bias (which may lead to inflated estimates of sensitivity and specificity). The fact that subgroup analyses of the better quality studies gave similar results to the main analysis tends to support the reliability of the authors' conclusions.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.

Research: The authors stated that the cost-effectiveness of D-dimer testing in the clinical setting has not been adequately evaluated.

**Bibliographic details**

**PubMedID**
12140491

**Other publications of related interest**
These additional published commentaries may also be of interest. Bounameaux H. Review: ELISA D-dimer is sensitive but not specific in diagnosing pulmonary embolism in an ambulatory clinical setting. Evid Based Med 2003;8:29.
Indexing Status
Subject indexing assigned by NLM

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.