Turbidimetric D-dimer test in the diagnosis of pulmonary embolism: a metaanalysis

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CRD summary
This review found that quantitative, latex turbidimetric D-dimer tests are sensitive but non-specific for the detection of pulmonary embolism in the emergency department setting. The review was well conducted and the conclusions are supported by the data presented.

Authors' objectives
To evaluate the test characteristics of quantitative, latex turbidimetric D-dimer tests in the diagnosis of pulmonary embolism (PE) in adults in the out-patient acute-care setting.

Searching
MEDLINE (1982 to 2002), EMBASE (1995 to 2002) and ISI Reference Update (1995 to 2002) were searched; some details of the search strategy were reported. The reference lists of included studies and previous systematic reviews were screened for additional relevant publications. Experts in the area of PE diagnosis and companies that manufacture or market the tests were contacted for unpublished studies.

Study selection
Study designs of evaluations included in the review
The authors did not report any inclusion criteria in relation to the study design.

Specific interventions included in the review
Studies that evaluated a turbidimetric latex D-dimer test for the diagnosis of PE were eligible for inclusion. The specific tests (with threshold for positive result in brackets) assessed in the included studies were Liatest (500 microg/L), MDA (500 microg/L), IL-test (200 microg/L), Plus (190 microg/L), Minutex (500 microg/L) and Tinaq (500 microg/L).

Reference standard test against which the new test was compared
The authors stated that, although a positive angiogram or autopsy is considered the reference standard for the diagnosis of PE, any of the following were considered acceptable reference standards: high probability ventilation-perfusion scan; computed tomography scan positive for PE; or positive lower extremity imaging study (ultrasound, impedance plethysmography, venogram, or computed tomography venogram). A negative angiogram is the reference standard for ruling out PE, but the following were considered acceptable reference standards: normal or very low probability ventilation-perfusion scan; or clinical follow-up documenting the absence of a thromboembolic event over at least 3 months. Studies that did not include one of the reference standards described above, or in which the reference standard was unclear, were excluded from the analysis.

Participants included in the review
The studies had to involve predominantly out-patient populations (at least 80%) presenting with symptoms and signs suspicious for PE to be included. Studies that reported on less than 80% out-patients were eligible for inclusion if data were available to calculated the sensitivity and specificity for the out-patient component of the study population. In the included studies, the mean age of the patients ranged from 44 to 66 years, the proportion of out-patients ranged from 80 to 100%, and the prevalence of PE ranged from 9 to 62%.

Outcomes assessed in the review
The authors did not report any inclusion criteria in relation to the outcomes. The primary outcomes reported in the review were the sensitivity and specificity.

How were decisions on the relevance of primary studies made?
Two reviewers independently reviewed abstracts identified through the searches. Any disagreements were resolved through discussion.

**Assessment of study quality**
The quality assessment focused on the potential for differential verification bias and patient spectrum. Studies were graded as A (excellent), B (susceptible to some bias) or C (indeterminate or poor) for each of the following items.

Reference standard: studies using same reference standard regardless of turbidimetric D-dimer results (A); different reference standard depending on the results of the turbidimetric D-dimer result (B); indeterminate or not meeting study protocol definition of an appropriate reference standard (C).

Patient spectrum: consecutive or random sampling of typical out-patient population presenting with symptoms and signs suspicious for PE (A); studies that selected only a small subgroup of individuals with suspected PE (B); studies that were indeterminate or did not meet the study protocol definition of an appropriate patient spectrum (C).

Information on whether the radiologist performing the reference standard was blind to the turbidimetric D-dimer result was also extracted, although this did not appear to contribute to the quality grading.

Grade C studies were excluded from the analysis.

The authors did not state how the papers were assessed for quality, or how many reviewers performed the quality assessment.

**Data extraction**
Data were extracted from each study meeting the inclusion criteria using a data collection form. Authors were contacted to confirm the data extraction or estimation of correctness and completeness, and to obtain missing data. Two reviewers independently confirmed numeric calculations and graphical extrapolations.

**Methods of synthesis**
How were the studies combined?
The analysis was based on the summary receiver operating characteristic (SROC) curve. The sensitivity and specificity were used to plot an unweighted SROC curve. A correction factor of 0.5 was added to each cell of the 2x2 table to avoid zero values in cells. The SROC curve analysis was based on a regression analysis of D (log diagnostic odds ratio) against S (logit true-positive rate plus logit false-positive rate). A random-effects model was used to calculate the average sensitivity and specificity across the studies.

How were differences between studies investigated?
When the beta coefficient in the SROC regression analysis was near zero and not statistically significant, heterogeneity was considered to be absent. Heterogeneity was also assessed by an examination of the SROC plot and of forest plots of sensitivity and specificity.

**Results of the review**
Nine studies (n=1,901) were included in the review.

All studies were rated as grade A for reference standard, while seven were rated as grade A for patient spectrum.

The sensitivity ranged from 88 to 100% and the specificity from 42 to 74%. The pooled sensitivity was 93% (95% confidence interval, CI: 89, 96) and the pooled specificity was 51% (95% CI: 42, 59). The SROC plot suggested that the studies were relatively homogeneous, with the exception of one study that showed a higher specificity than the others.
Authors' conclusions
The turbidimetric D-dimer test is sensitive but non-specific for the detection of PE in the emergency department setting.

CRD commentary
This review addressed a very clearly defined objective. However, the inclusion criteria lacked clarity. In particular, there appears to have been some confusion regarding the inclusion criteria and the quality assessment. Studies that failed to meet predefined quality criteria were excluded from the analysis, whereas studies that met some of the inclusion criteria would inevitably have met the quality criteria. A reasonable literature search was carried out which included extensive attempts to locate unpublished studies. Adequate details of the studies were tabulated, but some discussion of possible causes of the different prevalences of PE would have been helpful. The methods used to synthesise the results were appropriate, and the graphical presentations help the reader interpret the results of the review. One study was an obvious outlier and this was mentioned in the results; further discussion of reasons for this study's higher specificity in comparison with the other studies would have been helpful. The authors' conclusions are supported by the results presented.

Implications of the review for practice and research
Practice: The authors stated that, on the basis of diagnostic accuracy, their data suggest that the test characteristics of the immunoturbidimetric D-dimer assay are similar to those of the D-dimer, enzyme-linked immunosorbent assay.

Research: The authors did not state any implications for further research.

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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.