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THE ACCURACY OF THE ELISA D-DIMER TEST IN THE DIAGNOSIS OF PULMONARY EMBOLISM: A META-ANALYSIS

By

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ABSTRACT

THE ACCURACY OF THE ELISA D-DIMER TEST IN THE DIAGNOSIS OF PULMONARY EMBOLISM: A META-ANALYSIS

By

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The objective was to determine the sensitivity and specificity of the enzyme-linked immunosorbent assay (ELISA) D-dimer test in the diagnosis of pulmonary embolism (PE) in the adult emergency department population. A search of MEDLINE, EMBASE and bibliographies of previous systematic reviews was conducted with no language restriction. Two reviewers extracted data independently and assessed study quality based on the patient spectrum and reference standard. The analysis was based on a summary receiver operating characteristic (SROC) curve and pooled estimates for sensitivity and specificity using a random-effects model. The search yielded 52 publications. Eleven studies met the inclusion criteria and provided a sample of 2,126 subjects. The SROC curve analysis found significant heterogeneity among the 11 studies. Subgroup analysis of the 9 studies that used traditional ELISA D-dimer methods yielded the most valid pooled estimates with a sensitivity of 0.94 (95% CI: 0.88, 0.97), and a specificity of 0.45 (95% CI: 0.36, 0.55). Advanced age resulted in a lower specificity. A prolonged duration of symptoms decreased both sensitivity and specificity. The ELISA D-dimer test is highly sensitive but non-specific for the detection of PE in the acute care setting. This test may help clinicians safely rule-out PE, especially in the face of low and low-to-moderate pretest probabilities.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

The goal of any diagnostic test is to allow the clinician to revise the patient's probability of having the disease to a level above the treatment threshold or below the threshold that requires any further testing.[1] Where the physician sets the treatment threshold depends on the potential consequence of the disease (e.g., death vs. disability vs. full recovery), expense of the diagnostic test, treatment or both, and the associated risk(s) of the therapy. Similarly, the diagnostic threshold depends on the morbidity and mortality associated with a missed diagnosis. For conditions such as PE, the diagnostic threshold is low since the "cost" of missing the correct diagnosis is high. For example, the three-month mortality rate for untreated PE has been reported to be as high as 17.5%.[2] In most tests in the emergency department (ED), the clinician must decide at what diagnostic threshold the patient can be discharged home with appropriate follow-up, no further testing and no treatment. Unfortunately, given the lack of continuity of care and unreliable follow-up, the ED evaluation of patients who present with symptoms and signs of suspected serious diseases, such as PE, is expensive and complex.

In considering the use of any diagnostic test, it is important to establish a pretest probability of the disease being investigated.[1] This is equivalent to the prevalence of the disease among the ED population with similar presenting symptoms. The reported prevalence of PE in the typical ambulatory patient population presenting to the ED with signs and symptoms suspicious for PE is 15 to 30 %.[3-5] This patient population represents a select subset of patients presenting to the ED with dyspnea or chest pain that, after initial evaluation, remains unexplained. Clinicians will often attempt to stratify these patients into low, intermediate and high risk groups.[6] Stratification is based on a

combination of risk factors, presenting symptoms, physical examination findings, and initial screening tests. In an attempt to aid the physician in establishing a pretest probability, clinical models have been developed for deep venous thrombosis (DVT) and PE.[7,8] However, these risk stratification schemes are complex, difficult to remember, and often not entirely driven by "evidence". Not surprisingly, ED physicians find this a confusing clinical area for diagnostic testing.

Classic epidemiological risk factors associated with PE include a history of thromboembolic disease, immobility, recent surgery or trauma, malignancy, age, hypercoagulable state, oral contraceptive use, pregnancy, smoking, and history of significant pulmonary or cardiac disease.[2,9] However, a prospective cross-sectional study was unable to validate an association between PE and any of these classic risk factors in an ED patient population suspected of PE.[5] Selection bias may account for these findings since the attending physician's global clinical impression and suspicion for the diagnosis of PE was the main criterion used for entry into the study.[5] Thus physicians may have used these classic risk factors as part of their decision to enter patients into the study cohort. This observational study demonstrated that once a patient is placed in the subset of patients suspected of having PE, risk factors do not help differentiate between those with PE and those without PE. The only symptom found to have a statistically significant association with PE was unexplained dyspnea (RR 1.3), and this association was weak.[5] The clinical significance of this finding is uncertain since the majority of patients without PE also had this symptom. Tachycardia and tachypnea are described as the most common physical exam signs.[6] Unfortunately, the initial vital signs failed to discriminate between those with PE and those without PE in an at risk ED population.[5] Signs and symptoms of

PE are nonspecific and may mimic other disease conditions such as pneumonia or congestive heart failure, making the determination of the pretest probability for PE a clinical challenge.[10]

After completing the history and physical exam, the physician will often obtain a few initial screening tests. Electrocardiography (EKG) may show non-specific ST-T wave changes and left- or right-axis deviation with PE.[10] The classic findings of S1, Q3, T3 or right-bundle branch block are not commonly found, and require a rather large PE to be present before they are identified.[5, 6, 10] Chest x-ray is usually obtained to rule-out other disease processes that could explain the patient's symptoms. The chest x-ray is usually normal; however, small pleural effusions, focal atelectasis or ill-defined pleural-based infiltrates may be observed in patients with PE.[10] Arterial blood gas analysis may reveal an abnormal pO_2, pCO_2, and/or A-a gradient in patients with PE.[10] Unfortunately, these tests have low specificity and are not sensitive enough to rule-out pulmonary embolism.[11]

Where does this leave the ED physician and the patient suspected of having an acute PE? Stratification based on classic risk factors, physical exam findings and initial screening tests, is commonly suggested yet has not been validated in the ED setting.[3, 5] The seasoned emergency medicine physician may be able to use clinical experience and gestalt to accurately raise or lower the pretest probability from the 15 to 30 % pretest range. However, it is unlikely that this will place the patient above the treatment threshold committing them to anti-coagulation or below the diagnostic threshold allowing ED discharge. Further diagnostic testing is usually required.

The traditional approach to PE has been to utilize ventilation/perfusion (V/Q) scan as the initial diagnostic modality of choice. The PIOPED study was the largest prospective investigation evaluating the diagnostic accuracy of V/Q scans using angiogram as the gold standard.[4] This study enrolled over 1,000 patients and generated the test characteristics for V/Q scan that are still used today. A V/Q scan with high probability is considered diagnostic for PE with a LR of 18.[12] A normal/near-normal V/Q scan is considered diagnostic for ruling out PE with a LR of 0.1 and a false negative rate of only 2%.[12] Intermediate and low probability V/Q scan results are considered non-diagnostic and occur in 50 to 70% of patients, leaving the majority of patients below the treatment threshold and above the diagnostic threshold.[13] Since the PIOPED study, many research protocols investigating the accuracy of diagnostic tests for PE use angiogram as the reference standard only in the non-diagnostic categories of low or intermediate probability V/Q scan.

Helical computerized tomograhpy (CT) has recently been advocated as an alternative to V/Q scan. Two recent systematic reviews have determined that helical CT is not as sensitive as V/Q scan, although helical CT has a much lower rate of non-diagnostic results.[14, 15] Helical CT has been demonstrated to have excellent specificity and has the advantage of being able to visualize other structures in the thorax which may provide an alternative diagnosis.[11, 15] The greatest limitation of helical CT is the inability to visualize sub-segmental emboli and a lack of consistency in reporting.[14] The clinical significance of these small emboli is still uncertain.

Some diagnostic algorithms recommend using bilateral lower extremity venous dopplers and/or compression ultrasound if the helical CT or V/Q scan is equivocal.[10, 12]

Ultrasound has been shown to be positive for DVT in 20 to 50% of patients with PE and would warrant anticoagulation without further diagnostic studies.[13] However, this test is very insensitive for the diagnosis of PE since the original clot may have embolized, be confined to the calf, or located in the pelvic vessels without lower extremity thrombosis.[2] A recent study showed that a single negative ultrasound had a LR of only 0.5, leaving most patients above the diagnostic threshold.[16] An alternative strategy using serial lower extremity ultrasounds appears to be effective but is not practical in most ED settings.[8]

Fortunately, several new diagnostic tests have been introduced to assist in the ED work-up of suspected cases of PE. D-dimer has been advocated as a diagnostic tool that may obviate the need for additional diagnostic tests such as V/Q scan, helical CT scan, and angiogram.[13] D-dimer is a fibrin degradation product that is usually elevated in the presence of thromboembolic disease. Unfortunately, it is also elevated in such common diseases as inflammatory arthritidies, cancer, and infection. It may also be elevated following surgery or trauma. A number of different methods are currently available to measure D-dimer, including latex agglutination, whole-blood agglutination and enzyme-linked immunosorbent assay (ELISA).[11, 13] Until very recently, the rapid latex tests and bedside assays have had inadequate sensitivity to rule-out a life-threatening condition such as PE.[17, 18]

Since the published studies on the use of D-dimer to rule-out PE are of various size and quality, the accuracy and utility of the test is still debated. Previous systematic reviews evaluating the utility of D-dimer in the diagnosis of thromboembolsim were very broad in scope [11, 19, 20] and included DVT and PE, multiple testing methods, and both inpatient and outpatient populations. Thus, these findings may have limited applicability

to ED settings. The topic also warrants an updated meta-analysis to include more recent investigations using a rapid ELISA D-dimer testing method that is more practical in the ED setting. In order to limit the problems of clinical heterogeneity[21] found in previous systematic overviews and eliminate the problems of inter-observer reliability associated with qualitative tests, we chose to study only quantitative ELISA D-dimer tests in this review. The primary objective of this systematic review was to determine the accuracy of the ELISA D-dimer test in the diagnosis of pulmonary embolism in the ED. A secondary objective was to determine if the test characteristics change with respect to covariates such as age, comorbidity, or duration of symptoms.

METHODS

Research Question: What is the accuracy (e.g., sensitivity, specificity, likelihood ratios) of the ELISA D-dimer test in the diagnosis of pulmonary embolism in the adult patient presenting to the ED with a suspected PE?

Search Techniques: Computerized searching was performed using MEDLINE (January 1980 to January 1, 2001) to identify clinical studies assessing the utility of an ELISA D-dimer test in the diagnosis of PE. The search used the MeSH terms: *(pulmonary-embolism* OR *PE* OR *VTE)* AND (*D-dimer* OR *fibrin* OR *fibrinogen-degradation* OR *FDP* OR *fibrinogen-degradation-products*) AND (*ELISA* OR *enzyme-linked-immunosorbent-assay*) AND *Sensitivity and Specificity.* Using a similar approach, a search of EMBASE was also performed.

Study Selection: Two reviewers (MDB, BHR) independently examined the titles and abstracts of the references identified in the initial MEDLINE and EMBASE searches to determine if the study was relevant to the clinical question (relevance search).[22] Reviews and editorials were excluded immediately. The reference list of the articles chosen for inclusion in the meta-analysis and the reference list of prior systematic reviews [19, 20] were also screened to identify further studies for inclusion. In an attempt to identify other so-called "grey literature"[23], experts in the area of PE and the companies that market laboratory equipment that utilize ELISA D-dimer methods were contacted. Non-English language articles passing the initial screen were translated prior to full review.

Inclusion Criteria: To be included in the meta-analysis, the study must have been a prospective investigation involving a predominately outpatient population presenting

with symptoms and signs suspicious for PE. If a study included any inpatients, the study population must have been comprised of at least 80% outpatients or data must have been available to calculate sensitivity and specificity for the outpatient component of the study population.

Final Inclusion: Following the relevance search, the two primary reviewers (MDB, BHR) compared their exclusion logs to determine if there was any discordance. Where there was disagreement, consensus was reached by conference. A data collection form was used to abstract data from each study meeting the inclusion criteria. If a study met the inclusion criteria, reviewers attempted to contact the author to identify additional papers, confirm data extraction/estimation for correctness and completeness, and to obtain missing data. Two reviewers (MDB, BHR) independently confirmed numeric calculations and graphic extrapolations. The data was evaluated for the presence of publication bias using statistical methods (see Statistical Analysis).[24-26]

Reference Standards: Although a positive angiogram or autopsy is considered the gold standard for the diagnosis of PE, we considered any one of the following as acceptable surrogate reference standards: 1) high probability V/Q scan, 2) CT scan positive for PE, or 3) positive lower extremity imaging study (ultrasound, impedance plethysmography or venogram). A negative angiogram was considered the gold standard for ruling out PE. Acceptable surrogate reference standards for a negative diagnosis were: 1) normal or very low probability V/Q scan, or 2) clinical follow-up documenting the absence of a thromboembolic event over a minimum of 3 months.[27] If a reference standard is not used in all subjects, the study is susceptible to verification bias (work-up bias).[28-30] To minimize the effect of verification bias and to provide the most

conservative estimate for test sensitivity, any study that did not apply a reference standard to all subjects had the results analyzed on a "worse case" assumption, i.e. each subject lost to follow-up was assumed to have the worst outcome.

Quality Assessment: The rigorous inclusion/exclusion criteria functioned as the primary quality filter in this meta-analysis. The meta-analysis focused the appraisal of study quality on the potential for differential reference standard bias[30] and spectrum bias.[29] Differential reference standard bias is a more subtle form of verification bias and may occur when a negative test result is verified by a less rigorous standard than those with a positive test result.[30, 31] For example, a patient with a negative ELISA D-dimer result is verified by a single lower extremity ultrasound and outpatient follow-up, whereas a patient with a positive ELISA D-dimer result is verified by serial lower extremity ultrasound examinations and hospitalization. The reference standard and patient spectrum for each study was graded in regards to quality parameters (A - excellent, B - susceptible to some bias, C – indeterminate or poor) as outlined below:

- Reference standard: The potential for differential reference standard bias was assessed as follows.[30] Grade A - Those studies using the same reference standard regardless of the ELISA D-dimer result. Grade B - Studies using different reference standards depending on the results of the ELISA D-dimer test. Grade C - Indeterminate or not meeting the study protocol definition of an appropriate reference standard.
- Patient spectrum: The external validity (generalizability) of the meta-analysis depends upon the spectrum of disease included in each study and how the patient population was assembled.[31] Grade A - Patient spectrum would be expected to

include a consecutive or random sampling of a typical outpatient population presenting with symptoms and signs suspicious for PE. Grade B - Studies that selected only a small subgroup of subjects suspected of PE. Grade C - Indeterminate or not meeting the study protocol definition of an appropriate patient spectrum.

The blind interpretation of the test under investigation and the reference standard are typically considered important components in the critical appraisal of diagnostic tests.[32] However, since the interpretation of a quantitative ELISA D-dimer test is an objective measurement, it is less critical that the technician performing the D-dimer quantitative analysis be blinded to the clinical history or the reference standard.[28] There is potential for interpretation bias if the radiologist performing the reference standard was not blind to the ELISA D-dimer test result.[29] This information was obtained from the manuscript or by author query.

In order to provide the most conservative estimate of test characteristics, after each study was scored for quality, Grade C studies were excluded from the analysis.

Statistical Analyses: The analysis was based on a summary receiver operating characteristic (SROC) curve.[33, 34] When studies utilize different thresholds for positive and negative results, the reported sensitivity and specificity will differ among studies. A graphical display of the variability of the test characteristics between studies can be assessed with the SROC curve.[31] To simplify calculations, only single test thresholds and dichotomous results were used in the analysis. If a study reported results for more than one test threshold, a test threshold of 500 ng/ml was used since this is the most common cutoff used in clinical practice. The sensitivity and specificity for the single test

threshold identified for each study was used to plot an unweighted SROC curve.[34, 35] A correction factor of one-half was added to each cell to avoid calculation problems by having a value of zero in the 2x2 table.[34] This correction has not been found to significantly alter the results of the SROC curve.[34] The SROC curve analysis is based on a logit transformation of the data which plots the difference (D = logit TPR – logit FPR) on the y-axis and the sum (S = logit TPR + logit FPR) on the x-axis. The y-axis (D) is equivalent to the log diagnostic odds ratio and the x-axis (S) is a measure of how the test characteristics vary with the test threshold. A regression equation ($D = \alpha + \beta * S$) derived from the SROC curve analysis can be used to assess the heterogeneity among study results. If the β coefficient is near zero and not statistically significant, then evidence of significant heterogeneity is not present.[23] When there is little variability of test results (i.e. homogeneity), the SROC curve does not provide additional information over average sensitivity or specificity values.[35] A random-effects model was used to calculate the average sensitivity and specificity across studies.[31, 35, 36] The random-effects model accounts for between-study variability and provides a more conservative estimation as compared to the fixed-effects model.[33] Statistical tests related to the SROC curve were performed using Meta-Test (version 0.6, Boston, MA). All other statistical tests were performed using the SAS statistical application program (version 8.0, Cary, NC).

Sensitivity analysis was used to assess the effect of study quality on the overall results. The SROC curves were compared with and without the specified methodological flaw. *A priori* subgroup analyses were performed on studies using traditional ELISA methods, rapid ELISA methods, those using the 500ng/ml cutoff value, age, comorbidity, and the duration of symptoms. Comorbidity was defined as having surgery, trauma,

myocardial infarction, stroke, acute infection, disseminated intravascular coagulation, pregnancy, postpartum, or active cancer within the 10 days preceding the ED evaluation.[37]

In order to assess for the presence of publication bias, whereby smaller studies show effects different from those of larger studies, we used methods previously proposed by Galbraith[24] and Egger[25]. The standard normal deviate (SND) of the OR (calculated by dividing the OR by its SE) was regressed against its precision (as measured by the inverse of the SE) i.e., SND = $\alpha + \beta$*precision. The intercept α provides a measure of the degree of asymmetry resulting from publication bias. Data from a homogeneous or symmetrical set of trials will scatter around a line that runs through the 0 origin, whereas in the presence of publication bias, the intercept will deviate from 0. The absolute magnitude of α can therefore be used as one measure of the presence of publication bias.

RESULTS

Search: The MEDLINE search yielded 52 references. Eighteen were immediately deemed ineligible for full review (Tables 1 and 2). The relevance search had excellent agreement between the two reviewers with the simple agreement 92% and a Kappa of 0.83 (95% CI: 0.67, 0.99). An EMBASE search yielded 71 references; 7 additional references were identified as eligible for full review (Figure 1). The search for grey literature yielded 2 additional published articles.[38, 39]

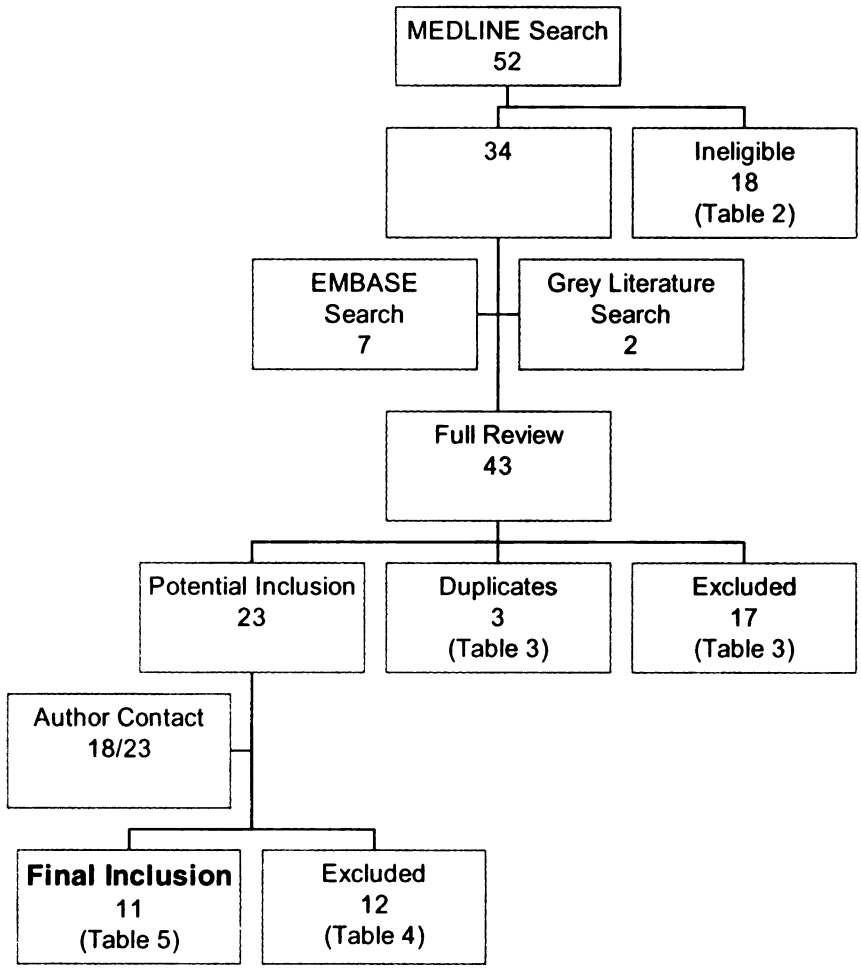
Table 1: Eighteen studies deemed ineligible after relevance screen (MEDLINE)

Author	Year	Reason
Lorut C,	1999	Review
Michiels JJ	2000	Review
Caliezi C	2000	Letter
Indik JH	2000	Review
Kline JA	2000	Review
Stein PD	1999	Review
Ndiaye A	1997	DVT after surg
Janssen M	1998	Review
Bounameaux H	1997	Review
Bounameaux H	1997	Review
Lee AY	1997	Review
Perrier A	1997	Review
Perrier A	1995	Review
Sie P	1995	Review
Bouman CS	1995	DVT
Bounameaux H	1994	Review
DVTENOX group	1994	DVT with heparin
Bounameaux H	1991	Review

Table 2. Reasons for ineligibility following initial relevance search of MEDLINE.

Primary Reason	Number of Reports
Review	14
Letter to editor	1
Subjects suspected for having DVT	3
Total	**18**

Figure 1. Search, inclusion and exclusion flow diagram. The "grey literature" was defined as those studies that were unpublished or with limited distribution.[14]



Inclusion: A complete manuscript review was performed on the remaining 43 articles. Dutch (1), French (4) and German (1) manuscripts required translation. Following full review, 3 studies were identified as duplicates and 17 others were excluded for various reasons (Table 3). In order to clarify important missing information and confirm data extraction, an attempt was made to contact the authors of the 23 remaining studies. Seventy-eight percent (18/23) of authors responded in some form to these queries. After obtaining additional information, a further 12 studies were excluded

(Table 4).[40-51] Eleven studies therefore met the inclusion criteria and provided a total

Table 3. Reasons for exclusion following full manuscript review.

Primary Reason	Number of Reports
Review paper	4
Duplicate publication	3
Latex D-dimer method	3
Grade C patient spectrum†	3
Grade C reference standard^	7
Total	**20**

Notes: † = Patient spectrum: Grade C - Indeterminate or not meeting protocol definition for adequate patient spectrum; ^ = Reference standard: Grade C - Indeterminate or not meeting protocol definition for adequate reference standard.

Table 4. Articles excluded (12) after quality rating.

Author	Year	Reason
Sijens P[40]*	2000	Grade C spectrum† #
Quinn D[41]	1999	Grade C spectrum #
Brimble S[42]	1998	Duplicate #
Duet M[43]	1998	Grade C spectrum
Reber G[44]	1995	Duplicate #
Bonnin F[45]*	1997	Grade C spectrum #
van Beek E[46]	1996	Data missing
Rochemaure J[47]	1995	Grade C spectrum
Flores J[48]	1995	Grade C reference standard^
Goldhaber S[49]	1993	Grade C spectrum #
van Beek E[50]	1993	Data missing
Bounameaux H[51]	1990	Grade C spectrum #

Notes: * = search result exclusively from EMBASE; † = Patient spectrum: Grade C - Indeterminate or not meeting protocol definition for adequate patient spectrum; ^ = Reference standard: Grade C - Indeterminate or not meeting protocol definition for adequate reference standard; # = after correspondence with author.

study population of 2,126 subjects. A summary of the major characteristics of each study is provided in Table 5.[37-39, 52-59]

Study Descriptions: The prevalence of disease among outpatients suspected of PE ranged from 17 to 58%, with most falling in the 20 to 40% range. In almost all studies, females were represented slightly more than males. Most studies included a broad range of ages except for one study with a mean age of 72 years[59] and another that

Table 5. Eleven studies of ELISA D-dimer in the diagnosis of pulmonary embolism: study characteristics and diagnostic test performance.

Study	Prevalence of PE (%)	N (% outpatient)	Mean* Age (y)	Male* Sex (%)	Test Threshold (ng/ml)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Study Quality (Reference Standard)^	Study Quality (Spectrum)†	Radiologist Blind
Demers et al, 1992[38]	20	84 (100)	NA	35	300	94 (69, 100)	52 (40, 64)	A	A	Yes
Ginsberg et al, 1993[53]	17	150 (100)	54	36	300	100 (87, 100)	35 (27, 45)	B	A	Yes
Lenzhofer et al, 1993[52]	19	107 (100)	54	36	250	88 (62, 98)	79 (69, 86)	B	A	No
de Moerloose et al, 1994[54]	34	150 (100)	NA	NA	500	100 (93, 100)	47 (37, 58)	B	A	No
de Moerloose et al, 1996[55]	24	195 (100)	60	44	500~	100 (92, 100)	38 (30, 46)	B	A	Yes
Perrier et al, 1997[56]	29	671 (100)	62	NA	500	99 (97, 100)	41 (37, 46)	B	A	No
Meyer et al, 1998[58]	42	142 (80)	55	41	500	92 (81, 97)	50 (39, 61)	A	A	Yes
Tardy et al, 1998[57]	42	96 (100)	81	34	500	100 (91, 100)	14 (7, 27)	A	B	Yes
Barro et al, 1999[59]	58	26 (100)	72	50	500	87 (59, 98)	27 (7, 60)	A	B	Yes
Heit et al, 1999[37]	31	61 (100)	63	44	500	88 (61, 98)	51 (36, 66)	A	B	Yes
Perrier et al, 1999[39]	23	444 (100)	61	47	500~	100 (97, 100)	47 (42, 53)	B	A	No

Notes: N = number of patients suspected of PE; * = demographics are close approximations based on the information available; † = Patient spectrum: Grade A - consecutive or random sampling of a typical outpatient population presenting with symptoms suspicious for PE, Grade B - potential for spectrum bias; ^ = Reference standard: Grade A - same reference standard regardless of the ELISA D-dimer, Grade B - potential for differential reference standard bias; NA = adequate data not available after author contact; ~ = used a rapid ELISA D-dimer method.

focused specifically on an elderly population[57] with a mean age of 81 years. Excluding these two outliers [57, 59], the mean age of the patients in the studies were similar with a range from 54 to 63 years. The regression analysis showed no statistical evidence of publication bias based on the p = 0.19, although the absolute value of the intercept was large (i.e., 98).[25, 26]

Quality Assessment: Only 2 studies were given a Grade A with respect to both of the key quality parameters, patient spectrum and reference standard (Table 5).[38, 58] One of these studies included 20% inpatients which was the maximum percentage of inpatients a study could have and still meet the inclusion criteria as defined in the research protocol.[58] Three of the studies included were given an "excellent" rating with regard to the reference standard, but were rated Grade B with respect to the patient spectrum. In contrast, six studies were given a Grade A with respect to the patient spectrum, but Grade B on the reference standard. In the majority (7/11) of studies, the radiologist was blind to the D-dimer results and any other clinical information.

Analyses: The sensitivity and specificity of each included study was calculated with the 95% confidence interval (CI) displayed (Figure 2 and Table 5). The pooled summary estimate using a random-effects model resulted in a sensitivity of 0.95 (95% CI: 0.90, 0.98) and a specificity of 0.45 (95% CI: 0.38, 0.52). However, this pooled estimate demonstrated statistically significant heterogeneity with a β of 0.43 (95% CI: 0.004, 0.87). The visual display provided by the logit regression plot (Figure 3) and the SROC curve shows moderate variability in the results (Figure 4).

Sensitivity Analyses: In order to explore the heterogeneity found in the overall results, a sensitivity analysis based on the key methodological quality parameters was

Figure 2. Sensitivity and specificity plot with the 95% CI displayed as horizontal lines. The circle at the bottom labeled REM is the pooled sensitivity and specificity using a random-effects model.

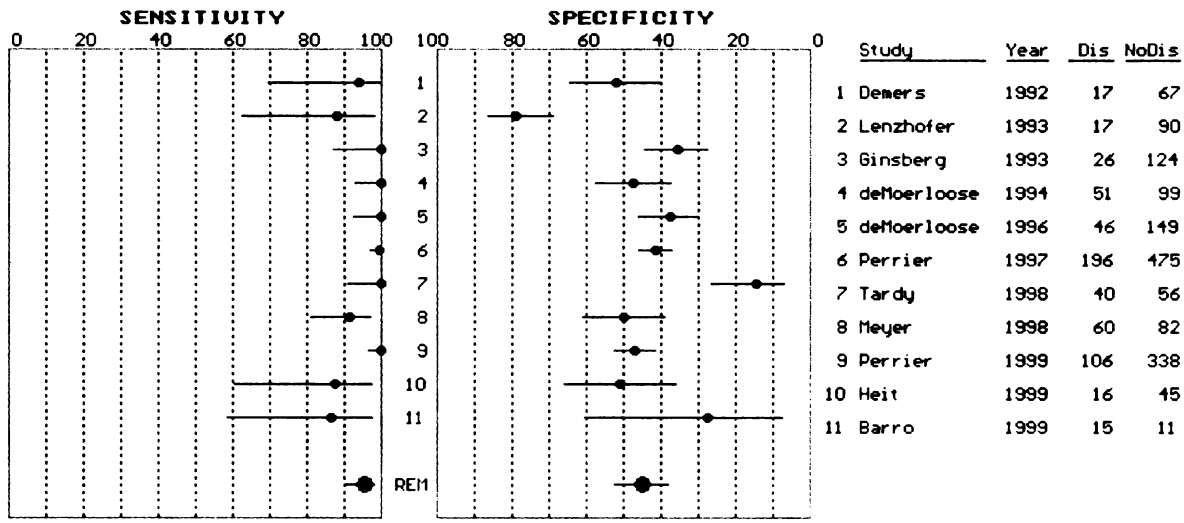


Figure 3. Logit regression plot. (D = logit TPR – logit FPR) on the y-axis and the sum (S = logit TPR + logit FPR) on the x-axis. The y-axis (D) is equivalent to the log diagnostic odds ratio and the x-axis (S) is a measure of how the test characteristics vary with the test threshold.

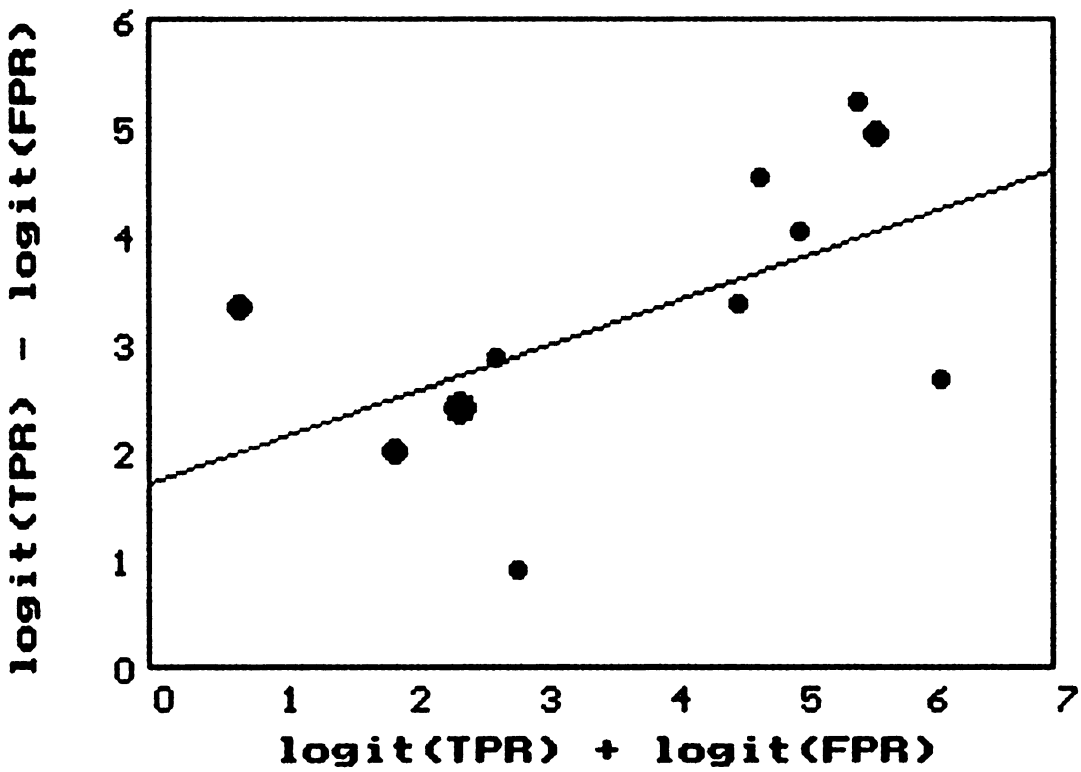
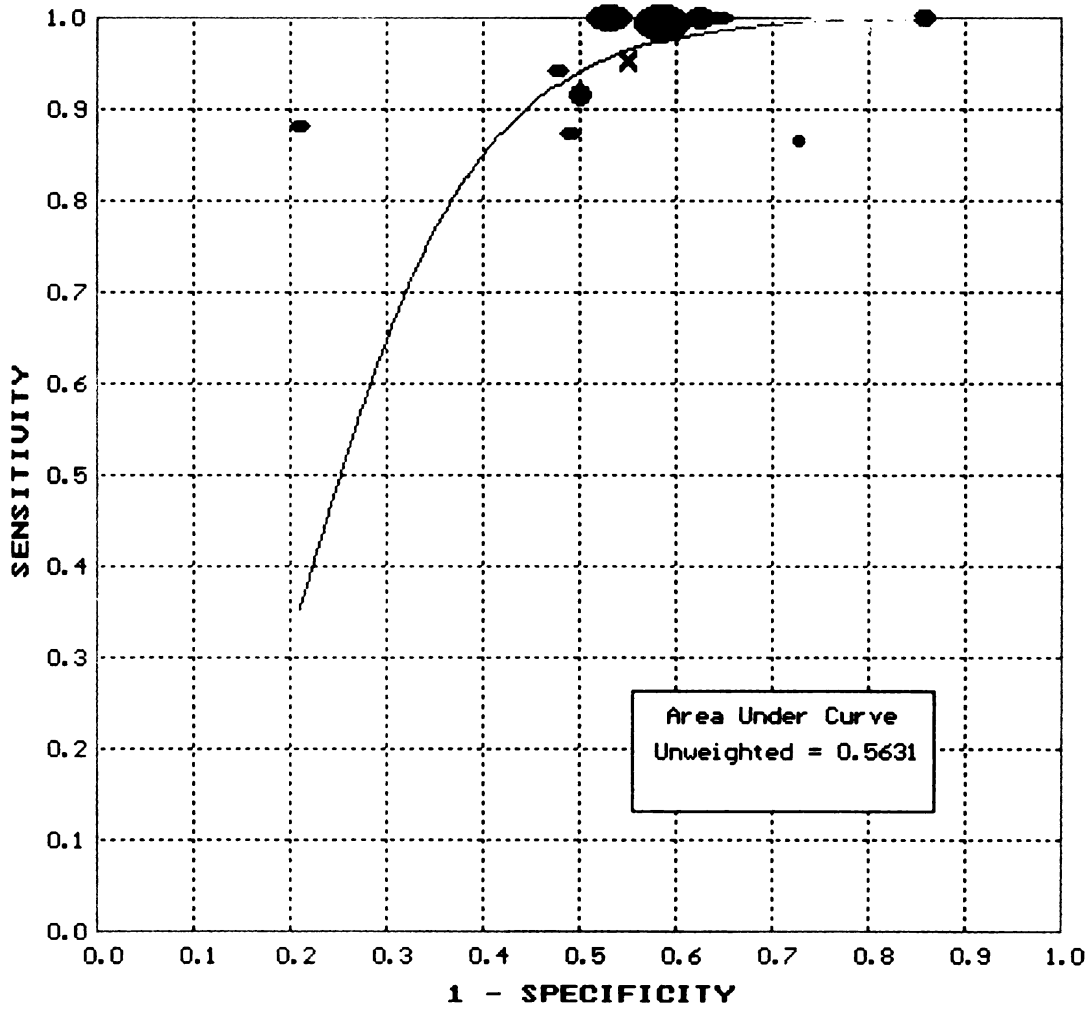


Figure 4. Summary receiver-operating characteristic (SROC) curve analysis of ELISA D-dimer in the diagnosis of PE. Plotted in each of the SROC graphs are individual studies depicted as ellipses. The x- and y-dimensions of the ellipses are proportional to the square root of the number of patients available to study the sensitivity and specificity, respectively, within the analysis. Also shown is the unweighted SROC curve limited to the range where data are available. The cross (x) represents the independent random-effects pooling of sensitivity and specificity values of the studies with the shaded box marking the zone of the 95% CI.



performed (Table 6). When the SROC curve was derived using only those studies with an "excellent" or Grade A quality rating (N = 5) in regard to the reference standard, the test for heterogeneity was not significant with a β of 0.18 (95% CI: - 0.52, 0.88). The pooled summary estimate for this subgroup using a random-effects model resulted in a sensitivity of 0.90 (95% CI: 0.83, 0.94) and a specificity of 0.40 (95% CI: 0.26, 0.55). In contrast, the subgroup of studies with a Grade A patient spectrum (N = 8) was found to have statistically significant heterogeneity. The proper blinding of the radiologist to the D-dimer test results had minimal effect on the results (Table 6). There were only 2 studies that used a rapid form of the ELISA D-dimer test, so a SROC curve analysis could not be performed. The average sensitivity for these 2 studies was higher (100%), when compared to the pooled results using traditional methods (sensitivity 94%). Using a

Table 6. Sensitivity analysis: random-effects pooled estimates of sensitivity and specificity for various study subgroups including test for heterogeneity.

Study Group	N	% Sensitivity, (95% CI)	% Specificity, (95% CI)	β, (95%CI)
Reference Standard: Grade A^	5	90 (83, 94)	40 (26, 55)	0.18 (-.52, .88)
Patient Spectrum: Grade A†@	8	97 (92, 99)	48 (41, 56)	0.46 (.10, .81)
Proper Blinding#	7	92 (85, 96)	39 (30, 49)	0.39 (-.16, .94)
Traditional ELISA	9	94 (88, 97)	45 (36, 55)	0.32 (-.18, .82)
Traditional ELISA 500 ng/ml*	6	95 (87, 98)	40 (32, 50)	0.55 (-.31, 1.41)
Rapid ELISA 500 ng/ml*~	2	100	44(40, 48)	N/A
Age ≥70	1	100	14 (7, 21)	N/A
No comorbidity@	3	89 (75, 96)	55 (46, 64)	0.59 (.04, 1.14)
Duration ≥4 days	1	73 (59, 86)	33 (19, 48)	N/A

Notes: N = number of studies included in pooled subgroup/sensitivity analysis; β = regression coefficient for the sum (logit TPR + logit FRP) which indicates heterogeneity among studies when the value is significantly different from zero; † = Patient spectrum: Grade A - Consecutive or random sampling of a typical outpatient population presenting with symptoms suspicious for PE; ^ = Reference standard: Grade A - Same reference standard regardless of the ELISA D-dimer; # = Proper blinding - radiologist interpreting reference standard blind to the ELISA D-dimer result; ~ = values reported are an average for the 2 studies; * = used a threshold of greater than 500 ng/ml as criteria for a positive D-dimer test; @ = statistically significant heterogeneity. N/A = not appropriate/applicable.

"worse case" assumption did not alter the pooled estimates since, in the majority of studies, very few cases were lost to follow-up. The only exception was the subgroup using the rapid ELISA method.[39, 55] When the "worse case" assumption was applied to this subgroup, the average sensitivity decreased to 95%.

Although there were only a few studies with sufficient data for subgroup analysis based on age, comorbidity, and symptom duration, all 3 of these covariates had a considerable effect on the test characteristics of the ELISA D-dimer test (Table 6). Older age ($\geq$70 years) was the only specific age-related subgroup that could be analyzed. The specificity of the ELISA D-dimer test in this elderly study population[57] was much lower (14%) than all of the other individual studies included in the meta-analysis (Figure 2). The subgroup analysis of the 3 studies with data on the population without comorbidity had a higher specificity (55%) but a lower sensitivity (89%). Only one study evaluated the effect of symptom duration on the ELISA D-dimer results.[37] If the duration of symptoms was greater than 3 days in this study population, both the sensitivity and specificity decreased (Table 6).

DISCUSSION

This systematic review attempted to identify the current published and unpublished literature regarding the use of ELISA D-dimer in the diagnosis of PE in the acute care setting. Following an exhaustive search, the application of stringent inclusion/exclusion criteria and rigorous selection methodology, we included 11 studies involving 2,126 patients in the study. The results demonstrate that the traditional ELISA technique is highly sensitive (94%), yet only moderately specific (45%). A highly sensitive test will assist the clinician in ruling out PE. Using evidenced-based medicine terms,[12, 32] the negative LR (-LR) of 0.1 for this test would be clinically helpful, especially when applied in the face of accurate pretest probability models for PE.[8, 60] For example, a patient with a pretest probability of 20% (low) in the face of a negative ELISA D-dimer would have a post-test probability of 2%; in such a case, further testing is probably not warranted. In contrast, the positive likelihood ratio (+LR) for this test is only 1.7 and is of limited value in most clinical scenarios.

An adequate reference standard (gold standard) and an appropriate spectrum of patients are key elements of study methodology when considering application of the results to clinical practice.[61] Although angiogram has long been considered the "gold standard" for the diagnosis of PE, it has been recommended that clinicians now use an outcome-based standard.[27] As expected, the majority of studies included in this overview used an outcome-based standard such as symptom-free follow-up and survival. Most ED physicians would consider the absence of a thromboembolic event or death over a 3-month period a valid outcome measure.[27] Studies that use a different reference standard, depending on the ELISA D-dimer test result, may provide an erroneously high estimate

for test sensitivity.[30] As expected, the 5 studies using a reference standard not susceptible to differential reference standard bias[30] (Grade A) had a lower pooled sensitivity (90%) and specificity (40%). However, because they had selected a subgroup of the target outpatient population suspected of PE, these studies were predominately of lower quality with respect to the patient spectrum (Grade B) and susceptible to spectrum bias (or assembly bias). These studies may have been representative of patient populations with comorbidity or a longer duration of symptoms. For example, Heit et al[37] selected a study population referred to the Mayo Clinic for angiography. Of all studies included, this was the only investigation that performed angiography on all subjects and therefore was the least susceptible to differential reference standard bias. However, the external validity of the results must be questioned since these subjects were not typical of the ED patient population suspected of having PE. Another study was rated "excellent" in regard to the reference standard but was rated Grade B with respect to the patient spectrum.[59] This study included only those patients suspected of PE who were subsequently admitted to the hospital, which explains the very high prevalence (58%) of PE. The specificity of the ELISA D-dimer may also be affected by the patient spectrum as demonstrated by the low specificity (14%) found in the study focused only on the elderly.[57] In a subsequent publication, investigators combined data from two of the studies included in the review[39, 56] and performed a subgroup analysis providing similar results with a specificity of 17% in those over 70 years.[62] The reasons for the much lower specificity in the elderly is unknown but may be related to comorbidity that raises the D-dimer levels in settings not confined to thrombo-embolism (such as cancer, inflammation, recent surgery).

Different forms of interpretation bias are another concern in the evaluation of diagnostic studies.[29] In order to limit diagnostic review bias, the radiologist performing the interpretation of the reference standard should be blinded to the results of the ELISA D-dimer test.[29] Previous investigators who have assessed the effects of design-related bias in studies evaluating diagnostic tests have found that the average effect of inappropriate blinding is small.[30] Our meta-analysis had similar findings, after excluding studies in which the radiologist was not blinded, there was not a clinically significant change in the pooled estimates of diagnostic accuracy. Among the studies with proper blinding that used follow-up as a reference standard (5/7), the personnel performing clinical follow-up were also blinded to the ELISA D-dimer test results and clinical course.

The traditional ELISA D-dimer has been shown to have excellent sensitivity but requires specialized equipment available only at major academic centers and is too time-consuming to be valuable in most ED settings.[2, 17] Therefore, studies using a rapid ELISA D-dimer method are important and were consequently reported as a subgroup. The two studies in this subgroup were among the largest included in the review and reported an impressive sensitivity of 100%.[39, 55] However, both of these investigations were prone to differential reference standard bias which may yield an erroneously high sensitivity.[29] For the clinician, the pooled results of studies using traditional methods would appear to be a more conservative estimate for test sensitivity (94%) compared to the perfect sensitivity (100%) reported by these two studies utilizing a rapid ELISA D-dimer method.

Despite the rigorous methodology used in this systematic review, there are inherent limitations in this type of analysis. Typically, the studies included in a meta-

analysis should be evaluated for the presence of publication bias using graphical and statistical methods.[25] Publication bias is expected to be a much greater problem in meta-analysis of diagnostic tests than in meta-analysis of randomized-controlled trials of therapeutic effects but there is no agreed upon method to assess publication bias for diagnostic meta-anlaysis.[33] Aware of these limitations, we did perform a regression analysis, which demonstrated possible evidence of publication bias given the large value of the intercept. However, the small number of studies included limits the statistical power of the test, and the intercept was not statistically significant.[25] Our search attempted to examine all literature on this topic but it is possible that some unpublished or other foreign language studies were missed. It may be that lower sensitivity results remained unpublished, which would inflate the pooled estimates. However, we searched extensively for other evidence of unpublished work, so we believe this bias to be limited.

There is also the possibility that some information may have been lost during translation of those studies published in non-English. For instance, we could not determine the reason for the unusually high specificity (80%) reported in one study published in German[52] and author contact was unsuccessful. Finally, in the original protocol, a subgroup analysis was planned to determine if the test characteristics might differ based on varying levels of pretest probability. While attempts were made to derive this information from the authors, in most cases pretest probability estimation was not performed, so additional information was not available. Consequently, there were insufficient data in the primary studies to comment on this important issue.

Restricting the systematic review to D-dimer tests that use an ELISA method makes it inappropriate to apply the results to clinical settings where alternative D-dimer

testing methods are used. However, a recent investigation has shown that a newer latex-based method had remarkably similar test characteristics (sensitivity of 96%, specificity of 45%)[63] to the summary estimates derived in this meta-analysis. A normal whole-blood agglutination D-dimer assay in combination with a normal alveolar dead-space fraction has also been shown to have adequate sensitivity to rule-out PE.[64] A systematic review by Kline et al[11] compared various D-dimer testing methods such as these. However, the methodology of this meta-analysis differed from ours with respect to the search, the inclusion criteria, and the quality assessment. In fact, only 4 of the studies were common to both reviews.[53, 55-57]

Notwithstanding the above concerns, this meta-analysis followed widely accepted methodology for the selection of studies, the data extraction process, the analysis of study quality, and the evaluation of subgroups.[65] Overall, the summary data reveal that the ELISA D-dimer is highly sensitive, but only moderately specific. Given these results, the D-dimer test may be a safe and efficient test to reduce the overall costs associated with "rule-out PE" assessment in the ED; although the cost-effectiveness of D-dimer testing in the clinical setting has not been adequately evaluated. Moreover, as rapid D-dimer tests become more readily available, the number of patients screened for PE will likely increase, which could result in more V/Q or CT scans ordered by physicians.[66] Pooling the results of studies using traditional ELISA methods provide the most valid pooled estimates. Although the studies utilizing a rapid ELISA D-dimer were large and would be useful for many non-academic medical centers, the sensitivity reported in these studies appear to be suspiciously high. The test characteristics of the ELISA D-dimer appear to change among certain subgroups of patients such as those having comorbidity or

prolonged symptom duration. In addition to assisting clinicians, the summary estimates may assist researchers performing decision analysis or developing a protocol to test a diagnostic algorithm for use in the ED.

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