




Age-Adjusted D-Dimer in the Prediction of Pulmonary Embolism: Systematic Review and Meta-analysis

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Abstract

Background: Pulmonary embolism (PE), depending on the severity, carries a high mortality and morbidity. Proper evaluation, especially in patients with low probability for PE, is important to avoid unnecessary diagnostic testing. **Objective:** To review the diagnostic utility of conventional versus age-adjusted D-dimer cutoff values in patients 50 years and older with suspected pulmonary embolism. **Methods:** Systematic review with univariate and bivariate meta-analysis. **Data sources:** We searched PubMed, MEDLINE, and EBSCO for studies published before September 20th, 2020. We cross checked the reference list of relevant studies that compares conventional versus age-adjusted D-dimer cutoff values in patients with suspected pulmonary embolism. **Study selection:** We included primary published studies that compared both conventional (500 µg/L) and age-adjusted (age × 10 µg/L) cutoff values in patients with non-high clinical probability for pulmonary embolism. **Results:** Nine cohorts that included 47720 patients with non-high clinical probability were included in the meta-analysis. Both Age-adjusted D-dimer and conventional D-dimer have high sensitivity. However, conventional D-dimer has higher false positive rate than age-adjusted D-dimer. **Conclusion:** Age-adjusted D-dimer cutoffs combined with low risk clinical probability assessment ruled out PE diagnosis in suspected patients with a decreased rate of false positive tests.

Keywords

D-dimer, pulmonary embolism, age-adjusted D-dimer, deep vein thrombosis

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Introduction

Pulmonary embolism (PE) is usually caused by deep vein thrombosis (DVT) and results in mechanical obstruction of 1 or more pulmonary arteries. The annual incidence of PE is estimated to be about 71 to 117 per 100 000 people,¹⁻³ and it carries a high mortality and morbidity depending on the severity of the PE and the patient's underlying co-morbidities.

Risk factors for developing DVT or PE can be summarized using the well-known Virchow's triad: endothelial damage (surgery, catheter, and trauma), hypercoagulability (malignancy, obesity, severe infection or inflammatory state, pregnancy, medications, and hereditary coagulation disorders), and venous stasis (immobility). Most patients with suspected acute PE present with dyspnea, tachycardia, pleuritic chest pain, low grade fever, tachypnea, cough, and/or hemoptysis.

The diagnostic evaluation for suspected PE depends on whether the patient is hemodynamically stable or unstable. For hemodynamically unstable patients or those with high

clinical probability of having PE, current guidelines recommend computed tomographic pulmonary angiography (CTPA) or other confirmatory imaging tests (such as bedside echocardiography looking for right ventricular strain) and initiation of treatment with no delay.⁴ For patients with non-high or unlikely clinical probability for PE (calculated using either Revised Geneva Score or Wells' Criteria for Pulmonary Embolism), plasma D-dimer measurement is recommended, and, if positive, CTPA or other confirmatory

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diagnostic imaging needs to be considered. One of the problems with using D-dimer assays in the PE diagnostic algorithm is its decreased specificity in older patients.

D-dimers are protein fragments that are released into the systemic circulation as a result of blood clot degradation. A normal D-dimer level is generally considered to be less than 500 µg/L (depending on the manufacturer) and elevated levels can be seen in the acute phase of PE during the first few days. False positive D-dimer values are commonly seen in older patients, patients with cancer or systemic infection, pregnancy, recent surgery, or trauma.⁵ D-dimer testing is mainly done with immunoassay testing, enzyme-linked immunosorbent assays (ELISA testing) or immunoagglutination technology.⁶

Pulmonary embolism can be excluded in most people with non-high or unlikely clinical probability with a normal conventional D-dimer value (less than 500 µg/L). However, using conventional D-dimer cutoff value for all patients has been questioned in the past few years due to its lower specificity in older patients. Age-adjusted (for patients >50, use age multiplied by 10) D-dimer cut-off value has been proposed for older patients.⁷ In a large multinational study evaluating 3346 patients with suspected PE using an age-adjusted D-dimer (compared to a fixed D-dimer cutoff of 500 µg/L) was associated with higher number of patients in whom PE could be safely ruled-out with no increase in the false-negative values. These results were more pronounced in patients 75 years and older.⁸ For patients 50 years and older, an age-adjusted D-dimer test has better specificity in excluding PE in those with non-high or unlikely clinical probability.⁹⁻¹² These findings will minimize the need for CTPA, thereby decreasing length of stay in the hospital or emergency department, healthcare costs, radiation exposure, and complications related to intravenous contrast use (e.g., allergic reactions and kidney injury).¹³⁻¹⁵ In contrast, there is a rare case report of false negative PE in a patient with normal age-adjusted D-dimer.^{16,17}

Methods

Protocol and Registration

The investigators structured this systematic review according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.¹⁸ The study protocol was registered with PROSPERO (CRD42018090529).

Eligibility Criteria and Study Selection

We included original studies that compared the diagnostic performance of D-dimer using the conventional and age-adjusted cutoff values in patients with non-high or unlikely clinical probabilities for PE. The D-dimer reporting must be a quantitative value. No language restriction was used. No publication-date limit was set. We included studies that met

the inclusion criteria. Two author reviewers independently selected the first set of articles, and the third reviewer reviewed the final selection and resolved the discrepancies between the first 2 reviewers.

We excluded studies that were done on nonhuman subjects. We also excluded study populations with high risk for thrombosis patients (defined as known history of PE or deep vein thrombosis, sepsis, or coagulation disorders).

Information Sources and Searches

On September 20th, 2020, we systematically searched PubMed, Medline and EBSCO database for studies that evaluated the diagnostic value of D-dimer cutoffs in patients with suspected PE. The search query combined synonyms for “D-dimer” with synonyms for “pulmonary embolism” and “elderly” (see Supplemental Appendix 1 for the search strategy). The articles were manually reviewed by 2 reviewers and duplicates removed.

Data Extraction Process

We reviewed the eligible studies for study design, location and characteristics of the study population, number of patients, clinical decision used for PE risk stratification, D-dimer assay and cutoff values used. Sensitivity, specificity, true positives, false positives, true negatives, and false negatives of both age-adjusted and conventional D-dimer values were recorded.

Risk of Bias Across Studies

The risk of bias and applicability was assessed using the revised tool for quality assessment of diagnostic accuracy studies (QUADAS-2). This is a validated risk of bias assessment tool for quality and applicability for diagnostic studies.¹⁹ The individual studies were appraised using the 4 domains components of the QUADAS-2: patient selection, index test, reference standard, and flow and timing.

Statistical Analysis

Descriptive statistics of sensitivity and specificity were calculated and plotted in paired forest plots for CDD and AADD with summary estimates. The overall test accuracy was evaluated using the diagnostic odds ratio (DOR) which was obtained from fitting DerSimonian-Laird univariate random effect model. The heterogeneity of DORs across the studies was examined by I^2 statistics, where $I=0$, no heterogeneity; $0 < I < 25$, mild heterogeneity; $25 \leq I < 50$ moderate heterogeneity; $50 \leq I < 75$, strong heterogeneity; $75 \leq I < 90$, considerable heterogeneity; $I > 90$, extreme heterogeneity.²⁰ Since the bivariate mixed modeling approach takes into account the correlation between

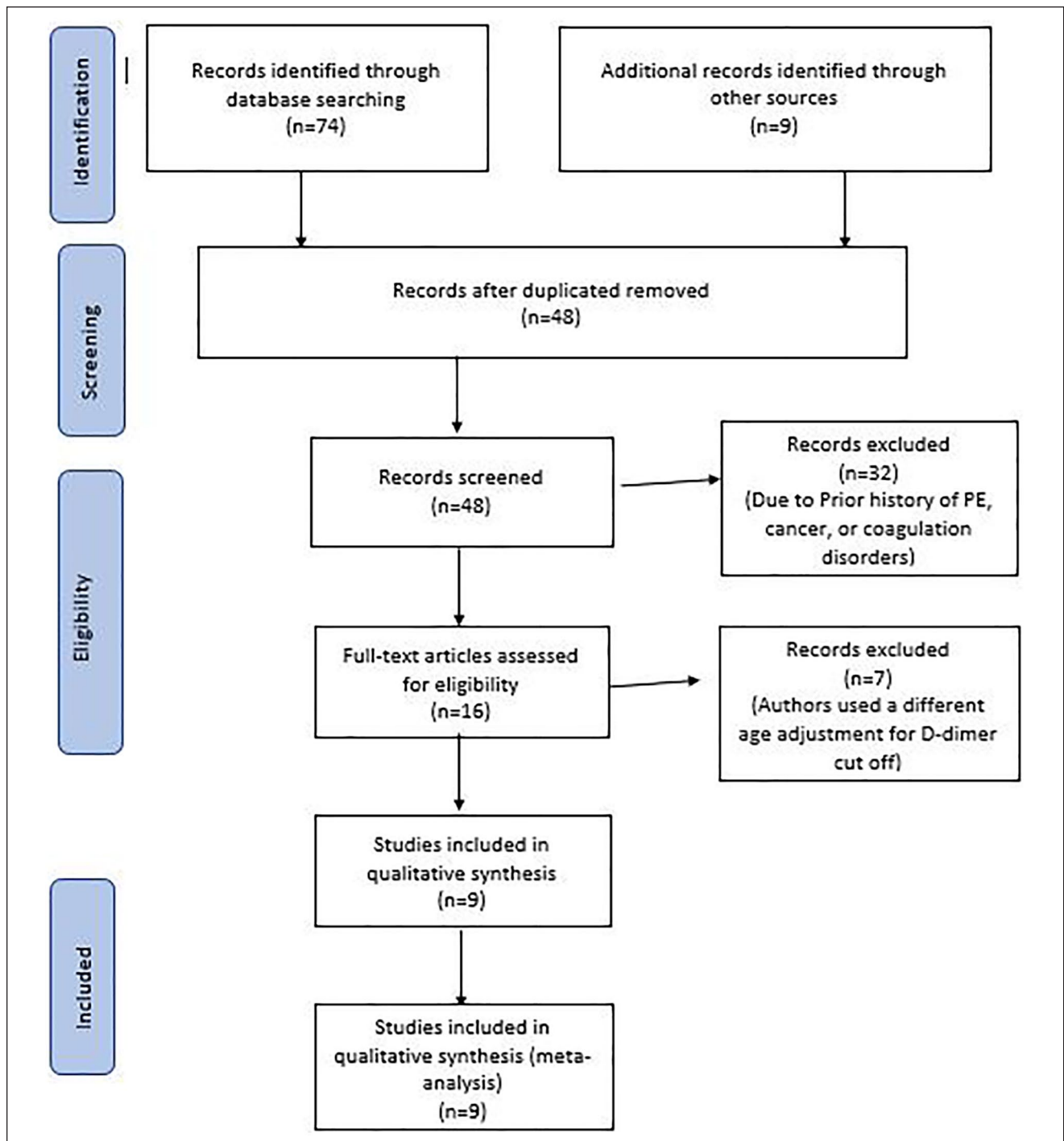


Figure 1. Selection flow diagram.

sensitivity and specificity values, data were analyzed using a bivariate linear mixed model for the logit-transformed pairs of sensitivity and specificity.²¹ The summary receiver operating characteristic (SROC) curves with a 95% CI ellipsoid and the area under the curve (AUC) were obtained. Finally, the SROC curves were plotted together with their summary estimates and confidence regions for comparison

purposes. The analysis was mainly conducted using the R package “mada.”²²

Results

There were 83 articles retrieved based on title and abstract from the literary database search (Figure 1). Sixteen

articles remained after full assessment by the authors. Further evaluation based on the study inclusion criteria led to 9 studies that were included for this analysis. These 9 studies were retrospective studies (Table 1). All included studies compared conventional versus age-adjusted D-dimer results in PE evaluation. Both sensitivity and specificity of age-adjusted D-dimer (AADD) and conventional D-dimer (CDD) were recorded in each of the individual studies. A 47 720-patient cohort composed the total population for all the studies.

Figure 2a and b show a forest plot of sensitivity and specificity of both conventional and age-adjusted D-dimer for each study. CDD study sensitivity and specificity ranged from 97.2% to 100% and 2.1% to 63.8%, respectively (with pooled sensitivity and specificity of 98.8% and 29.6% respectively). For the AADD, the study sensitivity and specificity ranged from 89.5% to 100% and 7% to 75.3%, respectively (with pooled sensitivity and specificity of 96% and 41.3%, respectively). Univariate analysis for heterogeneity showed moderate ($I^2=40\%$) and extreme heterogeneity ($I^2=100\%$) for CDD sensitivity and specificity, respectively. The AADD univariate analysis for heterogeneity showed strong ($I^2=74\%$) and extreme heterogeneity. The diagnostic odds ratio for CDD in the studies was 19.8 (95% CI 8.2-47.9) which means that the odds of diagnosing PE in a positive patient is 19.8 times higher than obtaining a positive result in a negative patient. The diagnostic odds ratio for AADD was 16.6 (95% CI 8.0-34.4) which means that the odds of diagnosing PE in a positive patient is 16.6 times higher than obtaining a positive result in a negative patient. The log transformed diagnostic odds ratios for the examined studies were used to account for confidence interval variation in the studies. The log transformed odds ratio ranged between 0.5 and 4 for CDD, and 0.97 and 5.1 for AADD across the studies. The random model pooled estimate of log transformed DORs was 2.98 (95% CI 2-3.9) for CDD and 2.81 (95% CI 2-3.5) for AADD.

In Figure 3, the bivariate random model showed the trade-offs between sensitivity and specificity using the SROC. For CDD, The AUC was 96% with a high model transformed sensitivity (μ , 97%; 95%CI=0.96%-98%) and transformed false positive rate (μ) of 78%; 95% CI, 66%-91%). For AADD, The AUC was 91% with a high model transformed sensitivity (μ , 96%; 95%CI=0.93%-98%) and transformed false positive rate (μ) of 61%; 95% CI, 43%-77%). For the purposes of comparison and visual inspection, Figure 4 shows AADD and CDD combined with trade-off between sensitivity and specificity.

The individual risk of bias assessment was completed using QUADAS-2 assessment tool. The majority of the studies were considered to have a low risk of bias (Table 2).

Discussion

This analysis shows that an age-adjusted D-dimer (age \times 10 $\mu\text{g/L}$) cutoff value can be effective and safe in the exclusion of PE and in the reduction of the risk of false positives when compared to conventional D-Dimer (500 $\mu\text{g/L}$) cutoff values in patients with non-high clinical probability for PE. The D-dimer age related elevation level (a false-positive result) may be partially attributed to frequency of race and comorbidities, including diabetes, cardiovascular disease, and disabilities.^{23,24}

For this analysis, data from 9 large retrospective studies were used to compare the diagnostic performance of D-dimer using the conventional and age-adjusted cutoff values in patients with non-high or unlikely clinical probability for PE. Total information from 47 720 patients was used, which showed a strong Age-adjusted D-Dimer sensitivity (mean, 97%; 95% CI, 89%-99%). When compared to CDD using the bivariate random model SROC Curve analysis, there was also a decreased false positive rate. These findings are consistent with prior reviews by Schouten et al.

Diagnostic management of PE aims to identify patients in which computed tomographic pulmonary angiography (CTPA) or other confirmatory imaging tests can be withheld using safe minimally invasive testing while avoiding a potentially fatal missed diagnosis. The routine use of CTPA exposes the patient to radiation as well as iodine contrast (allergic reactions and contrast induced nephropathy) leading to prolonged emergency department evaluation and increased healthcare cost. It would, therefore, be preferable to be able to exclude the diagnosis of PE without the need for CTPA. Fuchs et al²⁵ showed that using the AADD is cost-effective, potentially saving the United States health care system over \$80 million per year.²⁶

In comparison with prior studies, Douma et al. derived the age-adjusted D-dimer using the patient's age \times 10 as the threshold for additional testing in persons greater than 50 years of age. Subsequent systemic reviews and meta-analysis of cohort studies have shown the acceptability of using the age-adjusted threshold over the conventional D-dimer.⁹⁻¹²

Limitations

First, the various types of pretest probability assessment tools utilized as well as the different type of commercial D-dimer assays differed among the 9 cohorts. Thus, patients were not managed with same diagnostic testing. Second, the clinical probability of PE diagnosis and use of D-dimer relies heavily on the physician's assessment which may impact the final diagnosis. Finally, there is a significant heterogeneity among the studies in this analysis.

Table 1. Study Characteristics.

Studies [Number]	Suspected PE cases	AADD compared to conventional (Y/N)	age adjustment formula used ($10 \times \text{age} > 50$) (Y/N)	AADD sensitivity (%)	AADD specificity (%)	CDD sensitivity (%)	CDD specificity (%)	AADD true positive		AADD false negative		CDD true positive		CDD false positive		CDD true negative		CDD false negative	
								positive	negative	positive	negative	positive	negative	positive	negative	positive	negative		
Deeks et al. ¹⁸ [1]	785	Y	Y	100	46	100	34	42	327	276	0	42	397	206	0	0	0	0	0
Senior et al. ⁹ [2]	6,655	Y	Y	90	75	97	64	222	1580	4829	24	239	2318	4091	7	7	7	7	7
Dutton et al. ¹⁰ [3]	329	Y	Y	96	32	100	7	67	176	84	2	69	242	18	0	0	0	0	0
Sheele et al. ¹² [4]	3117	Y	Y	89	25	96	7	51	867	287	6	55	1075	79	2	2	2	2	2
Sharp et al. ²² [5]	31,094	Y	Y	93	64	98	54	471	11039	19548	36	497	13937	16650	10	10	10	10	10
Flores et al. ²³ [6]	362	Y	Y	98	46	97	35	96	142	122	2	96	171	93	3	3	3	3	3
Friz et al. ²⁷ [7]	481	Y	Y	98	7	100	2	106	347	26	2	108	365	8	0	0	0	0	0
Parry et al. ²⁸ [8]	1834	Y	Y	100	60	98	55	98	700	1033	3	100	773	960	2	2	2	2	2
Gupta et al. ²⁴ [9]	3063	Y	Y	97	17	100	7	76	814	163	2	78	905	72	0	0	0	0	0

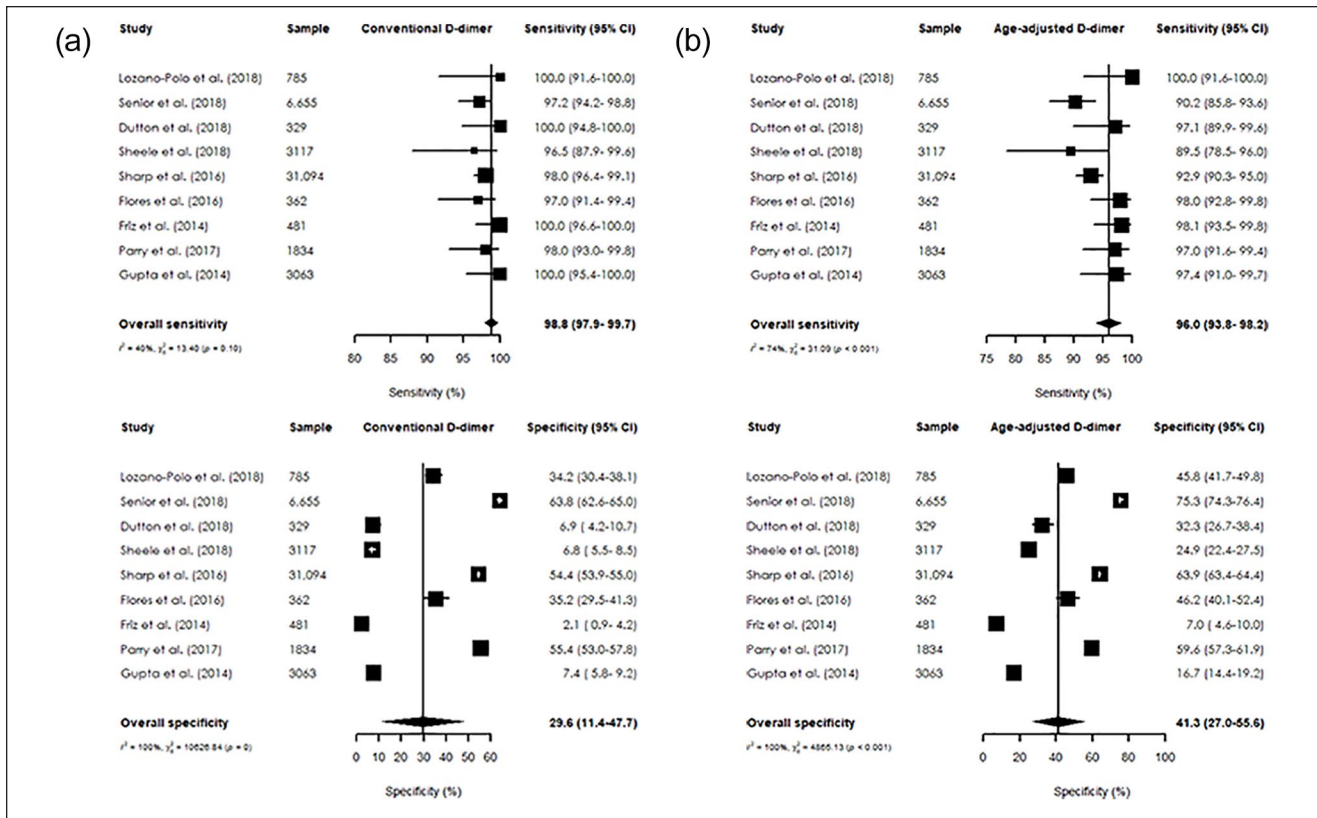


Figure 2. (a) Forest plot of sensitivity and specificity for conventional D-dimer and (b) forest plot of sensitivity and specificity for age-adjusted D-dimer.

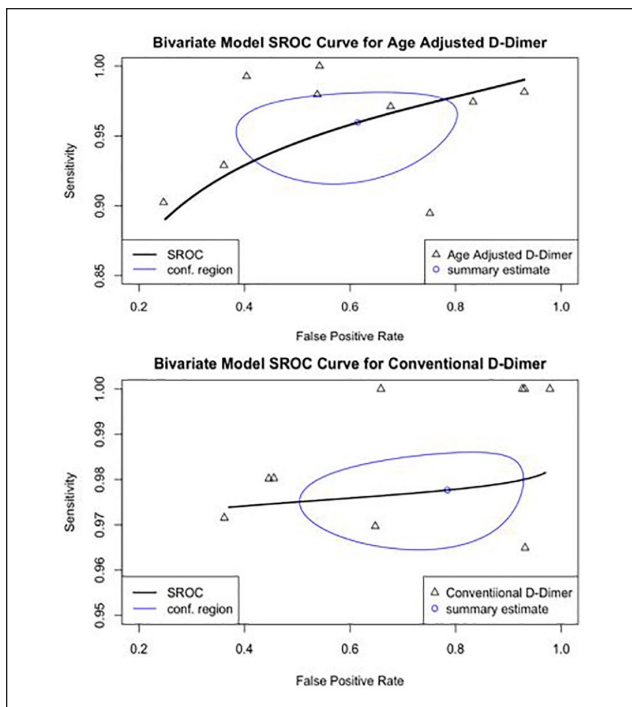


Figure 3. Bivariant random model of SROC curve for both age adjusted and conventional D-dimer.

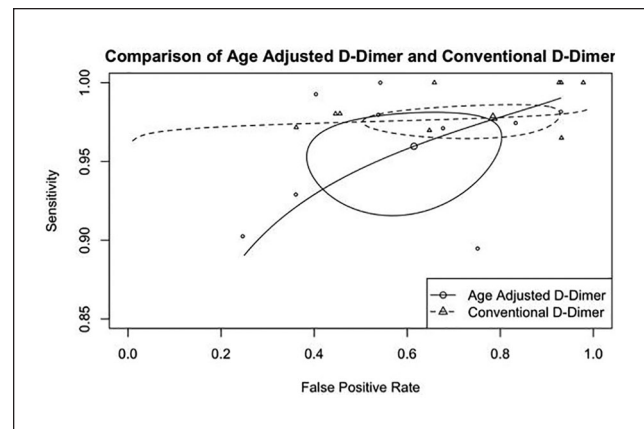


Figure 4. Age adjust and conventional D-dimer combined with trade off between sensitivity and specificity.

Conclusions

In this study, an age-adjusted D-dimer cutoff with combined low risk clinical probability assessment can rule out PE diagnosis in suspected patients with a decreased rate of false positive diagnosis in patients 50 years old or greater. Results of this meta-analysis agree with previous studies.

Table 2. Individual risk of bias using QUADAS-2.

Study	Risk of bias			
	Patient selection	Index test	Reference standard	Flow and timing
Deeks et al. ¹⁸ [1]	☺	☺	☺	☺
Senior et al. ⁹ [2]	☺	☺	☺	☺
Dutton et al. ¹⁰ [3]	☺	?	☺	☺
Sheele et al. ¹² [4]	☹	☺	☺	☺
Sharp et al. ²² [5]	☺	☺	☺	☺
Flores et al. ²³ [6]	☺	☺	☺	☺
Friz et al. ²⁷ [7]	☺	?	☺	☺
Parry et al. ²⁸ [8]	☺	☺	☺	☺
Gupta et al. ²⁴ [9]	☺	☺	☺	☺

☺, Low risk. ☹, High risk. ?, Unclear risk.

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Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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