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Diagnostic Accuracy of D-Dimer for Acute Aortic Syndromes: Systematic Review and Meta-Analysis

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Study objective: Acute aortic syndrome is a life-threatening emergency condition. Previous systematic reviews of D-dimer diagnostic accuracy for acute aortic syndrome have been contradictory and based on limited data, but recently published studies offer potential for a more definitive overview. We aimed to perform a systematic review and meta-analysis to determine the diagnostic accuracy of D-dimer for diagnosing acute aortic syndrome.

Methods: We searched MEDLINE, EMBASE, and the Cochrane Library from inception to February 2024. Additionally, the reference lists of included studies and other systematic reviews were thoroughly searched. All diagnostic cohort studies (prospective or retrospective) that assessed the use of D-dimer for diagnosing acute aortic syndrome compared with a reference standard test (eg, computed tomographic angiography (CTA), ECG-gated CTA, echocardiography, magnetic resonance angiography, operation, or autopsy) were included. Two independent reviewers completed study selection, data extractions and quality assessment using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. Data were synthesized using a bivariate meta-analysis model.

Results: Of 2017 potentially relevant citations, 25 cohort studies met the inclusion criteria, and 18 reporting the 500 ng/mL threshold were included in the primary meta-analysis. Risk of bias domains were mostly unclear due to limited study reporting. The summary sensitivity was 96.5% (95% credible interval [CrI] 94.8% to 98%) and summary specificity was 56.2% (95% CrI, 48.3% to 63.9%). Study specificity varied markedly from 33% to 86%, indicating substantial heterogeneity. Sensitivity analysis including the 7 studies reporting other thresholds showed summary sensitivity of 95.7% (95% CrI, 93.2% to 97.5%) and summary specificity of 57.5% (95% CrI, 50.1% to 64.6%).

Conclusion: D-dimer concentration has high sensitivity (96.5%) and moderate specificity (56.2%) for acute aortic syndrome, with some uncertainty around estimates due to risk of bias and heterogeneity. Previous meta-analysis reporting higher specificity may be explained by inclusion of case-control studies that may overestimate accuracy. [Ann Emerg Med. 2024;■:1-13.]

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INTRODUCTION

Background

Acute aortic syndrome is a deadly, time-dependent emergency condition affecting the thoracic aorta that includes acute aortic dissection, intramural hematoma, and penetrating ulcer. Although acute aortic syndrome remains an uncommon condition in the general population (annual incidence between 4.5 and 15 cases per 100,000 individuals), it usually presents with nonspecific symptoms and can lead to high morbidity and mortality.[1,2] Computed tomographic angiography (CTA) scanning of the aorta has high sensitivity and specificity for diagnosing acute aortic syndrome but incurs significant costs and risks of ionizing radiation, which may be substantial if CTA is used in a population with low prevalence of acute aortic syndrome.[3]

D-dimer is a routinely available blood test that clinicians can use to select patients for CTA. Evidence for D-dimer in acute aortic syndrome has progressively accumulated over the last 20 years, with 7 systematic reviews of D-dimer published between 2007 and 2021, along with 2 systematic reviews evaluating D-dimer alongside the aortic dissection detection risk score (ADD-RS).[4-12] Early systematic reviews of D-dimer were dominated by case-control studies, which are known to overestimate diagnostic accuracy, and even the most recent review included a substantial number of case-control studies.[5-8,10,13] Estimates of pooled D-dimer sensitivity from more recent reviews are reasonably

Editor's Capsule Summary

What is already known on this topic

Uncertainty exists regarding the accuracy of D-dimer measurements in evaluating those with possible acute aortic syndrome.

What question this study addressed

What are the published data on the diagnostic features of D-dimer for diagnosing acute aortic syndrome?

What this study adds to our knowledge

This meta-analysis and review reported that the D-dimer level has a sensitivity of 96.5% and specificity of 56.2% for diagnosing acute aortic syndrome.

How this is relevant to clinical practice

Measuring D-dimer levels can help detect those with acute aortic syndromes, but further study is needed to better characterize which patients benefit from this testing based on prior probabilities.

consistent at around 95% to 98% but specificity varies markedly from 42% to 70%.[4,5,9,10] This variation may reflect heterogeneity among the primary studies and whether the meta-analysis included case-control studies or were limited to cohort studies.[4,10] Studies evaluating tests in a diseased population and a separate control group are known to overestimate diagnostic performance compared with studies using a clinical cohort.[13,14]

The uncertain evidence for D-dimer in acute aortic syndrome led to a level C recommendation in the 2015 American College of Emergency Physician's clinical policy that D-dimer alone should not be used to exclude the diagnosis of aortic dissection.[15] Concurrently, the 2015 Academic Emergency Medicine consensus conference on developing a research agenda to optimize diagnostic imaging in the emergency department (ED) prioritized research to determine whether D-dimer can help improve the diagnostic yield or effectiveness of CTA for suspected thoracic aortic dissection.[16]

With important new evidence accumulating, we conducted a systematic review and meta-analysis of cohort studies on the diagnostic accuracy of D-dimer for acute aortic syndrome.[2,17-19]

MATERIALS AND METHODS

A systematic review was undertaken in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy statement and the guidelines published by Cochrane Screening and Diagnostic Test Methods Group.[20,21] This review was part of a larger Aortic Syndrome Evidence Synthesis project on Diagnostic strategies for suspected acute aortic syndrome and was registered on the International Prospective Register of Systematic Reviews database (CRD42022252121).[22]

Eligibility Criteria

We included all diagnostic cohort studies (prospective or retrospective) that assessed the use of D-dimer for diagnosing acute aortic syndrome compared with a reference standard test (eg, a definitive imaging modality such as CTA, ECG-gated CTA, echocardiography, and magnetic resonance angiography or confirmed/excluded by operation and autopsy). The study population of interest in our review consisted of people (any age) presenting to the ED with symptoms of acute aortic syndrome, including those with new-onset chest, back, or abdominal pain, syncope, or symptoms related to perfusion deficit. Studies including people with acute aortic syndrome following major trauma or as incidental findings were excluded. Studies using a case-control design (ie, studies in which patients were selected on the basis of the results of their reference standard test) were also excluded due to the potential for design-related bias, which tends to lead to an overestimation of diagnostic accuracy and are not generally representative of a test's accuracy in a clinical setting (a post hoc change).[13,23]

Data Sources and Searches

Several electronic databases, including MEDLINE (OvidSP from 1946), EMBASE (OvidSP from 1974), and the Cochrane Library (https://www.cochranelibrary.com), were searched from inception to February 2024 by an experienced information specialist (MC), who is a member of the research team. The search strategy used free text and thesaurus terms and combined synonyms relating to the topic of interest (eg, acute aortic syndrome and diagnostic strategies) with diagnostic testing terms (adapted Scottish Intercollegiate Guidelines Network filter for identifying diagnostic studies). Searches were supplemented by hand-searching the reference lists of all relevant studies (including existing systematic reviews), forward citation searching of relevant articles, contacting key experts in the field, and undertaking targeted searches of the World Wide Web using the Google search engine. No date or language restrictions were applied on any database. Further details on the search strategy can be found in Appendix E1 (available at http://www.annemergmed.com).

Study Selection

All titles were examined for inclusion by one reviewer (ME), and any citations that clearly did not meet the inclusion criteria (eg, nonhuman, unrelated to acute aortic syndrome) were excluded. All abstracts and full text articles were then examined independently by 2 reviewers (ME and AP). Any disagreements in the selection process were resolved through discussion or if necessary, arbitration by a third reviewer (SG) and included by consensus.

Data Extraction and Quality Assessment

Data relating to study design, methodological quality and outcomes were extracted by one reviewer (ME) into a standardized data extraction form and independently checked for accuracy by a second (AP). Any discrepancies were resolved through discussion to achieve agreement. Where differences were unresolved, a third reviewer's opinion was sought (SG). Where multiple publications of the same study were identified, data were extracted and reported as a single study.

The methodological quality of each included study was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool.[24] This instrument evaluates 4 key domains: patient selection, index test, reference standard, and flow and timing. Each domain is assessed in terms of risk of bias and concerns regarding the applicability of the study results (first 3 domains only). The subdomains about risk of bias include a number of signaling questions to help guide the overall judgment about whether a study is at high, low, or an unclear (in the event of insufficient data in the publication to answer the corresponding question) risk of bias. Appendix E2 (available at http://www.annemergmed.com) provides details of how these assessments were made.

Data Synthesis and Analysis

Indices of test performance were extracted or derived from data presented in each primary study. Two-by-two contingency tables of true-positive cases, false-negative cases, false-positive cases and true-negative cases were constructed and used to calculate the sensitivity and specificity for each study. We undertook meta-analysis to estimate the accuracy of D-dimer levels using a threshold set at 500 ng/mL, in accordance with previous meta-analyses that have identified this as the most commonly used threshold.[4-10] A sensitivity analysis was also undertaken and included any other eligible studies that did not report the 500 ng/mL threshold but reported accuracy for an alternative threshold.

The diagnostic data were analyzed using a bivariate random effects meta-analysis model.[25] The bivariate model preserves the 2-dimensional nature of the sensitivities and specificities and allows for correlation between them within studies. The random effects model takes into account heterogeneity between studies, which is generally expected in studies of diagnostic test accuracy.[21] We also used Deeks' funnel plot asymmetry test to assess publication bias in studies of diagnostic performance.[26] Further details of the statistical model used are provided in Appendix E3 (available at http://www.annemergmed.com).

All the analyses were conducted using Markov chain Monte Carlo simulations and implemented in the R software environment using Just Another Gibbs Sampler and rjags software packages.[27] Convergence to the target posterior distributions was assessed using the Gelman-Rubin convergence statistic.[28] A total 1,000,000 iterations with a burn-in of 100,000 and thinning of 10 were used to estimate the model parameters.

Results were presented as forest plots and scatter plots. Estimates of sensitivity and specificity with 95% credible intervals (CrIs, also known as Bayesian confidence intervals) were plotted to illustrate the variations among the synthesized studies. A 95% prediction interval (PrI) was reported to indicate the between-study heterogeneity and a range of values that might be expected in a future study.[29]

Patient and Public Involvement

Two representatives of the Aortic Dissection Charitable Trust (https://aorticdissectioncharitabletrust.org/) joined the Aortic Syndrome Evidence Synthesis project management team and helped to develop the study proposal. The findings of this review were presented at a webinar by SG for Aortic Dissection Charitable Trust members and sought their feedback on interpretation of the results.

RESULTS

Study Flow

Figure 1 summarizes the process of identifying and selecting relevant literature. Of the 2017 citations identified, 25 studies investigating D-dimer for suspected acute aortic syndrome met the inclusion criteria.[2,17-19,30-50] The majority of the articles were excluded primarily on the basis of an inappropriate target population (patients with acute aortic syndrome or not suspected acute aortic syndrome), intervention was not D-dimer, or an unsuitable publication type (ie, reviews, or abstract of full text studies). A full list of excluded studies with reasons for exclusion can be found in Appendix E4 (available at http://www.

annemergmed.com). More specifically, 10 case-control studies that reported comparisons to unselected controls with suspected acute aortic syndrome were excluded due to the high potential for bias.[13,23,51-60]

Study and Patient Characteristics

The design and patient characteristics of the 25 included studies are summarized in Table 1.[2,17-19,30-50] All studies were published between 2005 and 2023 and were undertaken in Asia (mainly China and Japan), Europe (mainly Italy and Germany), and North America.[2,19,30,31,33-37,39-42,44,45,48-50] Two studies were conducted across multiple countries.[43,47] Sample sizes ranged from 41 to 1,848 patients with the prevalence of acute aortic syndrome ranging from 0.9% to 64.8% and a weighted prevalence of 23.4%.[36,41,43,49] The mean age ranged from 53 to 63 years (not reported in 20 studies).[2,17-19,30-34,35,36-42,44,45,47,48,50]

Risk of Bias and Applicability Assessment

The overall methodological quality of the 25 included studies are summarized in Table 2 and Figure 2 (also see Appendix E5, available at http://www.annemergmed.com).[2,17-19,30-50] The methodological quality of the included studies was variable, with most studies having low or unclear risk of bias and applicability concerns in at least one item of the QUADAS-2 tool.

Risk of bias in patient selection was rated as low for studies reporting consecutive sampling and high for studies reporting convenience sampling. However, variation in the definition of the eligible population made judgments about patient selection difficult and may have influenced other quality criteria. The study by McLatchie et al[18] appeared to have much more inclusive eligibility criteria but was rated as having high risk of bias in flow and timing, principally due to a substantial portion of patients not receiving a reference test (imaging or follow-up). Here, 14 studies had at least one unclear risk of bias in the domain of index test

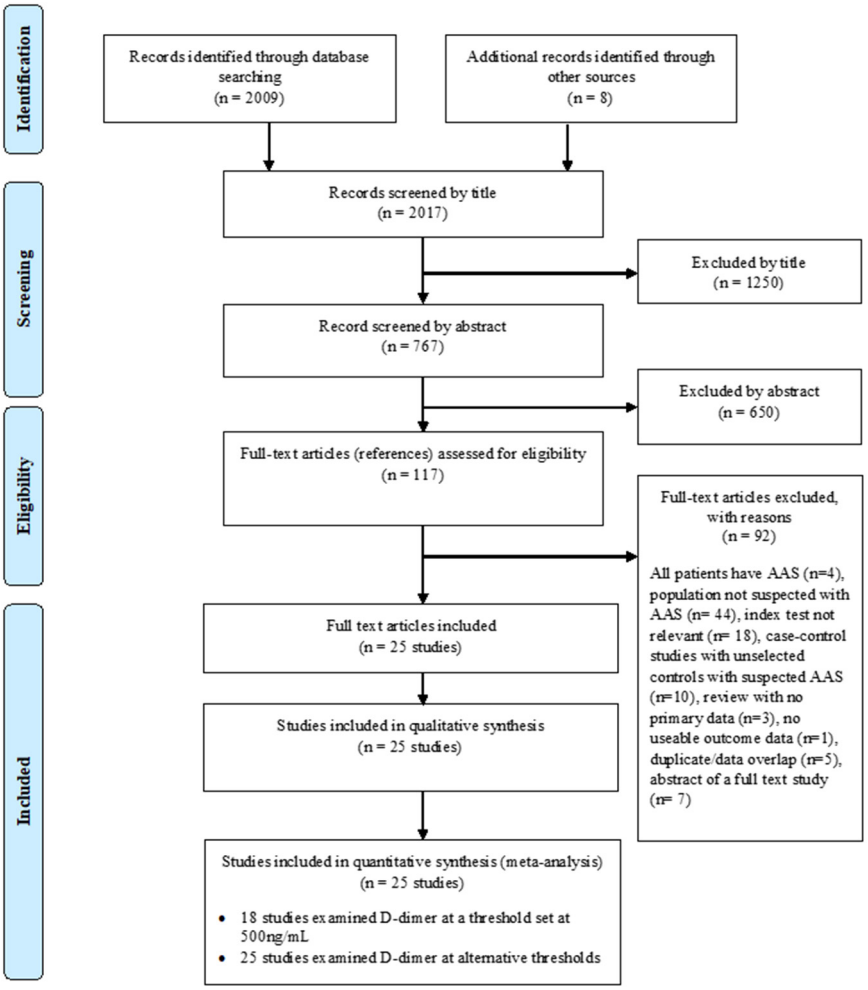

Figure 1. Study flow chart (adapted).

Table 1. Study and population characteristics.

Author, Y	Country/(Sites)	Population	Sample Size (N)	Mean Age (y)	Female	AAS or AAD	D-Dimer Cutoff Values (ng/mL)	Reference Standard
Akutsu et al,[30] 2005	Japan (1)	Suspected AAD	78	NR (median 68)	41.0%	38.5%	500	CT
Derksen et al,[31] 2018 (abstract)	USA (2)	Suspected AAD	91	NR	NR	7.7%	240	CTA
Ersel et al,[32] 2010	Turkey (1)	Suspected AAD	99	NR	36.4%	30.3%	246	CTA
Fan et al,[33] 2010[33]	China (1)	Suspected AAD	260	NR	28.5%	41.2%	260, 490, 790	TEE/TTE, CT and/or MRI
Giachino et al,[34] 2013	Italy (1)	Suspected AAD	126	NR	29.4%	41.3%	500	CT
Gorla et al,[35] 2017a	Germany (1)	Chest pain with suspected AAS	376	63	38.6%	22.6%	500	Imaging
Kodera and Kanda,[36] 2016 (abstract)	Japan (1)	Suspected AAD	162	NR	NR	64.8%	1000	Unspecified
Kotani et al,[37] 2017	Japan (1)	Chest pain with suspected AAS	887	NR	32.4%	13.9%	500	CT
Lee et a, l[17] 2022	South Korea (1)	Suspected AAS	204	NR (median 67)	39.7%	40.2%	500	CTA
Levcik et al,[38] 2013	Czech Republic (1)	Chest pain with suspected AAS	76	NR	50.0%	53.9%	500, 1000	CT, TEE, angiography, autopsy
Li et al,[39] 2010 (abstract)	China (1)	Suspected AAD	343	NR	NR	37.0%	500	CT
Li et al,[40] 2017	China (1)	Acute chest pain	790	NR	22.7%	25.6%	500	CTA
McLatchie et al,[18] 2023	UK (27)	Patients with symptoms potentially attributable to AAS	644	NR	NR	1.1%	500	CTA
Meng et al,[41] 2019	Canada (1)	Chest pain with suspected AAS	41	NR	NR	4.9%	500	CTA
Morello et al, [2] 2021	Italy (2)	Suspected AAS	443	NR (median 63)	33.3%	11.1%	500	CTA, TEE, MRA, surgery or autopsy
Nazerian et al,[42] 2014b	Italy (2)	Chest/back/abdominal pain, syncope, or perfusion deficit with suspected AAD	1035	NR	34.4%	22.5%	500	CTA
Nazerian et al,[43] 2018	Italy, Switzerland, Brazil, Germany (6)	Chest/back/abdominal pain, syncope, or perfusion deficit with suspected AAS	1848	62	37.7%	13.0%	500	CTA, TEE, MRA, surgery or autopsy; or 14-day clinical follow-up
Peng et al,[44] 2015	China (1)	Acute chest pain	76	NR	NR	46.1%	2110	CTA

Table 1. Continued.

Author, Y	Country/(Sites)	Population	Sample Size (N)	Mean Age (y)	Female	AAS or AAD	D-Dimer Cutoff Values (ng/mL)	Reference Standard
Spinner et al,[45] 2006	Germany (1)	Acute chest pain	82	NR	42.7%	31.7%	300	TEE, CT
Stanojlovic et al[46], 2013 (abstract)	Serbia (NR)	Suspected AAS	54	59	25.9%	59.3%	500	TTE, TEE, CT
Suzuki et al,[47] 2009	Europe, USA and Japan (14)	Suspected AAD	220	NR	34.1%	39.6%	500	Imaging
Wang et al[48], 2018	China (1)	Suspected AAD	333	53	31.2%	34.2%	323, 500	CT
Wilson et al,[49] 2016 (abstract)	USA (8)	Suspected AAD	220	56	57.0%	0.9%	500	CTA
Xue et al,[50] 2007	China (1)	Suspected AAD	43	NR	NR	37.2%	400	TEE, CT, and MRI
Zhang et al,[19] 2023	China (1)	Suspected AAS	697	NR	32.4%	46.3%	Youden's index: 0.51	CTA

AAS, acute aortic syndrome; *AAD*, acute aortic dissection; *CT*, computed tomography; *CTA*, computed tomography angiogram; *MRA*, magnetic resonance angiography; *MRI*, magnetic resonance imaging; *NR*, not reported; *TEE*, transesophageal echocardiography; *TTE*, transthoracic echocardiography.

or the reference standard due to a lack of clarity as to whether the reference standard results were interpreted without knowledge of the index test or vice versa.[30,31,35,36,38-41,45-50] The diagnostic cutoff values in most studies were preset, with the exception of 3 studies that calculated thresholds using a summary receiver operating curve analysis.[19,33,44] Although the majority of the studies used the general D-dimer cutoff value of 500 ng/mL, 8 studies used different thresholds, and 2 studies reported diagnostic accuracy using both 500 ng/mL and another cutoff value.[19,31-33,36,38,44,45,48,50] However, we decided that the 490 ng/mL threshold used by Fan et al[33] was unlikely to differ significantly from the 500 ng/mL threshold, so we included 18 studies with 7,978 participants in our meta-analysis to estimate the accuracy of D-dimer at a threshold set at 500 ng/mL, in accordance with existing reviews.[4-10]

The case mix of acute aortic syndrome was similar among studies that reported the data, with acute aortic dissection representing the most frequent subtype and intramural aortic hematoma or penetrating aortic ulcer accounting for most of the other cases. In general, 3 studies had high applicability concerns with patient selection, and 3 additional studies were considered to have unclear applicability concerns as details of the reference standard tests were not clearly specified.[35,36,41,45,47,48]

Diagnostic Performance of D-Dimer

The results of the meta-analysis are presented in Table 3. Figures 3 and 4A respectively show the forest plot and summary plot for the 18 studies reporting data for the 500 ng/mL threshold. The summary sensitivity (95% CrI) was 96.5% (94.8% to 98%), and the summary specificity (95% CrI) was 56.2% (48.3% to 63.9%). Sensitivity was generally high, the exception being the study of McLatchie et al[18] with sensitivity of 57% based on only 7 cases with acute aortic syndrome. Specificity varied markedly from 33% to 86%.[34,46] The pooled likelihood ratio for a positive test was 2.21 (95% CrI: 1.88 to 2.65), and the pooled likelihood ratio for a negative result was 0.06 (95% CrI: 0.04 to 0.09). The variance coefficients indicating statistical heterogeneity in sensitivities and specificities on the logit scale were estimated to be 0.42 (95% CrI 0.09 to 1.76) and 0.39 (95% CrI 0.18 to 0.93), respectively. The correlation coefficient (95% CrI) between logit sensitivity and specificity was −0.75 (-0.99 to -0.10). PrI provides a likely range for the true treatment effect in an individual study. The 95% PrI of sensitivity was 86.1% to 99.3%, suggesting moderate uncertainty in predicting the sensitivity of a new study. The 95% PrI of specificity was 25.3% to 83.1%, suggesting large uncertainty in predicting the specificity of a new study. The visual assessment of heterogeneity is also provided in

Table 2. QUADAS-2 quality assessment summary with review authors' judgments.

	Risk of Bias				Applicability Concerns		
Author, Y	**Patient Selection**	**Index Test**	**Reference Standard**	**Flow And Timing**	**Patient Selection**	**Index Test**	**Reference Standard**
Akutsu et al[30], 2005	LOW	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	LOW
Derksen et al[31], 2018 (abstract)	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	LOW
Ersel et al[32], 2010	UNCLEAR	LOW	LOW	UNCLEAR	LOW	LOW	LOW
Fan et al[33], 2010	UNCLEAR	HIGH	UNCLEAR	UNCLEAR	LOW	LOW	LOW
Giachino et al[34], 2013	LOW	LOW	UNCLEAR	LOW	LOW	LOW	LOW
Gorla et al[35], 2017a	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	UNCLEAR
Kodera and Kanda[36], 2016 (abstract)	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	UNCLEAR
Kotani et al[37], 2017	HIGH	LOW	LOW	UNCLEAR	LOW	LOW	LOW
Lee et al[17], 2022	UNCLEAR	LOW	UNCLEAR	LOW	LOW	LOW	LOW
Levcik et al[38], 2013	UNCLEAR	UNLEAR	UNCLEAR	UNCLEAR	LOW	LOW	LOW
Li et al[39], 2010 (abstract)	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	LOW
Li et al[40], 2017	LOW	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	LOW
McLatchie et al[18], 2023	HIGH	UNCLEAR	LOW	HIGH	LOW	LOW	LOW
Meng et al[41], 2019	HIGH	UNCLEAR	UNCLEAR	HIGH	HIGH	LOW	LOW
Morello et al[2], 2021	LOW	UNCLEAR	LOW	UNCLEAR	LOW	LOW	LOW
Nazerian et al[42], 2014b	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Nazerian et al[43], 2018	LOW	LOW	LOW	UNCLEAR	LOW	LOW	LOW
Peng et al[44], 2015	UNCLEAR	HIGH	UNCLEAR	LOW	UNCLEAR	LOW	LOW
Spinner et al[45], 2006	HIGH	UNCLEAR	UNCLEAR	HIGH	HIGH	LOW	LOW
Stanojlovic et al[46], 2013 (abstract)	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	LOW
Suzuki et al[47], 2009	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	UNCLEAR
Wang et al[48], 2018	HIGH	UNCLEAR	UNCLEAR	LOW	HIGH	LOW	LOW
Wilson et al[49], 2016 (abstract)	LOW	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	LOW
Xue et al[50], 2007	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	LOW
Zhang et al[19], 2023	LOW	HIGH	UNCLEAR	HIGH	LOW	LOW	LOW

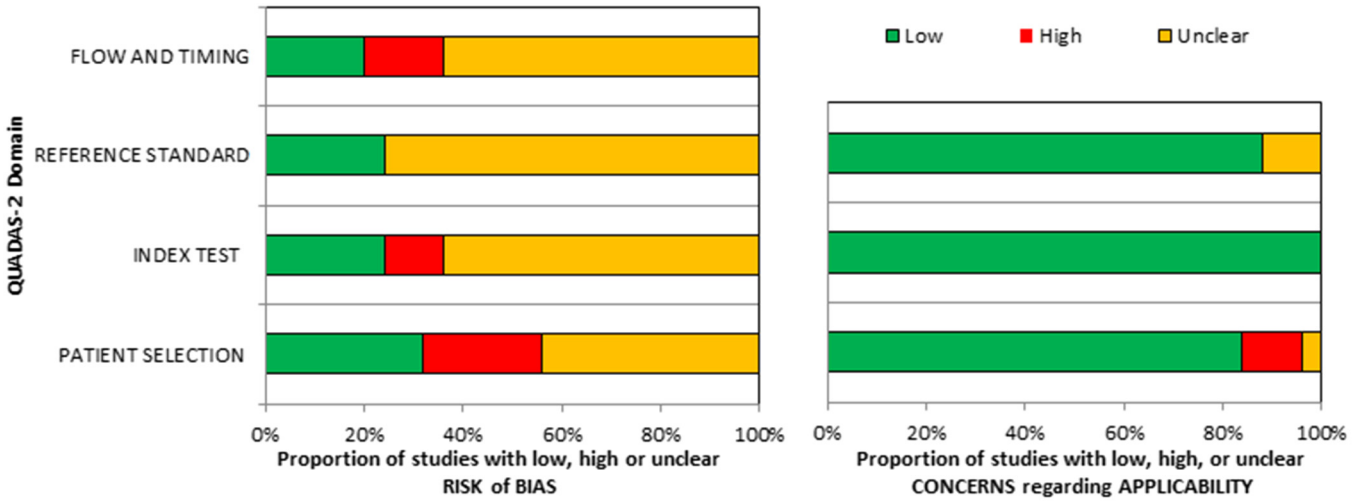

Figure 2. QUADAS-2 assessment summary graph with review authors' judgments.

Figure 4A through the predicted regions around the pooled estimates, which takes account of the variance of logit sensitivity and logit specificity as well as their correlations. Figures 5 and 4B show the forest plot and summary plot for the sensitivity analysis that included 7 additional studies that only reported D-dimer accuracy using an alternative to the 500 ng/mL threshold. The summary sensitivity (95% CrI) was 95.7% (93.2% to 97.5%), and the summary specificity was 57.5% (50.1% to 64.6%), suggesting that inclusion of studies with alternative thresholds did not markedly change the estimates of accuracy. The pooled likelihood ratio for a positive test was 2.25 (95% CrI: 1.93 to 2.68), and the pooled likelihood ratio for a negative result was 0.08 (95% CrI: 0.04 to 0.11). The variance coefficient indicating statistical heterogeneity in sensitivities and specificities on the logit scale were estimated to be 0.97 (95% CrI 0.42 to 2.48) and 0.48 (95% CrI 0.25 to 0.99), respectively. The correlation (95% CrI) between logit sensitivity and specificity was −0.57 (−0.85 to −0.09). The 95% PrI of sensitivity were 73% to 99.5%, suggesting moderate uncertainty in predicting the sensitivity of a new study. This result also suggests that studies included in the sensitivity analysis are more heterogeneous than the studies included with 500 ng/mL cutoff. The 95% PrI of specificity were 24% to 85.3%, suggesting large uncertainty in predicting the specificity of a new study. The visual assessment of heterogeneity is also provided in Figure 4B. through the predicted regions around the pooled estimates.

The Deeks' funnel plot test demonstrated no evidence of publication bias with P values >.05 for the main analysis (P=.78) and sensitivity analysis (P=.98). Further details are provided in Appendix E6 (available at http://www.annemergmed.com).

LIMITATIONS

The assessment of methodological quality was generally hampered by the poor quality of reporting in the included studies with the majority being classified as being at unclear risk of bias on most assessment domains. Patient selection on the basis of receiving definitive imaging for acute aortic syndrome may limit generalizability of findings to lower risk patients in whom D-dimer testing may be frequently used. Conversely, studies using clinical follow-up as an alternative to definitive imaging as a reference standard may miss acute aortic syndrome and overestimate sensitivity. Time delays between D-dimer measurement and performance of the reference standard may underestimate sensitivity. Exclusion of patients with suspected nonacute aortic syndrome pathology may overestimate specificity.

There was heterogeneity between the studies, especially in estimates of specificity, which increases the uncertainty around these estimates. This heterogeneity may reflect differences in study design, particularly patient selection and choice of reference standard or in population characteristics (as outlined above). Unfortunately, limited reported prevented meaningful explanation of whether study design or population characteristics (including age) could explain variation in estimates of diagnostic accuracy.

Although a number of abstracts were included in the current systematic review, differences often occur between data reported in conference abstracts and fully published articles; however, differences in results and effect estimates in meta-analyses are usually not very large.[61]

DISCUSSION

Our meta-analysis has shown that D-dimer has sensitivity of 96.5% and specificity of 56.2% for

Table 3. Pooled estimates from each analysis.

Strategy (N, n, Threshold)	Sensitivity (95% CrI) [95% PrI]	Specificity (95% CrI) [95% PrI]	Likelihood Ratio (95% CrI)	Variance for Logit Sensitivity and Specificity (95% CrI)	Correlation Coefficient Between Logit Sensitivity and Specificity (95% CrI)
D-dimer main analysis (N=18, n=7,978, 500 ng/mL)	96.5% (94.8%-98%) [86.1%-99.3%]	56.2% (48.3%-63.9%) [25.3%-83.1%]	LR+: 2.21 (1.88-2.65) LR−: 0.06 (0.04-0.09)	Sensitivity: 0.42 (0.09-1.76) Specificity: 0.39 (0.18-0.93)	−0.75 (−0.99 to −0.10)
D-dimer sensitivity analysis (N=25, n=9,228, 500 ng/mL or any other threshold used)*	95.7% (93.2%-97.5%) [73%-99.5%]	57.5% (50.1%-64.6%) [24%-85.3%]	LR+: 2.25 (1.93-2.68) LR−: 0.08 (0.04-0.11)	Sensitivity: 0.97 (0.42-2.48) Specificity: 0.48 (0.25-0.99)	−0.57 (−0.85 to −0.09)

CrI, Credible intervals; *LR+/LR−*; positive/negative likelihood ratio; *N*, number of studies; n, number of included patients; *PrI*, Prediction intervals.
*Any other D-dimer thresholds included the following: 240 ng/mL[31] 246 ng/mL,[32] 300 ng/mL,[45] 400 ng/mL[50] 1,000 ng/mL,[36] 2,110 ng/mL,[44] and the Youden's index=0.51.[19]

diagnosing acute aortic syndrome. This is similar to the diagnostic sensitivity of D-dimer for venous thromboembolism and suggests that D-dimer could have a similar role in ruling out acute aortic syndrome without imaging in a selected population with low but nonnegligible clinical probability of acute aortic syndrome (eg, 0.5% to 5%).[62]

We excluded case-control studies from our analysis due to the risk of design-related bias producing overestimation of diagnostic accuracy. The most recent meta-analysis of D-dimer for acute aortic syndrome included case-control studies and reported summary estimates of sensitivity and specificity of 96% and 70%, respectively.[10] The higher specificity may reflect design-related bias in the included case-control studies. An earlier meta-analysis by Asha et al[4] that was limited to cohort studies using the 500 ng/mL threshold reported sensitivity of 98% and specificity of 42%, but this was based on only 4 studies (1,557 participants).[30,33,42,47] Our main analysis was also limited to cohort studies using the 500 ng/mL threshold but included many additional studies published since 2015. Consequently, our review of 18 studies with 7,978 participants is the most robust and comprehensive to date.

The clinical implication of our analysis is that we now have sufficient data to estimate D-dimer accuracy for acute aortic syndrome and determine its role in diagnostic assessment, although uncertainties related to patient selection and risk of bias mean that recommendations for further research remain valid.[15,16] Using the 500 ng/mL threshold, D-dimer sensitivity is high but not perfect. Therefore, it may be used to rule out acute aortic syndrome in patients with a low clinical probability but should not delay imaging in those with high clinical probably. The modest specificity (56.5%) means that using D-dimer in patients with a very low clinical probability of acute aortic syndrome will produce a high false positive rate and may lead to overinvestigation. Clinical probability estimation is therefore crucial to using D-dimer in acute aortic syndrome diagnosis. The ADD-RS is the most widely validated structured method for estimating clinical probability of acute aortic syndrome and could be used to select patients for D-dimer testing.[11,12] However, it is not clear whether D-dimer is best targeted at low or moderate risk patients. European guidelines suggest using D-dimer in patients with a low risk of acute aortic syndrome, but this could lead to indiscriminate use of D-dimer in patients at negligible risk and a consequent increase in negative imaging. Canadian guidelines suggest using D-dimer in those with a moderate risk of acute aortic syndrome, but this may lead to missed acute aortic syndrome. Further research is required to determine how D-dimer is best used alongside

Study	TP	FP	FN	TN	Sens (95% CI)	Spec (95% CI)
Akutsu et al., 2005	30	22	0	26	1.00 (0.89–1.00)	0.54 (0.40–0.67)
Suzuki et al., 2009	84	71	3	62	0.97 (0.91–0.99)	0.47 (0.39–0.55)
Fan et al., 2010	104	52	3	101	0.97 (0.92–0.99)	0.66 (0.58–0.73)
Li et al., 2010	118	64	9	152	0.93 (0.87–0.96)	0.70 (0.64–0.76)
Giachino et al., 2013	41	41	1	20	0.98 (0.88–1.00)	0.33 (0.23–0.45)
Levcik et al., 2013	41	22	0	13	1.00 (0.91–1.00)	0.37 (0.23–0.54)
Stanojlovic et al., 2013	31	3	1	19	0.97 (0.84–0.99)	0.86 (0.66–0.95)
Nazerian et al., 2014b	229	514	4	288	0.98 (0.95–0.99)	0.36 (0.33–0.39)
Wilson et al., 2016	2	130	0	88	1.00 (0.34–1.00)	0.40 (0.34–0.47)
Gorla et al., 2017a	83	108	2	183	0.98 (0.92–0.99)	0.63 (0.57–0.68)
Kotani et al., 2017	119	436	4	328	0.97 (0.92–0.99)	0.43 (0.40–0.47)
Li et al., 2017	190	254	12	334	0.94 (0.90–0.97)	0.57 (0.53–0.61)
Nazerian et al., 2018	233	578	8	1029	0.97 (0.94–0.99)	0.64 (0.62–0.66)
Wang et al., 2018	100	39	14	180	0.88 (0.81–0.93)	0.82 (0.76–0.87)
Meng et al., 2019	2	19	0	20	1.00 (0.34–1.00)	0.51 (0.36–0.66)
Morello et al., 2021	48	162	1	232	0.98 (0.89–1.00)	0.59 (0.54–0.64)
Lee et al., 2022	80	49	2	73	0.98 (0.92–1.00)	0.60 (0.51–0.68)
McLatchie et al., 2023	4	248	3	389	0.57 (0.25–0.84)	0.61 (0.57–0.65)
Summary estimate (95% CrI)					0.97 (0.95–0.98)	0.56 (0.48–0.64)

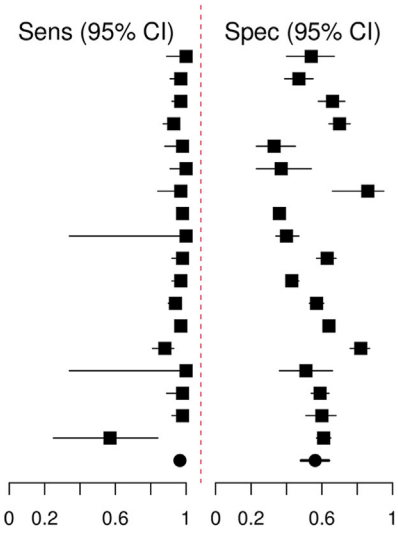

Figure 3. Forest plot for D-dimer main analysis at threshold 500 ng/mL (N=18).

clinical probability estimation to produce an appropriate trade-off between sensitivity and specificity. This may involve using decision-analytic modeling to weight the benefits of identifying acute aortic syndrome (true positives) against the harms and costs of overdiagnosis (false positives).[63]

Accumulating evidence now shows that using an age-adjusted D-dimer threshold can improve specificity when it is used to rule out pulmonary embolism.[64] We identified 2 studies reporting an age-adjusted thresholds suggesting a modest improvement in specificity compared to a fixed threshold in suspected acute aortic syndrome.[17,37] Further research, potentially using existing data sets, could determine whether an age-adjusted threshold for D-dimer is appropriate when used to rule out acute aortic syndrome.

In conclusion, D-dimer has 96.5% sensitivity and 56.2% specificity for acute aortic syndrome, suggesting a potential role in ruling out acute aortic syndrome in patients with a low but nonnegligible clinical probability. Further research, ideally a large multicenter study without selection bias, is required to determine how structured or gestalt clinical assessment can be used to identify an appropriate population for D-dimer testing and evaluate the effect of D-dimer testing on diagnosis and use of imaging. Conflicting results from previous meta-analyses

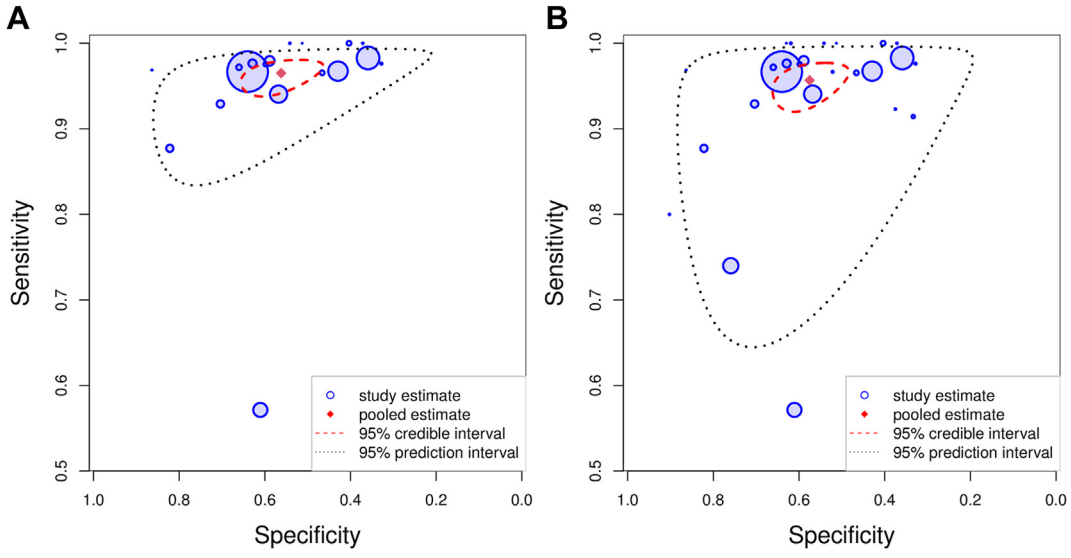

Figure 4. Summary plot for D-dimer. *A,* Main analysis (N=18). *B,* Sensitivity analysis (N=25).

Study	TP	FP	FN	TN	Sens (95% CI)	Spec (95% CI)
Akutsu et al., 2005	30	22	0	26	1.00 (0.89–1.00)	0.54 (0.40–0.67)
Spinner et al., 2006	24	35	2	21	0.92 (0.75–0.98)	0.38 (0.26–0.51)
Xue et al., 2007	16	10	0	17	1.00 (0.81–1.00)	0.63 (0.44–0.78)
Suzuki et al., 2009	84	71	3	62	0.97 (0.91–0.99)	0.47 (0.39–0.55)
Ersel et al., 2010	29	33	1	36	0.97 (0.84–1.00)	0.52 (0.40–0.63)
Fan et al., 2010	104	52	3	101	0.97 (0.92–0.99)	0.66 (0.58–0.73)
Li et al., 2010	118	64	9	152	0.93 (0.87–0.96)	0.70 (0.64–0.76)
Giachino et al., 2013	41	41	1	20	0.98 (0.88–1.00)	0.33 (0.23–0.45)
Levcik et al., 2013	41	22	0	13	1.00 (0.91–1.00)	0.37 (0.23–0.54)
Stanojlovic et al., 2013	31	3	1	19	0.97 (0.84–0.99)	0.86 (0.66–0.95)
Nazerian et al., 2014b	229	514	4	288	0.98 (0.95–0.99)	0.36 (0.33–0.39)
Peng et al., 2015	28	4	7	37	0.80 (0.64–0.90)	0.90 (0.77–0.96)
Kodera and Kanda, 2016	96	38	9	19	0.91 (0.84–0.95)	0.33 (0.22–0.46)
Wilson et al., 2016	2	130	0	88	1.00 (0.34–1.00)	0.40 (0.34–0.47)
Gorla et al., 2017a	83	108	2	183	0.98 (0.92–0.99)	0.63 (0.57–0.68)
Kotani et al., 2017	119	436	4	328	0.97 (0.92–0.99)	0.43 (0.40–0.47)
Li et al., 2017	190	254	12	334	0.94 (0.90–0.97)	0.57 (0.53–0.61)
Derksen et al., 2018	7	32	0	52	1.00 (0.65–1.00)	0.62 (0.51–0.72)
Nazerian et al., 2018	233	578	8	1029	0.97 (0.94–0.99)	0.64 (0.62–0.66)
Wang et al., 2018	100	39	14	180	0.88 (0.81–0.93)	0.82 (0.76–0.87)
Meng et al., 2019	2	19	0	20	1.00 (0.34–1.00)	0.51 (0.36–0.66)
Morello et al., 2021	48	162	1	232	0.98 (0.89–1.00)	0.59 (0.54–0.64)
Lee et al., 2022	80	49	2	73	0.98 (0.92–1.00)	0.60 (0.51–0.68)
McLatchie et al., 2023	4	248	3	389	0.57 (0.25–0.84)	0.61 (0.57–0.65)
Zhang et al., 2023	239	90	84	284	0.74 (0.69–0.78)	0.76 (0.71–0.80)
Summary estimate (95% CrI)					0.96 (0.93–0.98)	0.57 (0.50–0.65)

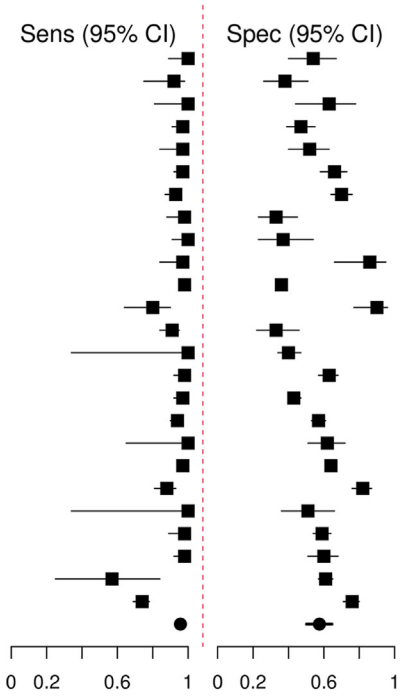

Figure 5. Forest plot for D-dimer sensitivity analysis including studies using 500 ng/mL or any other threshold (240 ng/mL, 246 ng/mL, 300 ng/mL, 400 ng/mL, 500 ng/mL, 1,000 ng/mL, 2,110 ng/mL, and Youden's index 0.51) (N=25).

probably reflect variable selection criteria and inclusion of case-control studies.

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