Systematic Review of Aortic Dissection Detection Risk Score Plus D-dimer for Diagnostic Rule-out Of Suspected Acute Aortic Syndromes

Paolo Bima, MD[1], Emanuele Pivetta, MD, PhD[1], Peiman Nazerian, MD[2], Mamoru Toyofuku, MD[3], Riccardo Gorla, MD, PhD[4], Eduardo Bossone, MD[5], Raimund Erbel, MD[6], Enrico Lupia, MD, PhD[1], and Fulvio Morello, MD, PhD[1]

ABSTRACT

Objectives: In patients at low clinical probability of acute aortic syndromes (AASs), decision on advanced aortic imaging is cumbersome. Integration of the aortic dissection detection risk score (ADD-RS) with D-dimer (DD) provides a potential pipeline for standardized diagnostic rule-out. We systematically reviewed and summarized supporting data.

Methods: Cross-sectional studies assessing integration of ADD-RS with DD for diagnosis of AASs were identified on MEDLINE, EMBASE and Web Of Science databases. Two reviewers independently screened articles, assessed quality, and extracted data. The quality of design and reporting was evaluated with the QUADAS-2 and STARD tools. Individual patient data were obtained, to allow analysis of both conventional (500 ng/mL) and age-adjusted ($DD_{age\text{-}adj}$) DD cutoffs. Data were summarized for four diagnostic strategies combining ADD-RS = 0 or ≤ 1, with DD < 500 ng/mL or < $DD_{age\text{-}adj}$. The statistical heterogeneity of the diagnostic variables was estimated with Higgins' I^2. Pooled values were calculated for variables showing nonsignificant heterogeneity.

Results: After screening of 680 studies, four articles (including a total of 3,804 patients) met inclusion criteria. One prospective study provided a low risk of bias/applicability concerns, while methodologic limitations were found in the other three retrospective studies. Statistical heterogeneity was negligible for sensitivity and negative likelihood ratio (LR) values and significant for specificity and positive LR values of all diagnostic strategies. Pooled sensitivity was 99.9% (95% confidence interval [CI] = 99.3% to 100%, I^2 = 0) for ADD-RS = 0 and DD < 500 ng/mL or < $DD_{age\text{-}adj}$, 98.9% (95% CI = 97.9% to 99.9%, I^2 = 0) for ADD-RS ≤ 1 and DD < 500 ng/mL, and 97.6% (95% CI = 96.3% to 98.9%, I^2 = 0) for ADD-RS ≤ 1 and DD < $DD_{age\text{-}adj}$.

From the [1]S.C.U. Medicina d'Urgenza, Molinette Hospital, A.O.U. Città della Salute e della Scienza, Torino, Italy; the [2]Department of Emergency Medicine, Careggi University Hospital, Firenze, Italy; [3]Wakayama Medical Center, Wakayama, Japan; the [4]Department of Clinical and Interventional Cardiology, IRCCS Policlinico San Donato, San Donato Milanese, Italy; the [5]Cardiology Division, Cardarelli Hospital, Napoli, Italy; and the [6]Institute for Medical Informatics, Biometry and Epidemiology, University Hospital Essen, University Duisburg-Essen, Essen, Germany.
Received December 17, 2019; revision received March 12, 2020; accepted March 16, 2020.
All authors except PB were authors of manuscripts reviewed in this systematic review. PB participated as study investigator in one study reviewed in this systematic review. PN reports grant money to conduct research from Università degli Studi di Firenze (16DPPN). FM reports grant money to conduct research from the Italian Ministry of Health (GR-2013-02355449, unrelated to the present work) and honoraria from Boehringer Ingelheim and Bayer for lectures and educational activities unrelated to the present work.
Supervising Editor: Chrisopher R. Carpenter, MD.
Author contributions: FM, PN, and PB conceived the study; PB and FM performed literature search and evaluated the manuscripts; PB, EP, and FM analyzed the data and drafted the manuscript; FM coordinated the study group and data collection; EP provided statistical supervision; and PN, MT, RG, EB, RE, and EL provided and analyzed patient-level data, reviewed data analyses, and contributed to manuscript revision.
Supervising Editor: Chrisopher R. Carpenter, MD.
Address for correspondence and reprints: Fulvio Morello, MD, PhD; e-mail fmorello@cittadellasalute.to.it.
ACADEMIC EMERGENCY MEDICINE 2020;27:1013–1027.

doi: 10.1111/acem.13969
ISSN 1553-2712

Conclusions: Despite methodologic limitations, integration of ADD-RS = 0 or ≤ 1 with DD < 500 ng/mL shows negligible heterogeneity and consistently high sensitivity across studies, thus supporting reliability for diagnostic rule-out of AASs. Data supporting ADD-RS = 0 plus $DD_{age\text{-}adj}$ appear preliminary and require further scrutiny.

Acute aortic syndromes (AASs) are deadly cardiovascular emergencies involving the thoracic aorta. They include acute aortic dissection, intramural aortic hematoma, penetrating aortic ulcer, and aortic rupture.[1] AASs represent unique diagnostic challenges because they are relatively rare diseases (4–6 cases/100,000 individuals/year), but their presenting symptoms are unspecific and frequent in emergency department (ED) visits. For instance, chest pain accounts for ~6% of ED visits (8-10 million visits/year in the United States), abdominal pain for ~6%, and syncope for ~2%.[2–5] Conclusive diagnosis requires advanced imaging techniques, mostly contrast-enhanced computed tomography angiography (CTA), but owing to radiation, contrast exposure and resource limitations, CTA cannot be performed in all patients with AAS-compatible symptoms.[6] Consequently, decision on advanced imaging for suspected AASs is cumbersome, as shown by substantial variability in CTA ordering within emergency physicians, high misdiagnosis rates (up to 39%), and low diagnostic efficiency (as low as 2% of CTA examinations turning out positive in North American series).[7–9]

For standardized clinical probability assessment of AASs, the reference tool indicated by guidelines is the aortic dissection detection risk score (ADD-RS), based on 12 risk factors organized in three categories (Data Supplement S1, Table S1, available as supporting information in the online version of this paper, which is available at http://onlinelibrary.wiley.com/doi/10.1111/acem.13969/full).[10,11] Using the ADD-RS, patients can be classified in three risk-categories (ADD-RS = 0 or low risk, ADD-RS = 1 or intermediate risk, ADD-RS > 1 or high risk) or in two risk categories (ADD-RS ≤ 1 or low probability, ADD-RS > 1 or high probability). In guidelines by the European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association, standardized probability assessment, in association with thorough physical examination, history collection, and clinical reasoning, designs a pipeline for standardized diagnostic evaluation of stable patients with suspected AASs. However, the ADD-RS does not substitute clinical reasoning and is not recommended by the American College of Emergency Physicians in isolation.[12]

D-dimer (DD), a fibrinogen degradation product well established for the rule-out of pulmonary embolism (PE), is also a highly sensitive and moderately specific biomarker of AASs.[13,14] The standard DD cutoff for AASs is 500 ng/mL. A key determinant of DD specificity is age, with a higher incidence of false-positive results in elderly patients. For PE rule-out, application of an age-adjusted DD ($DD_{age\text{-}adj}$) increases specificity and efficiency without affecting sensitivity.[15] Two studies have reported that also for AASs, $DD_{age\text{-}adj}$ may increase specificity with a small trade-off in sensitivity.[16,17] A single cutoff for PE and AASs could be very practical, as both conditions are invariably considered in differential diagnosis in patients with truncal pain and both imply decision on CTA.[18]

The rationale of integrating ADD-RS with DD testing is that very few cases of AASs are predicted to occur in patients with ADD-RS = 0 or ≤ 1 and a negative DD test result.[14,19] In this study, we aimed to provide a systematic review of studies evaluating the integration of ADD-RS with DD. For diagnostic variables with low statistical heterogeneity across studies, we aimed to determine pooled estimates. To also evaluate diagnostic bundles applying $DD_{age\text{-}adj}$, we obtained primary data from the investigators of the selected studies.

METHODS

Registration

The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) website, with CRD42019137508. This study followed PRISMA statement and the recommendations included in the Cochrane Handbook Accuracy and in the PRISMA-DTA statement.[20,21] Institutional review board ethical approval was not needed because of the reviewing nature of this study.

Search Strategy

In June 2019, we conducted a thorough online search on MEDLINE, EMBASE, and Web of Science databases. Detailed search strategies are presented in Table 1. We subsequently hand-searched the reference

Table 1
Detailed Database Search Strategies

Literature Database	Search Query
MEDLINE	((((“Aneurysm, Dissecting”[Mesh]) AND “Fibrin Fibrinogen Degradation Products”[Mesh]) OR (acute aortic syndrome AND D-dimer))) OR “Aortic Dissection Detection Risk Score”)
EMBASE	(('acute aortic syndrome'/exp OR 'acute aortic syndrome' OR 'aortic dissection'/exp OR 'aortic dissection') AND ('d dimer'/exp OR 'd dimer') OR 'aortic dissection detection risk score') NOT 'conference abstract':it NOT review:it NOT letter:it
Web of Science	TOPIC: ((“acute aortic syndrome” OR “aortic dissection” OR “dissecting aneurysm” OR “Aortic Dissection Detection Risk Score”) AND (“D-dimer” OR “Fibrin Degradation Product”))

lists of all articles identified in our searches and of systematic reviews and meta-analyses on this topic.

Inclusion/Exclusion Criteria

Two investigators independently reviewed the titles and abstracts of the studies to assess eligibility. The full-text article of the potentially eligible articles was next obtained to evaluate inclusion/exclusion criteria. Any disagreement was solved by consensus. The study design was gathered from Asha and Miers,[14] representing the reference meta-analysis for DD in AASs. Studies were included if: 1) they were original research primarily assessing integration of ADD-RS with DD for the diagnosis of AASs; 2) they were cross-sectional diagnostic studies; 3) prospective or retrospective enrollment was based on one or more AAS-compatible symptoms among chest pain, abdominal pain, back pain, syncope, perfusion deficit; 4) the ADD-RS was calculated; 5) the DD level was measured; 6) the diagnosis was confirmed or excluded with satisfactory criteria (advanced imaging with CTA, transesophageal echocardiography, magnetic resonance angiography, aortography, surgery or autopsy; in alternative, clinical case adjudication based on clinical data review and/or follow-up data); and 7) absolute numbers of true positive (TP), true negative (TN), false positive (FP), and false negative (FN) were reported or could be derived.

Studies were excluded if the design was case–control or case series due to high potential biases and the impossibility to calculate pretest probability.[22] Conference abstracts were excluded because they are not peer-reviewed, the results may not be final, and insufficient detail is provided for quality assessment.

Data Extraction and Analysis

The reporting of this systematic review follows the Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies (PRISMA-DTA checklist, provided as Data Supplement S1, Table S2).[21] Two reviewers extracted data independently from the selected articles. The extracted data included first author, date of publication, study period, number of study sites, study setting, study design, inclusion/exclusion criteria, number of participants analyzed and excluded, DD assay used, DD reference range, and reference standard used. They also extracted the study population characteristics (age, sex, time from symptom onset to evaluation); ADD-RS distribution; DD level; AAS subtype; alternative final diagnoses made for patients without AASs; and reporting the absolute number of TP, TN, FP, and FN.

Two investigators independently assessed the quality of study design using the QUADAS-2 tool and the quality of reporting using the STARD tool.[23,24] QUADAS-2 assessment was done in compliance with the original background document.[23] For the domain “patient selection,” we identified a high risk of bias if the sample was not consecutive, if the study was not done in the ED, if symptoms leading to patient inclusion did not include at least chest pain (representing the most common presenting symptom of AASs), and if patient enrollment was based on results of DD or advanced imaging and not on clinical presentation. For the domain “index test,” we identified a high risk of bias if the threshold of the index test was not prespecified or if the result of the index test was interpreted after applying the reference standard. For the domain “reference standard,” a high risk of bias was identified if patients were not subjected to advanced aortic imaging (CTA, transesophageal echocardiography, magnetic resonance angiography, or aortography), surgery, or autopsy. For patients not subjected to advanced imaging, surgery, or autopsy, case adjudication based on independent clinical data review and/or follow-up data was considered satisfactory. For the domain “flow and timing,” a high risk of bias was identified if studies included a significant (>5%) proportion of patients evaluated >14 days after symptom onset. Agreement between the reviewers was assessed with Cohen’s κ statistic. Types of diagnostic bias and

anticipated skews in observed sensitivity/specificity were evaluated according to Kohn et al.[22]

Based on clinical reasoning and previous evidence, we planned to analyze the DD test results based on two different cutoffs: 500 ng/mL and an age-adjusted cutoff (DD_{adj}).[18] For the latter, the DD result was interpreted as follows: in patients younger than 50 years, an AAS was excluded in those with a DD value lower than 500 ng/mL. In patients aged 50 years or older, the DD test result was considered negative in those with a DD value lower than their age multiplied by 10. Briefly, DD_{adj} (ng/mL) was calculated as age (years) × 10 ng/mL (with a minimum of 500 ng/mL).[15] To conduct an individual patient-level meta-analysis, the authors of all the selected studies were contacted to obtain missing data. For each study, a database was obtained reporting for each included patient, the age in years, the ADD-RS, the absolute DD level, and the final diagnosis.

In the meta-analysis, we analyzed the performance of the following integrated strategies for diagnostic rule-out of AASs (i.e., if string satisfied, rule-out AASs): 1) ADD-RS ≤ 1 and DD < 500 ng/mL; 2) ADD-RS ≤ 1 and DD < $DD_{age-adj}$; 3) ADD-RS = 0 and DD < 500 ng/mL; and 4) ADD-RS = 0 and DD < $DD_{age-adj}$. We built 2 × 2 contingency tables for each diagnostic strategy using the number of TP, FP, FN, and TN. For negative likelihood ratio (LR) values of strategies with a sensitivity of 100%, contingency tables with zero value were handled by adding a 0.5 continuity correction and the 95% CI was estimated using a bootstrapping approach.[25] The failure rate was calculated as FN/(FN + TN), i.e., number of patients with AASs satisfying rule-out criteria divided by the total number of patients satisfying rule-out criteria.[26] The rule-out efficiency was calculated as (TN + FN)/(TP + FP + TN + FN), i.e., number of patients ruled-out by each integrated strategy divided by total number of patients tested. Heterogeneity was determined using the Higgins' I^2. For variables showing nonsignificant heterogeneity, we calculated pooled values using fixed or random models as appropriate, based on inter- and intrastudy variability.

The Pauker and Kassirer decision threshold model was applied to calculate two theoretical thresholds: a testing threshold (i.e., the probability of AAS at which there is no difference between performing the test and withholding the treatment) and a test–treatment threshold (i.e., the probability of AAS at which there is no difference between performing the test and administering the treatment).[27] Statistical analysis was carried out using Stata 13.1.

RESULTS

Literature Search

Within 680 studies identified by the systematic database research, 12 studies were selected for full-text review (Figure 1) and four studies met all the inclusion criteria.[16,28–30] Three studies were designed to investigate the diagnostic test characteristics of ADD-RS plus DD < 500 ng/mL,[28–30] and one investigated the integration of ADD-RS with DD < $DD_{age-adj}$.[16] The study characteristics are summarized in Table 2 and the final diagnoses of the participant patients are detailed in Table S3. The case mix of AASs was similar among studies, with acute aortic dissection representing the most frequent subtype and intramural aortic hematoma or penetrating aortic ulcer accounting for most of the other cases. Some specificities were found in the study by Kotani et al.,[16] which included a larger number of patients with complicated aneurysms (ruptured/with impending rupture or infectious). This study also reflects the higher prevalence of intramural hematomas in Japan and Asia. The pooled prevalence of AASs (mean ± SD) across the four studies was 18.0% ± 5.3%, which is substantially higher than reported in North American ED series, but also substantially lower than in most diagnostic biomarker studies, including the first key prospective multicenter study of DD.[9,31–33] The pooled prevalence of "classic" acute aortic dissection was 67.3%, of intramural aortic hematoma was 18.7%, and of penetrating aortic ulcer was 6.8%. A higher observed prevalence of AASs than in general ED practice could lead to spectrum bias (falsely raising sensitivity).

The study by Nazerian et al.[30] was the only prospective multicenter study. Its primary aim was to define the failure rate of a diagnostic rule-out strategy integrating ADD-RS (= 0 or ≤ 1) with DD < 500 ng/mL. A secondary analysis applying $DD_{age-adj}$ has also been published.[17] In this trial, the criterion standards for case adjudication were conclusive aortic imaging (by CTA, transesophageal echocardiography, or magnetic resonance angiography), surgery, or autopsy. Enrollment preceded final decision on aortic imaging, and patients who were not subjected to any of these criterion standards during the ED visit were subjected to 14-day follow-up. Patients or family members were interviewed by telephone with a structured

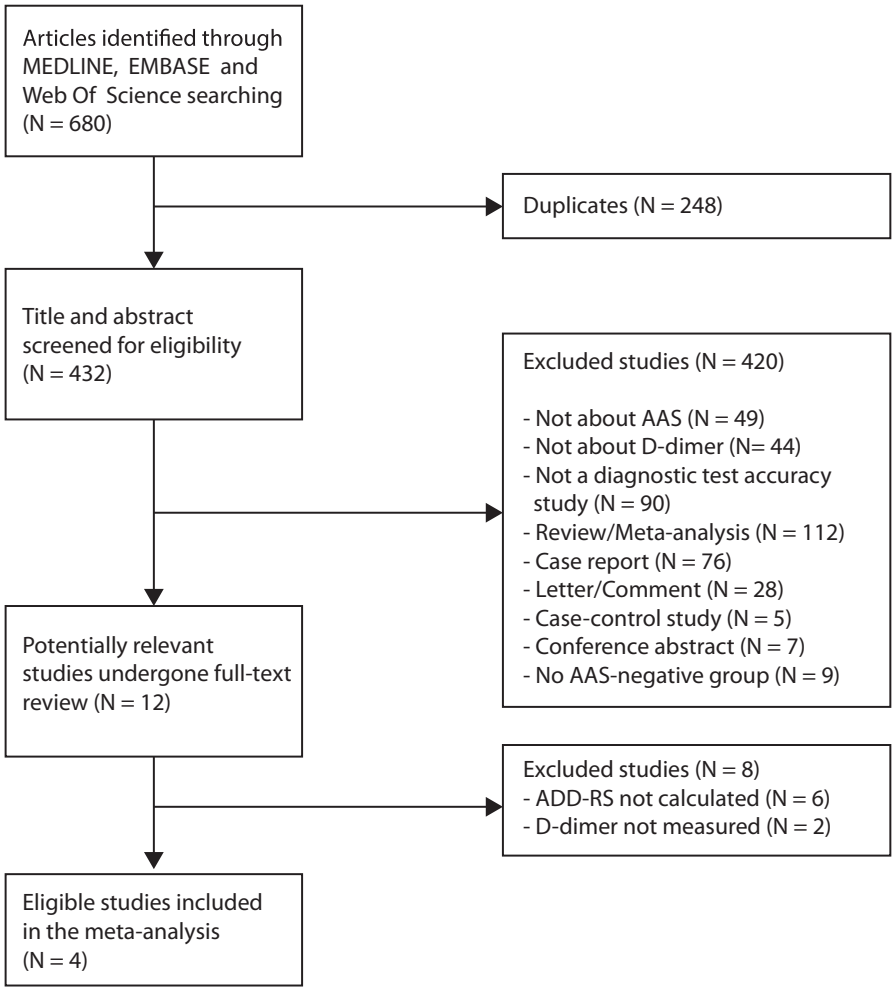


Figure 1. PRISMA flow diagram of study search and selection. AAS = acute aortic syndrome; ADD-RS = aortic dissection detection risk score.

questionnaire or underwent an outpatient visit after ED discharge, evaluating diagnosis of any aortic disease, subsequent ED visits, hospital admission, and death. Reviewers defining case adjudication had access to hospital charts and discharge documents. Criterion standard imaging was obtained during the index visit in 45% of patients, and during follow-up in 1.6% of patients. Patients dismissed from the ED and with a negative follow-up were 34.3%, potentially leading to differential verification bias, with a decrease in observed sensitivity and specificity. During follow-up, two patients were lost and three cases of AASs were diagnosed. Three patients died without advanced imaging or surgery. They all had a positive DD test result and therefore could not be regarded as potential FN cases.

The studies by Nazerian et al.,[28] Gorla et al.,[29] and Kotani et al.[16] were retrospective. In these studies, an exact time definition of symptoms triggering enrollment was not reported by the authors. This raises concern about the potential inclusion of patients with non-acute symptoms, in whom the chance of FN cases is higher. In the study by Nazerian et al.,[28] data were obtained from a registry of ED patients undergoing advanced aortic imaging for clinically suspected AAS. The study cohort largely overlapped with another study from the same groups that focused on validation of the ADD-RS per se.[34] For 29% of enrolled participants, a DD test result was not available, leading to patient exclusion. This could introduce partial verification bias (which could raise sensitivity), but the characteristics of the patients in the included and excluded groups were similar. A post hoc analysis showed that only 17 patients (1.6%) presented with history of pain >14 days; four of them had an AAS. One of these patients (symptoms for 15 days) had a normal DD. However, exact time data were missing for 39.2% of the enrolled patients.

In Gorla et al.,[29] patients were enrolled if they were admitted to the ED for chest pain and if they were

Table 2
Characteristics of Included Studies

	Nazerian, 2014[28]	Gorla, 2017[29]	Kotani, 2017[16]	Nazerian, 2018[30]
Study period	Jan 2008 to Mar 2013	Jan 2001 to May 2014	Jan 2011 to Apr 2014	Jan 2014 to Dec 2016
No. of study sites	2	1	1	6
Setting				
Country	Italy	Germany	Japan	United Kingdom, Switzerland, Germany, Italy
Hospital	Large referral	NR	Large referral	Large referral
Department	ED	ED	ED	ED
Participants, *n* (% of enrolled)	1,035 (71%)	376 (100%)	545 (61.4%)	1,848 (99.9%)
Participants excluded for unavailable index test, *n* (%)	420 (29%)	0 (0%)	66 (6.9%)	48 (2.5%)
AASs, *n* (% enroll.)	233 (22.5%)	85 (22.6%)	123 (13.9%)	241 (13%)
AD, *n* (% AAS)	199 (85.4%)	61 (71.8%)	47 (38.2%)	178 (73.9%)
IMH, *n* (% AAS)	31 (13.3%)	11 (12.9%)	42 (34.1%)	35 (14.5%)
PAU, *n* (% AAS)	3 (1.3%)	13 (15.3%)	8 (6.5%)	10 (4.1%)
Other, *n* (% AAS)	0	0	26 (21.1%)*	18 (7.5%)†
ADD-RS, *n* (% with AAS)				
0	322 (19, 5.9%)	189 (1, 0.5%)	75 (4, 5.3%)‡	437 (12, 2.7%)
1	508 (133, 26.2%)	130 (30, 23.1%)	399 (88, 22.1%)‡	1070 (96, 9.0%)
2–3	205 (81, 39.5%)	57 (54, 94.7%)	71 (24, 33.8%)‡	341 (133, 39.0%)
Study design	Prospective enrollment, retrospective analysis	Retrospective	Retrospective	Prospective
Inclusion criteria	Chest/back/abdominal pain, syncope or perfusion deficit + alt-D not established + clinical suspicion leading to CTA	Chest pain + DD available at presentation	Acute chest pain + admission to hospital + DD available	Chest/back/abdominal pain, syncope, or perfusion deficit + clinical suspicion
Exclusion criteria	NR	NR	Hemodynamic instability, STEMI, ED discharge, death in ED, referral to other hospital	Primary trauma, unwillingness or inadequacy to participate
Patient sampling	NR	NR	NR	Consecutive
Reference standard	CTA	Unspecified advanced imaging study	CTA	CTA, TEE, MRA, surgery or autopsy; if unavailable, 14-day clinical follow-up
Age (years), mean (±SD)	67 (±14)	63 (±12)	70 (±14)	62 (±12)
Male	66%	61%	63.4%	62.3%
Duration of symptoms (hours)	48 (7–96)‡§	NR	82% < 24 hours	7.5 (2-30)§
DD assay	HemosIL D-dimer HS, STA-Liatest D-Di	Innovance D-dimer	Liatest D-dimer, Hexamate D-dimer	HemosIL D-dimer HS, STA-Liatest D-Di, TriniLIA D-dimer, Innovance D-dimer
DD cutoff	<500 ng/mL	≤500 ng/mL	If age ≤ 50 years: < 500 ng/mL If age> 50 years: < (age × 10) ng/mL	<500 ng/mL
DD, test characteristics				
Sensitivity	98.3%	97.6%	96.0%	96.7%
Specificity	35.9%	63.2%	58.0%	64.0%

AAS = acute aortic syndrome; AD = aortic dissection; alt-D = alternative diagnosis; CTA = computed tomography angiography; IMH = intramural aortic hematoma; MRA = magnetic resonance angiography; NR = not reported; PAU = penetrating aortic ulcer; TEE = transesophageal echocardiography.
*Includes: ruptured aortic aneurysm (7.3%), impending rupture of aortic aneurysm (10.6%), infectious aortic aneurysm (3.2%).
†Includes only spontaneous (nontraumatic) rupture of thoracic aorta.
‡Original data provided by the authors for the present analysis and not included in the original manuscript.
§Values are reported as median (IQR).

Table 3
Assessment of Study Quality According to QUADAS-2[23]

	Risk of Bias				Applicability Concerns		
Study	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Nazerian, 2014[28]	L	L	L	U	L	L	L
Gorla, 2017[29]	H	L	U	U	L	L	U
Kotani, 2017[16]	H	L	L	L	L	L	L
Nazerian, 2018[30]	L	L	L	L	L	L	L

L = low-risk; H = high-risk; U = unclear.

subjected to a DD assay. These criteria could bias against atypical presentations not involving chest pain. The clinical judgment of the physician ordering DD was not recorded. Hence, PE and not AAS could have represented the chief differential diagnosis in some patients. Indeed, the rate of PE in this cohort was 14.5%, significantly higher than in the other studies. The authors declare that in study patients, CTA was used per guidelines, based on clinical judgment and on DD test result. All diagnoses of AASs were confirmed by advanced aortic imaging. Since the actual number of patients subjected to advanced imaging is unknown and clinical case adjudication was not based on a prespecified follow-up, observed sensitivity could be raised due to differential verification bias.

In the study by Kotani et al.,[16] patients were also enrolled if they presented with acute chest pain and if they received a DD assay. The exact time interval from symptom onset to sampling was not presented, and the DD assay was used per a prespecified hospital protocol not detailed in the article. The analysis was conducted only on patients admitted to hospital after the ED visit, while patients dismissed from the ED were excluded. This could lead to spectrum bias, raising sensitivity in the enrolled sample. Restriction to admitted patients potentially biases toward a more clinically severe population, while rule-out strategies ideally apply to patients in whom early ED discharge represents a meaningful option. However, the final prevalence of AASs was 13.9%, indicating adequate representation of low-probability patients. Additional exclusion criteria were ST elevation on ECG and hemodynamic instability. Both criteria are in line with ESC recommendations, as patients with these clinical characteristics are not amenable to rule-out criteria.[11] The DD assay was interpreted using the $DD_{age\text{-}adj}$ cutoff. As in Gorla et al., enrollment criteria focused on chest pain, excluding alternative clinical presentations and likely included patients with a clinical suspicion of PE and not only of AASs. However, the prevalence of PE was generally low (3.8%), while the prevalence of acute coronary syndromes was the highest, indicating potential bias toward coronary artery disease.

Quality Assessment

The quality assessment conducted using the QUADAS-2 is shown in Table 3 and in Data Supplement S1, Figure S1. For only one study, the judgment was "low" in all seven domains, indicating an overall low risk of bias and concern regarding applicability.[30] In one study, the judgment was "low" in three of seven domains.[29]

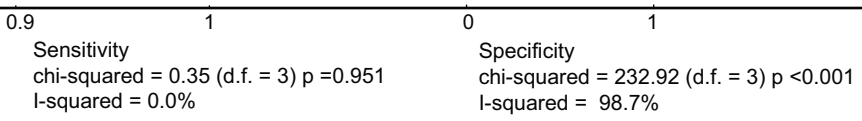
The quality of reporting of the included studies, analyzed according to the STARD 2015 statement, is detailed in Table S4. Most studies showed suboptimal quality regarding type of sample enrollment, how missing data on the index test and reference standard were handled, sample size calculation, whether any clinical intervention was done between the index test and the reference standard, study registration, and accessibility of the full protocol. The agreement between the reviewers for components of the study quality assessment tools was good ($\kappa = 0.67$, 95% CI = 0.54 to 0.80).[35]

Meta-analysis

A total of 3,804 patients were included in the meta-analysis, including 675 (17.7%) with AASs. To evaluate strategies integrating either the 500 ng/mL or the $DD_{age\text{-}adj}$ cutoff, individual patient-level data were used. Contingency tables and coupled forest plots were obtained (Figure 2). For all strategies, statistical heterogeneity was negligible for sensitivity ($I^2 = 0\%$) and significant for specificity values. Subanalyses excluding patients with ADD-RS = 0, shown in Data Supplement S1, Tables S5 and S6, indicated that results were not substantially affected by inclusion of patients at lowest pretest probability of AASs. Negative and positive LR values of the diagnostic strategies are

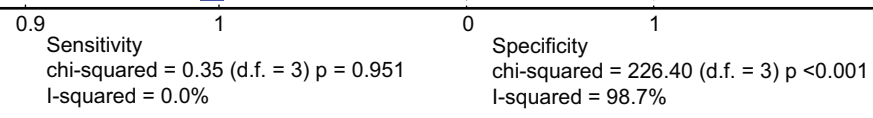
(a) ADD-RS =0 and D-dimer <500 ng/mL

Study	TP	FP	FN	TN	Sens plot	Sens (95% CI)	Spec plot	Spec (95% CI)
Nazerian, 2014	233	710	0	92		1.000 (0.984, 1.000)		0.115 (0.094, 0.139)
Gorla, 2017	85	164	0	127		1.000 (0.958, 1.000)		0.436 (0.379, 0.496)
Kotani, 2017	116	414	0	15		1.000 (0.969, 1.000)		0.035 (0.020, 0.057)
Nazerian, 2018	240	1314	1	293		0.996 (0.977, 1.000)		0.182 (0.164, 0.202)



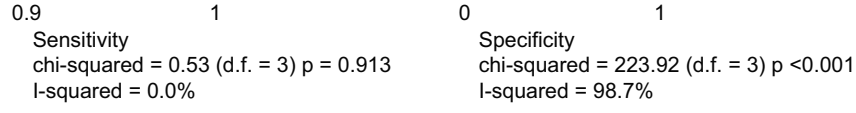
(b) ADD-RS =0 and D-dimer <$DD_{age\text{-}adj}$

Study	TP	FP	FN	TN	Sens plot	Sens (95% CI)	Spec plot	Spec (95% CI)
Nazerian, 2014	233	693	0	109		1.000 (0.984, 1.000)		0.136 (0.113, 0.162)
Gorla, 2017	85	157	0	134		1.000 (0.958, 1.000)		0.460 (0.402, 0.520)
Kotani, 2017	116	410	0	16		1.000 (0.969, 1.000)		0.044 (0.027, 0.068)
Nazerian, 2018	240	1290	1	317		0.996 (0.977, 1.000)		0.197 (0.178, 0.218)



(c) ADD-RS ≤1 and D-dimer <500 ng/mL

Study	TP	FP	FN	TN	Sens plot	Sens (95% CI)	Spec plot	Spec (95% CI)
Nazerian, 2014	231	560	2	242		0.991 (0.969, 0.999)		0.302 (0.270, 0.335)
Gorla, 2017	83	109	2	182		0.976 (0.918, 0.997)		0.625 (0.567, 0.681)
Kotani, 2017	115	275	1	154		0.991 (0.953, 1.000)		0.359 (0.314, 0.406)
Nazerian, 2018	238	686	3	921		0.988 (0.964, 0.997)		0.573 (0.549, 0.597)



(d) ADD-RS ≤1 and D-dimer <$DD_{age\text{-}adj}$

Study	TP	FP	FN	TN	Sens plot	Sens (95% CI)	Spec plot	Spec (95% CI)
Nazerian, 2014	226	518	7	284		0.970 (0.939, 0.988)		0.354 (0.321, 0.388)
Gorla, 2017	82	96	3	195		0.965 (0.900, 0.993)		0.670 (0.613, 0.724)
Kotani, 2017	114	234	2	195		0.983 (0.939, 0.998)		0.455 (0.407, 0.503)
Nazerian, 2018	236	595	5	1012		0.979 (0.952, 0.993)		0.630 (0.606, 0.653)

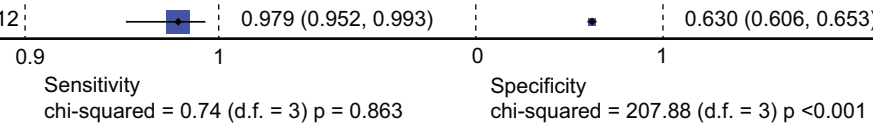


Figure 2. Contingency tables and coupled forest plots of sensitivity and specificity values. Heterogeneity was determined using the Higgins' I^2. ADD-RS = aortic dissection detection risk score; $DD_{age\text{-}adj}$ = age-adjusted D-dimer; FN = false negative; FP = false positive; TN = true negative; FP = false positive.

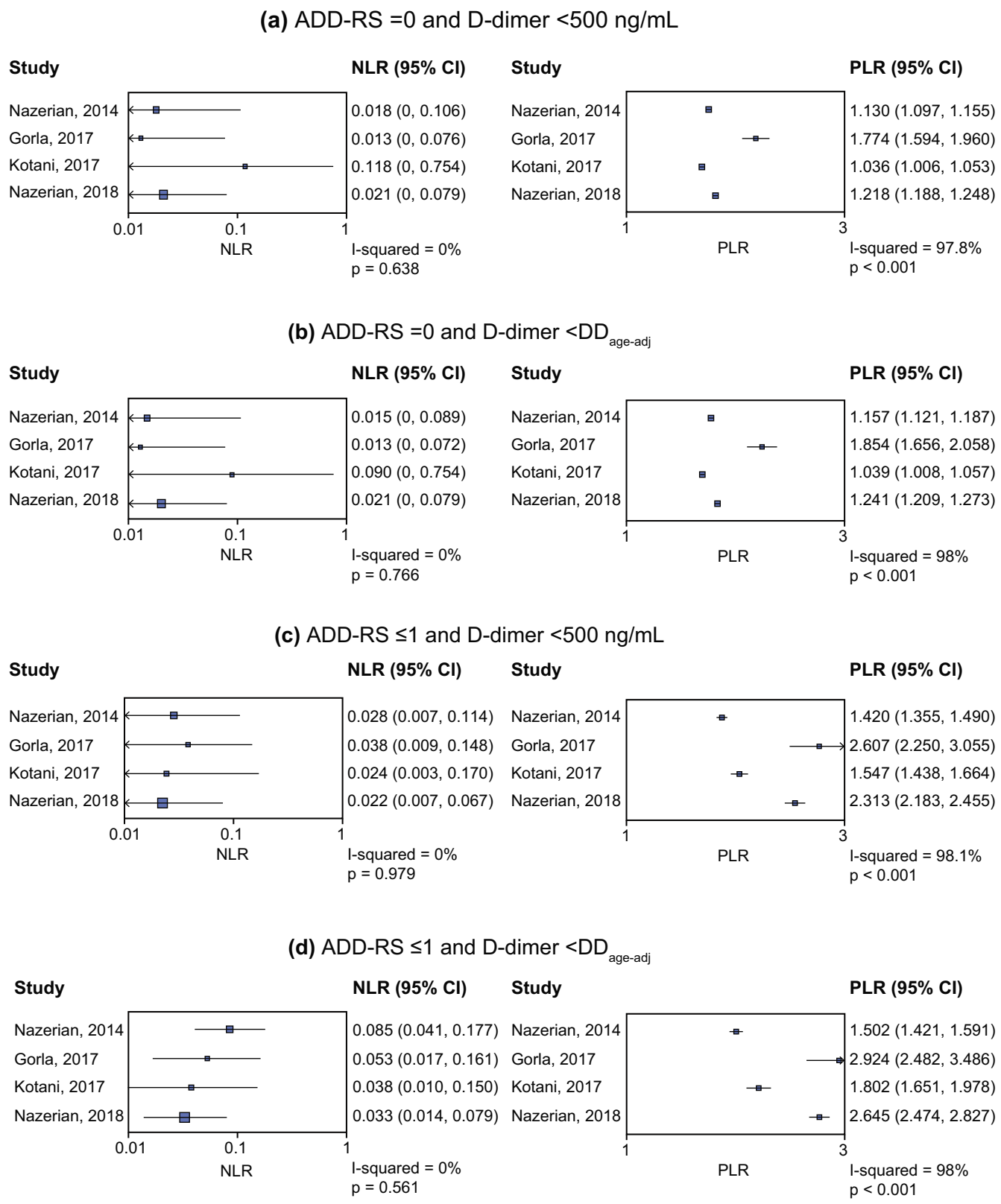


Figure 3. Forest plots of the negative and positive likelihood ratio values. Heterogeneity was determined using the Higgins' I^2. ADD-RS = aortic dissection detection risk score; $DD_{age-adj}$ = age-adjusted D-dimer; NLR = negative likelihood ratio; PLR = positive likelihood ratio.

shown in Figure 3. Heterogeneity was negligible for the negative LR (I^2 = 0%) and significant for the positive LR values of the diagnostic strategies.

Forest plots of failure rate and efficiency values are shown in Figures 4 and 5. Failure rate values had low to moderate heterogeneity for ADD-RS = 0 and

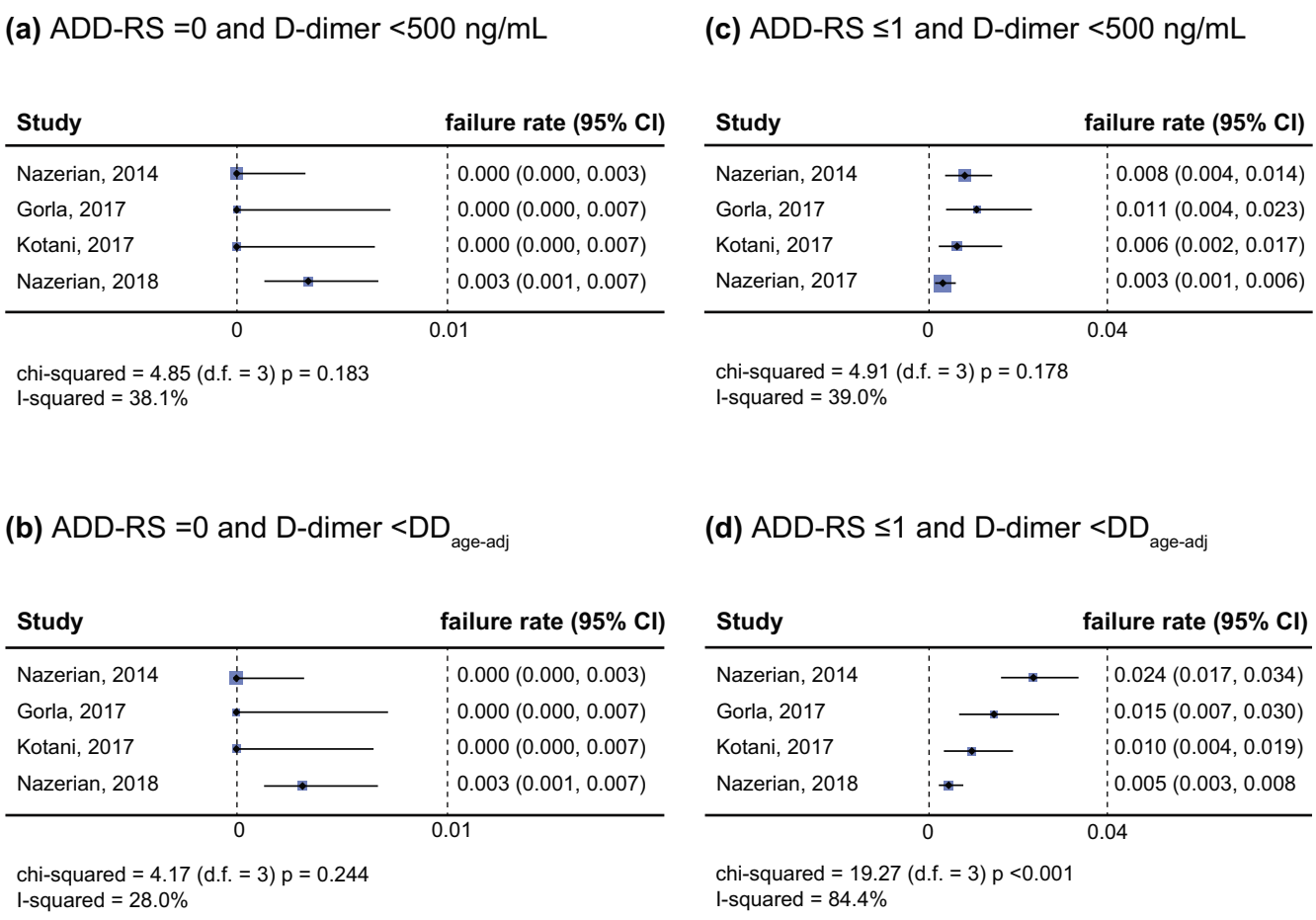


Figure 4. Forest plots of the failure rate values. Heterogeneity was determined using the Higgins' I^2. ADD-RS = aortic dissection detection risk score; $DD_{age\text{-}adj}$ = age-adjusted D-dimer.

DD < 500 ng/mL (I^2 = 38.1%), ADD-RS = 0 and DD < $DD_{age\text{-}adj}$ (I^2 = 28%), ADD-RS ≤ 1 and DD < 500 ng/mL (I^2 = 39%); heterogeneity was significant for ADD-RS ≤ 1 plus DD < $DD_{age\text{-}adj}$ (I^2 = 84.4%). Efficiency values had significant heterogeneity for all diagnostic strategies.

Pooled estimates of diagnostic variables underlying diagnostic rule-out (sensitivity, negative LR, and failure rate) and showing nonsignificant heterogeneity across studies are summarized in Table 4. Diagnostic variables showing high heterogeneity were not to reported, as limited inference on pooled values can be done. For ADD-RS = 0 and DD < 500 ng/mL, pooled sensitivity was 99.9% (99.3% to 100%), negative LR was 0.032 (0 to 0.086), and failure rate 0.1% (0% to 0.3%). For ADD = 0 and DD < $DD_{age\text{-}adj}$ sensitivity was 99.9% (99.3% to 100%), negative LR was 0.027 (0 to 0.081), and failure rate was 0.1% (0% to 0.2%). For ADD-RS ≤ 1 and DD < 500 ng/mL, sensitivity was 98.9% (97.9% to 99.9%), negative was LR 0.025 (0.001 to 0.049), and failure rate was 0.6% (0.2% to 0.9%). For ADD-RS ≤ 1 and DD < $DD_{age\text{-}adj}$, sensitivity was 97.6% (96.3% to 98.9%) and negative LR was 0.048 (0.022 to 0.074). For this strategy, pooled failure was not computed due to significant heterogeneity.

Test–Treatment Threshold

Test–treatment thresholds were calculated for diagnostic strategies including DD < 500 ng/mL (Figure S2). According to this model, the ADD-RS = 0 and DD < 500 ng/mL strategy should be performed if the clinical probability of AASs is between 1.7 and 23.2%, while the ADD-RS ≤ 1 and DD < 500 ng/mL strategy should be performed when the pretest probability is between 1.1 and 44.8%.

DISCUSSION

We provide a systematic review and summary of studies assessing integration of ADD-RS with DD for diagnosis of AASs. Only four papers satisfied the predefined inclusion criteria, underlying the relative

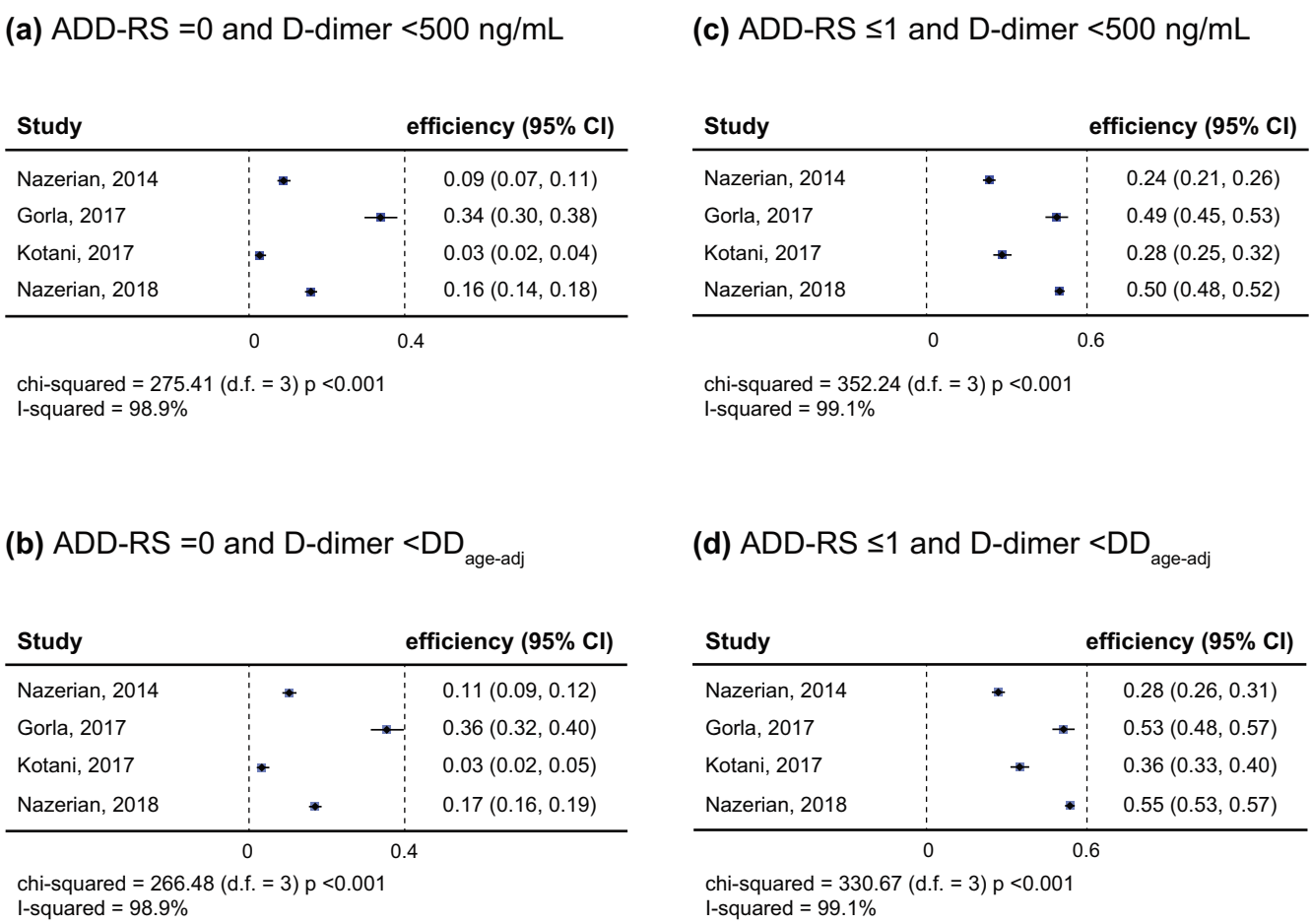


Figure 5. Forest plots of the efficiency values. Heterogeneity was determined using the Higgins' I^2. ADD-RS = aortic dissection detection risk score; $DD_{age\text{-}adj}$ = age-adjusted D-dimer.

Table 4
Pooled Estimates of Diagnostic Variables Underlying Diagnostic Rule-out

	Sensitivity (%, 95% CI)	Negative LR (95% CI)	Failure rate (%, 95% CI)
ADD-RS = 0 and DD < 500 ng/mL	99.9% (99.3%–100%)	0.032 (0-0.086)	0.1% (0%–0.3%) 1 in 1,000 (333–∞)
I-squared, p	0%, 0.95	0%, 0.64	38.1%, 0.18
ADD-RS = 0 and DD < $DD_{age\text{-}adj}$	99.9% (99.3%–100%)	0.027 (0-0.081)	0.1% (0%–0.2%) 1 in 1000 (500–∞)
I^2, p-value	0%, 0.95	0%, 0.77	28%, 0.24
ADD-RS ≤ 1 and DD < 500 ng/mL	98.9% (97.9%–99.9%)	0.025 (0.001–0.049)	0.6% (0.2%–0.9%) 1 in 167 (111–500)
I^2, p-value	0%, 0.91	0%, 0.98	39%, 0.19
ADD-RS ≤ 1 and DD < $DD_{age\text{-}adj}$	97.6% (96.3%–98.9%)	0.048 (0.022–0.074)	NA
I^2, p-value	0%, 0.86	0%, 0.56	84.4%, <0.001

ADD-RS = LR = likelihood ratio; NA = not applicable due to significant heterogeneity.

paucity of data. However, the total number of included patients was substantial (n = 3,804). All studies postdated the latest guidelines of the American Heart Association and the European Society of Cardiology, and only one (Nazerian et al.[28]) was cited in the latest clinical policy of the American College of Emergency Physicians.[11,12,36] One was a prospective multicenter trial, while the other three were retrospective studies. All were performed in the ED and mostly involved patients with chest pain, but inclusion criteria partly differed. This key limit reflects the absence of a standard definition of patients suspected of having AASs and amenable to rule-out strategies. Therefore, methodologic and clinical heterogeneity between available studies mandate caution in efforts to pool and summarize data.

Significant statistical heterogeneity was found for specificity, positive LR, and efficiency. This likely reflects differences in the clinical case mix of study cohorts. For these variables, data pooling could be misleading and were therefore omitted. AASs cases were instead homogenous across studies, thus leading to negligible statistical heterogeneity for sensitivity and negative LR values and allowing meaningful data pooling for these variables. Also in a previous meta-analysis of high-quality studies (which also included Nazerian et al.[28]), the heterogeneity was low for sensitivity and negative LR, and substantial for specificity and positive LR.[14]

Acquisition of primary data allowed us to evaluate diagnostic strategies incorporating also $DD_{age\text{-}adj}$, already in use for PE rule-out. When using ADD-RS = 0, $DD_{age\text{-}adj}$ provided pooled sensitivity and negative LR values similar to those of the "classical" 500 ng/mL cutoff. Instead, when using ADD-RS ≤ 1, DD < 500 ng/mL outperformed DD < $DD_{age\text{-}adj}$ in terms of pooled sensitivity and negative LR. These data suggest that DD < $DD_{age\text{-}adj}$ could be evaluated in further studies only if the pretest probability is presumed to be very low. $DD_{age\text{-}adj}$ might provide increased specificity over 500 ng/mL, but the statistical heterogeneity found across studies does not allow any conclusion.

Consensus is lacking on what should reproducibly define a clinical suspicion of AASs. Hence, differences between physicians and centers can be profound. In North American retrospective series of patients undergoing CTA for suspected AAS, the prevalence of AASs was ~3%.[8,37] In a vast out-of-hospital study evaluating the ADD-RS in nontraumatic emergencies, the prevalence of AASs was 0.9%.[38] In the studies reviewed herein, the prevalence of AASs was 13% to 23%. Application of rule-out strategies to patient populations at lower pretest probability of AASs is expected to result in lower failure rates, with a trade-off in efficiency.

Caution is needed when considering application of ADD-RS and DD based strategies in clinical practice. First, ADD-RS, a decision rule derived from a retrospective register of AASs, has low specificity.[37] In addition, ADD-RS derivation methods have not been published, and it is currently unknown whether use of the ADD-RS provides any advantage in terms of diagnostic accuracy and of CTA ordering, compared to clinical gestalt.[39,40] In the future, focused ED-centered studies may provide alternative and more specific probability assessment tools. Second, DD also lacks specificity. Therefore, indiscriminate application of ADD-RS and DD to unselected ED patients with AAS-compatible symptom(s) would paradoxically increase the number of CTA ordered. Such slippery slope must be avoided.[41]

Based on previous data, in terms of specificity, we speculate that the ADD-RS/DD rule-out pathway could best apply to stable patients with ADD-RS = 1 owing to clinical manifestations providing per se higher specificity (i.e., pulse deficit, neurologic deficit, aortic valve insufficiency).[42] Caution is needed in patients with hypotension, which also potentially defines clinical instability and might prompt toward a fast track for advanced imaging irrespective of DD test results. However, in clinical practice, most cases with ADD-RS = 1 will be driven by pain features (severe, sudden, ripping pain), providing higher sensitivity but lower specificity. To maximize benefits, a pragmatic approach could be to request DD only after three-dimensional evaluation of clinical history, physical examination, first-line imaging, and blood test results, in patients still lacking a clear alternative diagnosis or in whom rule-out of AASs is considered imperative for decision on hospital admission versus discharge or administration of anticoagulant/antiplatelet therapies, which could be harmful in presence of an AAS.

LIMITATIONS

Only one study (49% of patients) was judged to provide a low risk of bias/applicability concerns.[30] Two studies (42% of patients)[16,28] had issues in one of the QUADAS domains, and one study (10% of patients)

had a generally lower quality profile.[29] In one study, the case mix of AASs slightly differed, with fewer cases of acute aortic dissections and higher prevalence of the other forms.[16] Overall, the potential bias types most frequently encountered were: 1) partial verification bias, due to patients excluded because discharged from the ED or due to unavailable DD test result (leading to potential upward skew in sensitivity and downward skew in specificity), and 2) differential verification bias, due to inclusion of patients subjected to clinical follow-up without advanced aortic imaging (leading to potential downward skew in sensitivity and specificity). The accuracy of DD for diagnosis of AASs may also slightly differ among subtypes, with higher risk of false-negative cases in patients with intramural hematomas and focal dissections.[43,44] Therefore, methodologic and clinical heterogeneity between available studies mandate caution in data pooling and summarization.

A key issue affecting two studies (24% of patients) is that the authors selected patients with chest pain and a DD test result, potentially also introducing individuals with suspected PE.[16,29] In clinical terms, this aspect may be secondary, because both PE and AASs are typically considered in differential diagnosis, share DD as the key biomarker, and require CTA for conclusive diagnosis. A suspicion of AAS by the attending physicians was clearly defined in two studies (76% of patients) led by the same primary investigators.[28,30] This might limit external validity.

With the exception of the ADvISED trial, there was general uncertainty about the timing of the index test. Hence, a minority of patients with symptoms dating > 14 days were possibly enrolled, including few cases of AASs in their subacute or chronic phase. Since DD levels tend to decrease over time after development of AASs, this is expected to increase the number of patients with AASs presenting as FN (differential verification bias, with potential downward skew in estimates of sensitivity and failure rate).[45]

CONCLUSIONS

Only four studies have evaluated integration of aortic dissection detection risk score with D-dimer for diagnosis of acute aortic syndromes, with methodologic differences that must be carefully considered. However, the total number of included patients is reasonably large (n = 3,804), and negligible heterogeneity was found for sensitivity and negative likelihood ratio values. Available studies consistently show that aortic dissection detection risk score = 0 or ≤ 1 plus D-dimer < 500 ng/mL are highly sensitive diagnostic strategies and support their reliability for rule-out of acute aortic syndromes. For age-adjusted D-dimer, available data appear largely preliminary and further studies are required. Nonetheless, further prospective trials, especially in low-prevalence populations, are needed to confirm the results of this meta-analysis.

REFERENCES

1. Bossone E, LaBounty TM, Eagle KA. Acute aortic syndromes: diagnosis and management, an update. Eur Heart J 2018;39:739–49d.
2. Goodacre S, Cross E, Arnold J, Angelini K, Capewell S, Nicholl J. The health care burden of acute chest pain. Heart 2005;91:229–30.
3. Alshekhlee A, Shen WK, Mackall J, Chelimsky TC. Incidence and mortality rates of syncope in the United States. Am J Med 2009;122:181–8.
4. Amsterdam EA, Kirk JD, Bluemke DA, et al. Testing of low-risk patients presenting to the emergency department with chest pain: a scientific statement from the American Heart Association. Circulation 2010;122:1756–76.
5. Owens PL, Barrett ML, Gibson TB, Andrews RM, Weinick RM, Mutter RL. Emergency department care in the United States: a profile of national data sources. Ann Emerg Med 2010;56:150–65.
6. Klompas M. Does this patient have an acute thoracic aortic dissection? JAMA 2002;287:2262–72.
7. Hansen MS, Nogareda GJ, Hutchison SJ. Frequency of and inappropriate treatment of misdiagnosis of acute aortic dissection. Am J Cardiol 2007;99:852–6.
8. Lovy AJ, Bellin E, Levsky JM, Esses D, Haramati LB. Preliminary development of a clinical decision rule for acute aortic syndromes. Am J Emerg Med 2013;31:1546–50.
9. Ohle R, Anjum O, Bleeker H, Wells G, Perry JJ. Variation in emergency department use of computed tomography for investigation of acute aortic dissection. Emerg Radiol 2018;25:293–8.
10. Rogers AM, Hermann LK, Booher AM, et al. Sensitivity of the aortic dissection detection risk score, a novel guideline-based tool for identification of acute aortic dissection at initial presentation: results from the international registry of acute aortic dissection. Circulation 2011;123:2213–8.
11. Erbel R, Aboyans V, Boileau C, et al. 2014 ESC gon the diagnosis and treatment of aortic diseases: document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the

European Society of Cardiology (ESC). Eur Heart J 2014;35:2873–926.
12. Diercks DB, Promes SB, Schuur JD, Shah K, Valente JH, Cantrill SV. Clinical policy: critical issues in the evaluation and management of adult patients with suspected acute nontraumatic thoracic aortic dissection. Ann Emerg Med 2015;65:e12.
13. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 2014;35:69a–k.
14. Asha SE, Miers JW. A systematic review and meta-analysis of D-dimer as a rule-out test for suspected acute aortic dissection. Ann Emerg Med 2015;66:368–78.
15. Righini M, Van Es J, Den Exter PL, et al. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. JAMA 2014;311:1117–24.
16. Kotani Y, Toyofuku M, Tamura T, et al. Validation of the diagnostic utility of D-dimer measurement in patients with acute aortic syndrome. Eur Heart J Acute Cardiovasc Care 2017;6:223–31.
17. Morello F, Mueller C, Soeiro AM, et al. Response by Morello, et al. to letters regarding article, "Diagnostic Accuracy of the Aortic Dissection Detection Risk Score Plus D-Dimer for Acute Aortic Syndromes: The ADvISED Prospective Multicenter Study". Circulation 2018;138:448–9.
18. Suzuki T, Eagle KA. Biomarker-assisted diagnosis of acute aortic dissection. Circulation 2018;137:270–2.
19. Baez AA, Cochon L. Improved rule-out diagnostic gain with a combined aortic dissection detection risk score and D-dimer Bayesian decision support scheme. J Crit Care 2017;37:56–9.
20. Deeks JJ, Bossuyt PM, Gatsonis C. Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 1.0.0. 2013.
21. McInnes MDF, Moher D, Thombs BD, et al. Preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies: the PRISMA-DTA statement. JAMA 2018;319:388–96.
22. Kohn MA, Carpenter CR, Newman TB. Understanding the direction of bias in studies of diagnostic test accuracy. Acad Emerg Med 2013;20:1194–206.
23. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155:529–36.
24. Bossuyt PM, Reitsma JB, Bruns DE, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. BMJ 2015;351:h5527.
25. Marill KA, Chang Y, Wong KF, Friedman AB. Estimating negative likelihood ratio confidence when test sensitivity is 100%: a bootstrapping approach. Stat Methods Med Res 2017;26:1936–48.
26. van Es N, van der Hulle T, van Es J, et al. Wells rule and D-dimer testing to rule out pulmonary embolism: a systematic review and individual-patient data meta-analysis. Ann Intern Med 2016;165:253–61.
27. Pauker SG, Kassirer JP. The threshold approach to clinical decision making. N Engl J Med 1980;302:1109–17.
28. Nazerian P, Morello F, Vanni S, et al. Combined use of aortic dissection detection risk score and D-dimer in the diagnostic workup of suspected acute aortic dissection. Int J Cardiol 2014;175:78–82.
29. Gorla R, Erbel R, Kahlert P, et al. Accuracy of a diagnostic strategy combining aortic dissection detection risk score and D-dimer levels in patients with suspected acute aortic syndrome. Eur Heart J Acute Cardiovasc Care 2017;6:371–8.
30. Nazerian P, Mueller C, Soeiro AM, et al. Diagnostic accuracy of the aortic dissection detection risk score plus D-dimer for acute aortic syndromes: the ADvISED Prospective Multicenter Study. Circulation 2018;137:250–8.
31. Suzuki T, Distante A, Zizza A, et al. Diagnosis of acute aortic dissection by D-dimer: the International Registry of Acute Aortic Dissection Substudy on Biomarkers (IRAD-Bio) experience. Circulation 2009;119:2702–7.
32. Taylor RA, Iyer NS. A decision analysis to determine a testing threshold for computed tomographic angiography and D-dimer in the evaluation of aortic dissection. Am J Emerg Med 2013;31:1047–55.
33. Wang Y, Tan X, Gao H, et al. Magnitude of soluble ST2 as a novel biomarker for acute aortic dissection. Circulation 2018;137:259–69.
34. Nazerian P, Giachino F, Vanni S, et al. Diagnostic performance of the aortic dissection detection risk score in patients with suspected acute aortic dissection. Eur Heart J Acute Cardiovasc Care 2014;3:373–81.
35. Byrt T. How good is that agreement? Epidemiology 1996;7:561.
36. Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with Thoracic Aortic Disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. Circulation 2010;121:e266–369.
37. Ohle R, Anjum O, Bleeker H, McIsaac S. What is the specificity of the aortic dissection detection risk score in a low-prevalence population? Acad Emerg Med 2019;26:632–8.

38. Yamashita A, Maeda T, Kita Y, et al. The impact of prehospital assessment and EMS transport of acute aortic syndrome patients. Am J Emerg Med 2018;36:1188–94.
39. Hill JM, Murphy TG, Fermann GJ. Aortic dissection detection risk score: a clinical decision rule that needs some parenting. Acad Emerg Med 2019;26:695–7.
40. Smith LM, Miller CD. Acute aortic dissection: is there something better than physician gestalt? Acad Emerg Med 2018;25:464–6.
41. Fatovich DM. The inverted U curve and emergency medicine: overdiagnosis and the law of unintended consequences. Emerg Med Australas 2016;28:480–2.
42. Ohle R, Kareemi HK, Wells G, Perry JJ. Clinical examination for acute aortic dissection: a systematic review and meta-analysis. Acad Emerg Med 2018;25:397–412.
43. Ohlmann P, Faure A, Morel O, et al. Lower circulating Sta-Liatest D-Di levels in patients with aortic intramural hematoma compared with classical aortic dissection. Crit Care Med 2009;37:899–901.
44. Gorla R, Erbel R, Kahlert P, et al. Diagnostic role and prognostic implications of D-dimer in different classes of acute aortic syndromes. Eur Heart J Acute Cardiovasc Care 2017;6:379–88.
45. Eggebrecht H, Naber CK, Bruch C, et al. Value of plasma fibrin D-dimers for detection of acute aortic dissection. J Am Coll Cardiol 2004;44:804–9.

Supporting Information

The following supporting information is available in the online version of this paper available at http://onlinelibrary.wiley.com/doi/10.1111/acem.13969/full

Data Supplement S1. Supplemental material.

PennState Health
Emergency Medicine
Residency Program Director

Penn State Health Milton S. Hershey Medical Center is seeking an Emergency Medicine Residency Program Director to join our exceptional academic team located in Hershey, PA. This is an excellent opportunity to join an outstanding academic program with a national reputation and inpact the lives of our future Emergency Medicine physicians.

What We're Offering:

- Competitive salary and benefits
- Sign-On Bonus
- Relocation Assistance
- Leadership for Emergency Medicine Residency Program
- Comprehensive benefit and retirement options

What We're Seeking:

- MD, DO, or foreign equivalent
- BC/BE by ABEM or ABOEM
- Leadership experience
- Outstanding patient care qualities
- Ability to work collaboratively within a diverse academic and clinical environment

FOR MORE INFORMATION PLEASE CONTACT:

Heather Peffley, PHR CPRP
Physician Recruiter
Penn State Health

Email: hpeffley@pennstatehealth.psu.edu
Website: careers.pennstatehealth.org

What the Area Offers:

Located in a safe family-friendly setting, Hershey, PA, our local neighborhoods boast a reasonable cost of living whether you prefer a more suburban setting or thriving city rich in theater, arts, and culture. Known as the home of the Hershey chocolate bar, Hershey's community is rich in history and offers an abundant range of outdoor activities, arts, and diverse experiences. We're conveniently located within a short distance to major cities such as Philadelphia, Pittsburgh, NYC, Baltimore, and Washington DC.