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Accuracy of a diagnostic strategy combining aortic dissection detection risk score and D-dimer levels in patients with suspected acute aortic syndrome

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Abstract

Aims: The European Society of Cardiology recently proposed a novel diagnostic algorithm combining the aortic dissection detection (ADD) risk score with D-dimer level assessment for detecting acute aortic syndromes (AASs) in patients presenting with chest pain. The diagnostic accuracy of this strategy is yet to be validated.

Methods: We retrospectively identified 376 patients with chest pain and available D-dimer on admission to the emergency department of our institution between January 2011 and May 2014. The ADD risk score was calculated using retrospective blinded chart review. A score ⩽1 was defined as 'low probability', whereas a score >1 as 'high probability'. AASs were diagnosed in 85 (22.6%) patients.

Results: Patients with AAS more frequently had a 'high probability' score than AAS-negative patients (63.5% vs 1.0%; $P<0.001$). An ADD risk score ⩾1 had a sensitivity of 98.8% and a specificity of 64.6% for diagnosing AAS with a failure rate of 0.5%, whereas an ADD risk score ⩾2 had a sensitivity of 63.5% and a specificity of 98.9% with a failure rate of 9.7%. Among the patients with a 'low probability' score, D-dimer had a sensitivity and specificity for the detection of AAS, respectively, of 93.5% and 63.2%, with a negative predictive value of 98.9% and a failure rate of 1.1%.

Conclusions: A 'high probability' ADD score detected AAS with good specificity. A 'low probability' score combined with negative D-dimer safely and efficiently ruled out AAS with a low failure rate.

Keywords

D-dimer, aortic dissection detection risk score, acute aortic syndrome, acute aortic dissection, emergency department

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Introduction

Acute aortic syndromes (AASs) are considered among the most lethal cardiovascular diseases due to their high mortality within the first hours after symptom onset. Thus prompt diagnosis and appropriate therapeutic interventions are fundamental to enhance survival. However, given the low incidence (2.6 to 3.5 cases per 100,000 person-years)

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and the non-specific presenting symptoms and signs, AASs require a high clinical index of suspicion.[1,2] In this regard, the European Society of Cardiology (ESC) guidelines on aortic diseases proposed a novel diagnostic algorithm combining the aortic dissection detection (ADD) risk score with D-dimer (D-d) level assessment in order to detect AAS rapidly in patients presenting with chest pain.[3,4] The aim of our study was to validate the diagnostic performance of this new approach.

Methods

Patient selection and study population

This retrospective study included patients admitted for chest pain to the emergency department of the West German Heart and Vascular Center, Essen, Germany with available D-d levels at presentation, between January 2011 and May 2014. Among 522 patients in whom D-d levels were tested at admission, 376 (72%) had chest pain and constituted the study population. The standard data entry form included information on patient demographics, history, clinical presentations, physical findings, imaging study results and patients outcome, including mortality. Type A and B AAD, intramural haematoma (IMH) and penetrating aortic ulcer (PAU) were defined according to ESC guidelines on aortic diseases.[3]

Clinical risk score

The ADD clinical risk score encompassed 12 clinical risk markers classified into three categories (predisposing conditions, pain features and physical findings); the score was calculated based on the number of categories where at least one risk marker was present.[4]

Predisposing conditions were: history of Marfan syndrome or other connective tissue disease, family history of aortic disease, history of known thoracic aortic aneurysm and history of recent aortic manipulation.

Pain features were: abrupt onset of pain, severe pain intensity and a ripping or tearing quality of pain. In those reports where a pain scale was available, a value between 7 and 10 was considered as intense pain.

Physical findings were: pulse asymmetry or systolic blood pressure differential (>20 mmHg) between extremities, focal neurological deficit, new murmur of aortic regurgitation, shock state, or hypotension (systolic blood pressure <90 mmHg).

As stated in the ESC guidelines, an ADD risk score ≤ 1 was defined as 'low probability' whereas an ADD risk score >1 was defined as 'high probability'.[3]

D-dimer

For the quantification of D-d in sodium-citrate plasma, a microparticle-enhanced immunoassay using monoclonal antibody 8D3 (0.16 mg/l lower limit of normal; 0.5 mg/l, upper limit of normal; Innovance D-Dimer; Dade Behring, Marburg, Germany) was employed with a BCS coagulation analyser (Dade Behring, Marburg, Germany).

Statistical analysis

Continuous variables are presented as means ± standard deviation; categorical variables are presented as frequencies and percentages. Categorical variables were compared using the two-sided chi-square or, when appropriate, the two-sided Fisher's exact test. Comparison of normally distributed continuous variables between two groups was performed using the unpaired, two-sided Student's t-test.

The diagnostic performance of the ADD risk score was tested by computing sensitivity, specificity, negative and positive predictive value (NPV and PPV) in all patients. Failure rate was calculated as the number of patients with AAS and a negative test (ADD risk score or D-d) divided by all patients with a negative test (ADD risk score or D-d).

Receiver operating characteristic (ROC) analysis was used to determine the sensitivity and specificity of D-d at the cutoff value of 0.5 mg/l for the diagnosis of AAS. A value of $P<0.05$ was considered statistically significant. All statistical analyses were performed using the SPSS software package (version 21.0; SPSS, Chicago, IL, USA).

Results

Clinical characteristics of the study population

Of the 376 patients evaluated (mean age 63.1±12.1 years, 61.4% male), 85 (22.6%) had a final diagnosis of AAS; among them, 33 (38.8%) patients had type A AAD, 28 (32.9%) type B AAD, 13 (15.3%) PAU and 11 (12.9%) IMH. For these patients, inhospital mortality was 15.3% (13/85), while, according to the type of AAS, 10 deaths occurred in type A AAD (30.3%) and three in type B AAD (10.7%).

Of the 291 (77.3%) patients in which AAS was ruled out, 35 (12.0%) had stable angina pectoris, 19 (6.5%) acute coronary syndrome, 42 (14.5%) pulmonary embolism, 29 pleuritis (10.0%) and 166 (57.0%) musculoskeletal chest pain. Age and sex were not significantly different between the AAS and the non-AAS group (Table 1).

The prevalence of the ADD risk markers is reported in Table 1. Predisposing conditions, typical pain features and physical findings were most frequently observed in patients with AAS. Among the predisposing conditions, a family history of aortic disease, recent aortic manipulation and known thoracic aortic aneurysm occurred more frequently in patients with AAS than in AAS-negative patients. As for the pain features, abrupt onset, severe intensity and ripping/tearing pain were more frequently reported in patients with

Table 1. Patient demographics and prevalence of the aortic dissection detection risk markers.

	Overall (n=376; 100%)	AAS (n=85; 22.6%)	No AAS (n=291; 77.4%)	*P* value
Demographics				
Age (years)	63.1 ± 12.1	65.6 ± 12.0	62.3 ± 12.6	0.20
Male sex	231 (61.4%)	56 (65.9%)	175 (60.1%)	0.70
ADD risk markers				
Predisposing conditions	37 (9.8%)	28 (32.9%)	9 (3.1%)	<0.001
Marfan syndrome	3 (0.8%)	2 (2.4%)	1 (0.3%)	0.13
Family history of aortic disease	3 (0.8%)	3 (3.5%)	0 (0.0%)	0.01
Known aortic valve disease	2 (0.5%)	0 (0.0%)	3 (1.0%)	1.00
Recent aortic manipulation	13 (3.5%)	9 (10.6%)	4 (1.4%)	<0.001
Known thoracic aortic aneurysm	16 (4.3%)	15 (17.6%)	1 (0.3%)	<0.001
Pain features	173 (46.0%)	78 (91.8%)	95 (32.6%)	<0.001
Abrupt onset of pain	154 (41.0%)	69 (88.2%)	85 (29.2%)	<0.001
Severe pain intensity	119 (31.6%)	58 (68.2%)	61 (21.0%)	<0.001
Ripping or tearing pain	17 (4.5%)	17 (20.0%)	0 (0.0%)	<0.001
Physical findings	43 (11.4%)	40 (47.1%)	3 (1.0%)	<0.001
Pulse deficit or SBP differential	26 (6.9%)	26 (30.6%)	0 (0.0%)	<0.001
Focal neurological deficit	11 (2.9%)	11 (12.9%)	0 (0.0%)	<0.001
Murmur of aortic insufficiency	5 (1.3%)	4 (4.7%)	1 (0.3%)	0.002
Hypotension or shock state	11 (2.9%)	8 (9.4%)	3 (1.0%)	<0.001

AAS: acute aortic syndrome; ADD: aortic dissection detection; SBP: systolic blood pressure.

Table 2. Aortic dissection detection risk score in the study population.

ADD risk score	Overall (n=376; 100%)	AAS (n=85; 22.6%)	No AAS (n=291; 77.4%)
0	189 (50.3%)	1 (1.2%)	188 (64.6%)
1	130 (34.6%)	30 (35.3%)	100 (34.4%)
2	48 (12.8%)	45 (52.9%)	3 (1.0%)
3	9 (2.3%)	9 (10.6%)	0 (0.0%)
Low probability (score ⩽1)	319 (84.8%)	31 (36.5%)	288 (99.0%)
High probability (score >1)	57 (15.2%)	54 (63.5%)	3 (1.0%)

AAS: acute aortic syndrome; ADD: aortic dissection detection.

AAS than in those without AAS. Similarly, an increased rate of all the risk factors associated with the physical findings was observed in the AAS group.

ADD risk score

The results of the ADD risk score calculation are reported in Table 2. A score of 0 was found in 1.2% of AAS patients versus 64.6% of patients without AAS. On the contrary, a score of 2 or 3 was more frequently observed in patients with a final diagnosis of AAS (52.9% and 10.6%, respectively) compared to that observed in AAS-negative patients (1.0% and 0.0%, respectively), whereas there were similar rates of a score of 1 between the groups (35.3% and 34.4%, respectively) (Figure 1(a)).

Patients with AAS more frequently had a 'high probability' score as compared to those without AAS (63.5% vs 1.0%, respectively; $P<0.001$), whereas 99% of AAS-negative patients had a 'low probability' score (Figure 1(b)).

Interestingly, 36.5% (31/85) of AAS patients had a 'low probability' score (Figures 1 and 2).

For the detection of AAS, a ADD risk score ⩾1 was associated with good sensitivity (98.8%), NPV (99.5%) and failure rate (0.5%), but it had a low specificity (64.6%) and PPV (44.9%). On the other hand, by using an ADD risk score ⩾2 as the cutoff value, a significant improvement in specificity (98.9%) and PPV (94.7%) was observed, despite the worsening of sensitivity (63.5%), NPV (87.5%) and failure rate (9.7%) (Table 3).

D-dimer

D-d levels according to the different risk groups are presented in Table 4.

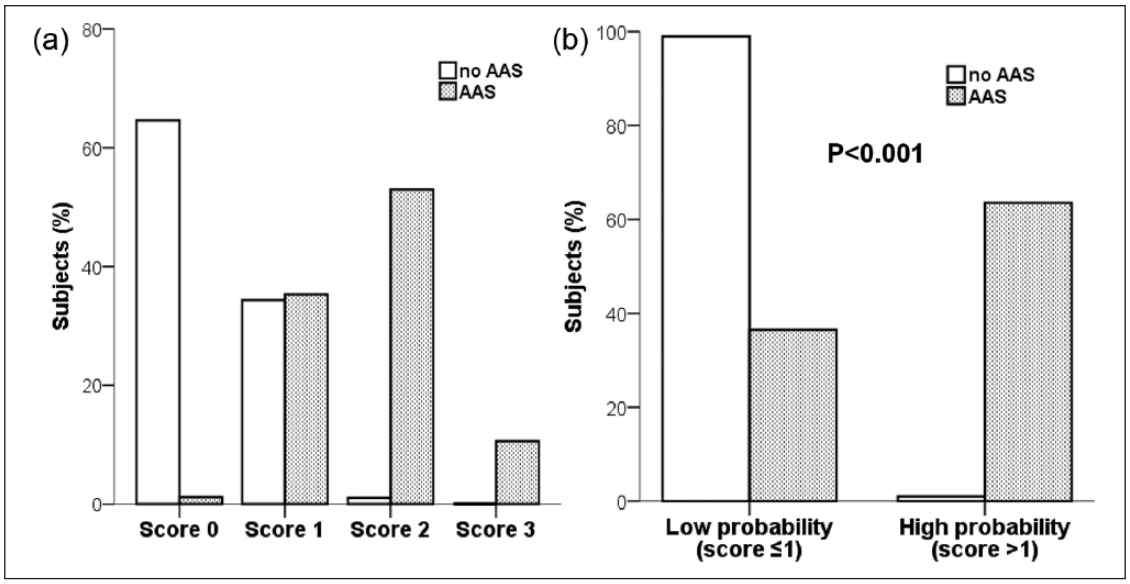

Figure 1. Prevalence of acute aortic syndrome (AAS) in the study population according to the aortic dissection detection risk score (a) and to the 'low vs. high probability' score classification (b).

Patients with AAS had higher D-d levels overall compared to AAS-negative patients (13.1±11.9 mg/l vs 1.9±5.0 mg/l, respectively; $P<0.001$). Moreover, according to the ADD risk score, patients with AAS having either a 'low probability' or a 'high probability' score showed significantly increased D-d levels compared to AAS-negative patients within the same risk group.

Interestingly, AAS patients with a 'high probability' score also had higher D-d levels than did AAS patients with a 'low probability' score as well (15.5±12.6 mg/l vs 8.9±9.3 mg/l, respectively; $P=0.012$) (Figure 3(a)).

Among the 31 patients with a final diagnosis of AAS despite a 'low probability' score, 29 had a positive D-d >0.5 mg/l (Figure 2). The two AAS patients who had negative results for both the ADD risk score and D-d were found to have PAU.

The diagnostic performance of D-d alone and combined with the ADD risk score is presented in Table 5.

The area under the curve (AUC) on ROC analysis was 0.91 (95% confidence interval (CI) 0.88–0.94; $P<0.001$) for D-d in all study patients (Figure 3(b)); at a cutoff level of 0.5 mg/l, D-d showed good diagnostic properties for the detection of AAS, with a sensitivity of 97.6%, specificity of 63.2%, NPV of 98.9% and failure rate of 1.1%.

In patients with an ADD risk score of 0, the D-d threshold of 0.5 mg/l had a sensitivity of 100% and a specificity of 67.5%, with a NPV of 100% and a failure rate of 0%. In patients with a 'low probability' score, we obtained a ROC curve with a AUC of 0.84 (95% CI 0.76–0.92; $P<0.001$) (Figure 3(c)); at a cutoff level of 0.5 mg/l, D-d showed a sensitivity of 93.5% and a specificity of 63.2%, with a NPV of 98.9% and a failure rate of 1.1%.

Discussion

We demonstrated that the ADD risk score, applied to patients presenting with chest pain, detects AAS in those with a 'high probability' score with a specificity of 98.9% and a PPV of 94.7%. However, the score had a failure rate of 9.7%, because 36.5% of patients with AAS had a 'low probability' score. In this group, the presence of a negative D-d efficiently ruled out AAS with a NPV of 98.9% and a failure rate of 1.1%.

There are only a few studies in the literature that investigated the sensitivity and specificity of the ADD clinical risk score.

Rogers et al. retrospectively calculated the ADD risk score in 2538 patients with AAD enrolled in the International Registry of Acute Aortic Dissection (IRAD). The authors reported a sensitivity of 95.7% and 59.2% for patients with a score ⩾1 and a score ⩾2, respectively, which was also confirmed in our study. However, the study did not provide any estimation of the specificity and did not consider the added diagnostic value of D-dimer testing.[5]

Nazerian et al. tested the sensitivity and specificity of the ADD risk score in 1328 patients with suspected AAD.[6] The authors observed that a score ⩾1 is highly sensitive (91.1%) but poorly specific (39.8%) for the diagnosis of AAS, whereas a score ⩾2 is poorly sensitive (32.7%) but highly specific (85.7%). In our study, we observed that of 57 patients with a 'high probability' score, 54 (94.7%) actually received a final diagnosis of AAS. This finding supports the pathway proposed in the flowchart of the ESC guidelines, which recommends in 'high probability' patients to perform transthoracic echocardiography and

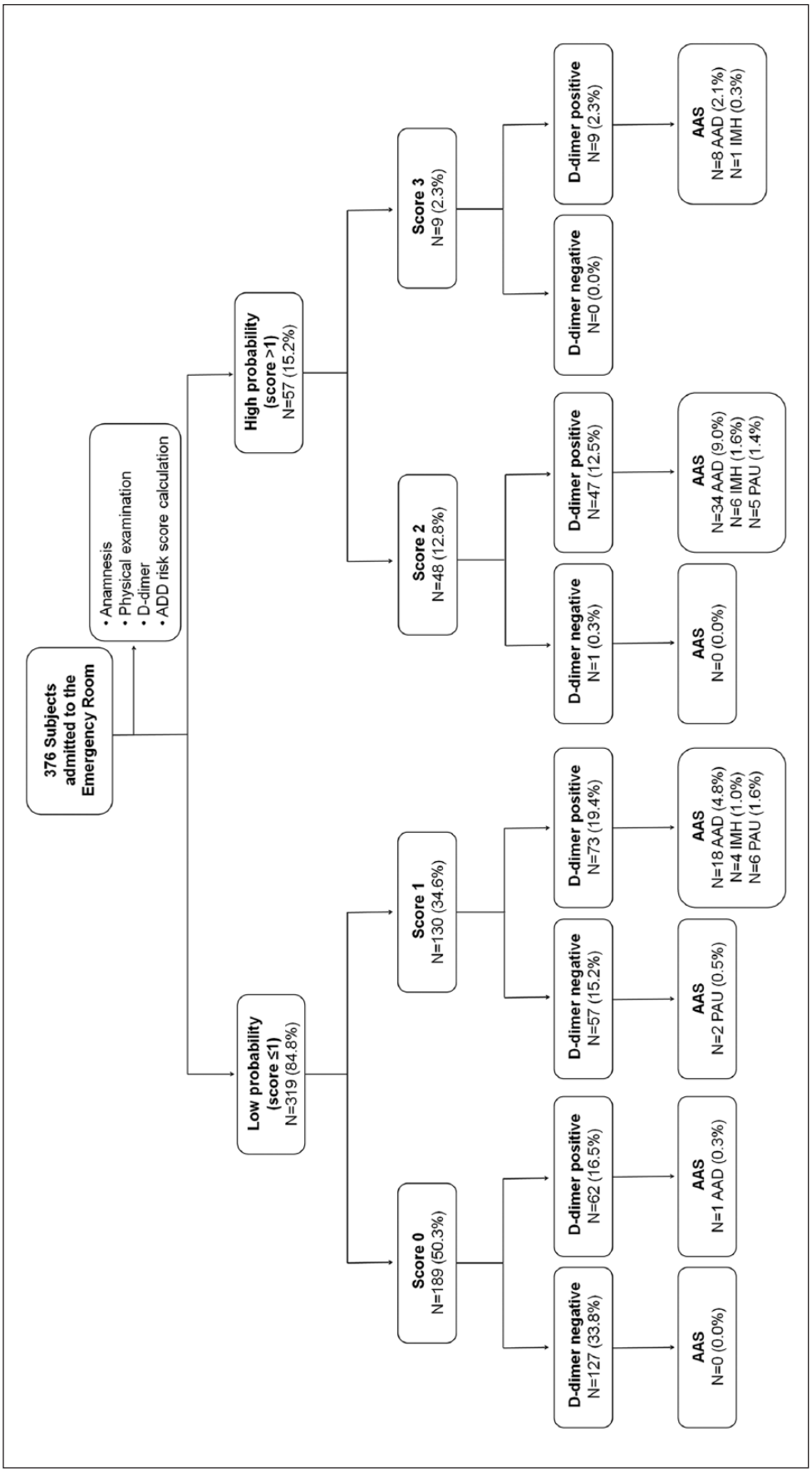

Figure 2. Flow diagram of the study. AAS: acute aortic syndrome; ADD: aortic dissection detection; IMH: intramural haematoma; PAU: penetrating aortic ulcer.

Table 3. Diagnostic performance of the aortic dissection detection risk score at a cutoff value of 1 or 2.

ADD risk score	Sensitivity	Specificity	PPV	NPV	Failure rate
⩾1	98.8%	64.6%	44.9%	99.5%	0.5%
⩾2	63.5%	98.9%	94.7%	87.5%	9.7%

ADD: aortic dissection detection; PPV: positive predictive value; NPV: negative predictive value.

Table 4. D-dimer levels according to the aortic dissection detection risk score.

ADD risk score	Overall (n=376; 100%)	AAS (n=85; 22.6%)	No AAS (n=291; 77.4%)	*P* value
All risk classes	4.4 ± 8.5	13.1 ± 11.9	1.9 ± 5.0	<0.001
0	1.7 ± 4.6	14.9[a]	1.7 ± 4.5	NA
1	3.8 ± 7.3	8.7 ± 9.4	2.4 ± 6.0	<0.001
2	14.8 ± 12.7	15.7 ± 12.6	1.2 ± 1.3	0.048
3	14.5 ± 13.6	14.5 ± 13.6	NA	NA
Low probability (score ⩽1)	2.6 ± 6.0	8.9 ± 9.3	1.9 ± 5.1	<0.001
High probability (score >1)	14.7 ± 12.7	15.5 ± 12.6	1.2 ± 1.3	<0.001

AAS: acute aortic syndrome; ADD: aortic dissection detection.
[a]This is a single value because there was only one patient in this group.

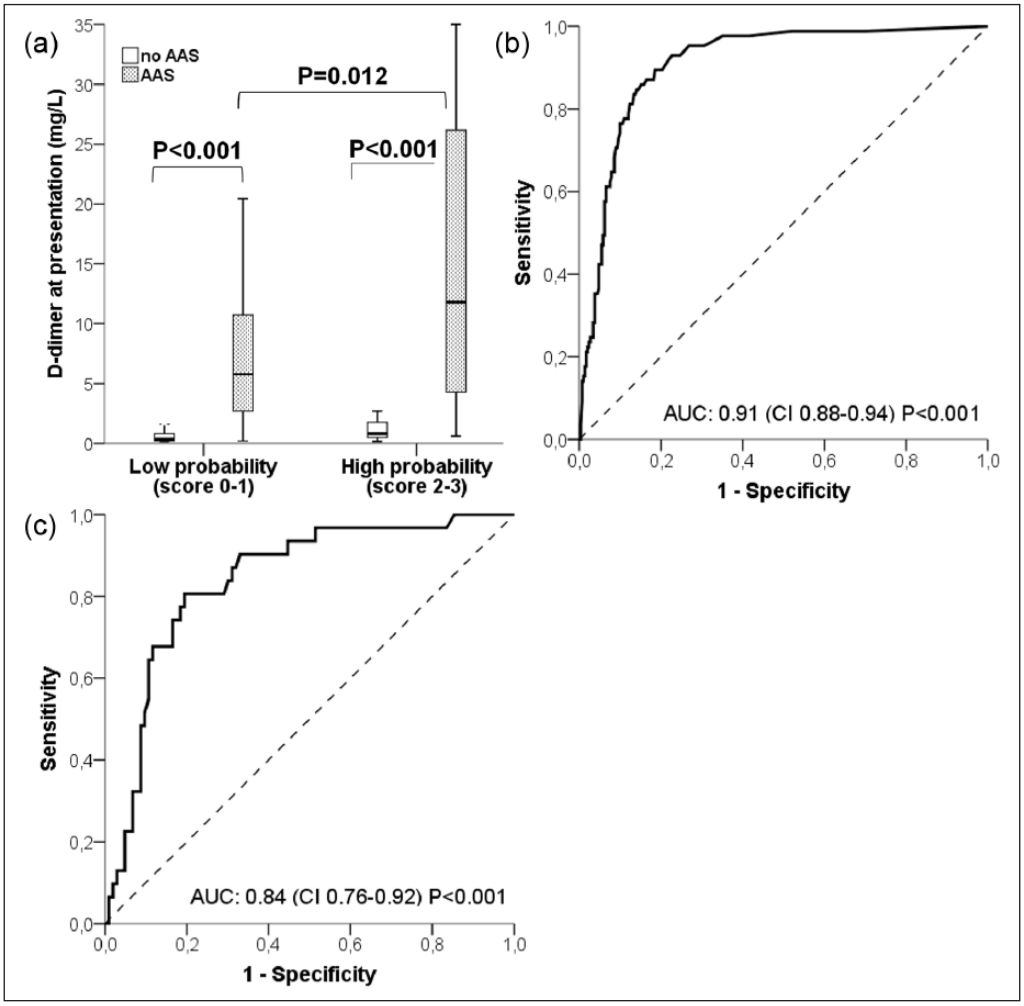

Figure 3. D-dimer (D-d) levels according to the presence of acute aortic syndrome (AAS) in patients with 'low' or 'high' probability aortic dissection detection (ADD) risk score (a); receiver operating curve analysis showing the diagnostic performance of D-d to detect AAS in all patients (b) and in those with a 'low probability' ADD risk score (c). AUC: area under the curve; CI: 95% confidence interval.

Table 5. Diagnostic performance of D-dimer at a cutoff value of 0.5 mg/l according to the aortic dissection detection risk score.

Patients	Sensitivity	Specificity	PPV	NPV	Failure rate
All	97.6%	63.2%	43.7%	98.9%	1.1%
Score 0	100%	67.5%	1.6%	100%	0%
Low probability (score ⩽1)	93.5%	63.2%	21.5%	98.9%	1.1%

PPV: positive predictive value; NPV: negative predictive value.

computed tomography or transoesophageal echocardiography without D-d testing.[3]

The role of D-d as a diagnostic biomarker for AAD is well established in the literature and has been thoroughly investigated in previous studies.[7–12] The largest study, involving 220 patients with a clinical suspicion of AAD, was carried out by Suzuki et al. and it reported a sensitivity of 97%, specificity of 47% and NPV of 97.6%.[13] These results were also confirmed in a recent meta-analysis, which reported in a pooled population of 734 patients a sensitivity of 96% and a specificity of 56%, with a NPV of 96%.[14] Our study seems to support this finding.

Nazerian et al. were the first to report the diagnostic performance for the combined use of the ADD risk score and D-d in patients with suspected AAD.[15] In patients with a 'low probability' ADD risk score ⩽1, they calculated for D-d a sensitivity of 98.7% and a specificity of 35.7%, with a PPV of 25.6%, a NPV of 99.2% and a failure rate of 0.8%. In our study, the sensitivity, PPV, NPV and failure rate were similar (93.5%, 21.5%, 98.9% and 1.1%, respectively). However, the specificity was substantially higher (63.2%) in our study, driven by a lower ratio between AAS-negative patients with a positive D-d and all AAS-negative patients (106/288, 36.8%), as compared to that in the study from Nazerian et al. (436/678, 64.3%). This could be explained by the older age of their population (67.3±14.3 vs 62.3±12.6), which may be responsible for an ageing-related increase of D-d levels.[16] Similarly, the selection of patients in whom D-d measurements are performed is another important aspect that should also be taken into account as a major determinant of specificity.

Therefore, D-d seems to play a pivotal role when assessed in individuals with a 'low probability' ADD risk score. Firstly, a negative D-d rules out AAS, owing to the excellent NPV; secondly, a positive D-d warrants further aortic imaging, which may lead to the detection of AAS in patients with an atypical presentation that would remain undetected on the basis of the ADD risk score alone.

However, D-d assessment may also have some pitfalls when applied to different classes of AAS. Ohlmann et al. observed that some patients with IMH may have a negative result to D-d testing, although our data do not seem to support this finding.[17]

However, in our study, two patients with a 'low probability' score and a negative D-d actually received a final diagnosis of PAU. It has yet to be clarified whether D-d levels also increase in this setting; it is possible that the degree of D-d release in PAU may differ greatly according to the size, depth and time course of the ulcer within the aortic wall, which can vary among patients.[18] Further studies are needed to address this issue fully.

There are several limitations to this study. Due to the retrospective design, 'available D-d at presentation' and 'chest pain' were the main search criteria used to select the study population, thus excluding atypical presentations of AAS. Moreover, the decision of whether to assess D-d levels was left to the clinical judgement of the treating physicians. Moreover, our findings should be interpreted in light of a 22.6% incidence of aortic pathology, which is higher than that reported in the literature.[3] Therefore, our results apply to a selected population in which there is a clinical suspicion of AAS or an alternative diagnosis is not immediately evident.

To overcome this limitation, we believe the ESC diagnostic flowchart should be validated in a multicentre prospective study involving larger cohorts of patients presenting to emergency departments with chest pain.

In summary, a combined approach using the ADD risk score and D-d assessment is of paramount importance in the diagnostic work-up to confirm or rule out AAS.

The ADD risk score detected AAS with good specificity and PPV in patients with a 'high probability' score. On the other hand, the combination of a negative D-d with a 'low probability' score safely and efficiently ruled out AAS with no need for further tests.

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Conflict of interests

The authors declare that there is no conflict of interest.

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