The Diagnosis of Acute Aortic Syndrome in the Emergency Department (DAShED) Study: An observational cohort study of people attending the Emergency Department with symptoms consistent of Acute Aortic syndrome

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The Diagnosis of Acute Aortic Syndrome in the Emergency Department (DAShED) Study: An observational cohort study of people attending the Emergency Department with symptoms consistent of Acute Aortic syndrome.

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Text abstract and keywords

The Diagnosis of Acute Aortic Syndrome in the Emergency Department (DAShED) Study: An observational cohort study of people attending the Emergency Department with symptoms consistent of Acute Aortic syndrome.

Abstract

Background: The diagnosis of acute aortic syndrome (AAS) is commonly delayed or missed in the ED. We describe characteristics of ED attendances with symptoms potentially associated with AAS, diagnostic performance of CDTs and physicians, and yield of CTA.

Methods: This was a multi-centre observational cohort study of adults attending 27 UK EDs between 26/09/2022 and 30/11/2022, with potential AAS symptoms: chest, back or abdominal pain, syncope or symptoms related to malperfusion. Patients were preferably identified prospectively, but retrospective recruitment was also permitted. Anonymised, routinely collected patient data including components of CDTs, was abstracted. Clinicians treating prospectively identified patients were asked to record their perceived likelihood of AAS, prior to any confirmatory testing. Reference standard was radiological or operative confirmation of AAS. 30-day electronic patient record follow-up evaluated whether a subsequent diagnosis of AAS had been made and mortality.

Results: 5548 patients presented, with a median age of 55 years (IQR 37-72; n=5539). 14 (0.3%; n=5353) had confirmed AAS. 10/1046 (1.0%) patients in whom the ED clinician thought AAS was possible had AAS. 5/147 (3.4%) patients in whom AAS was considered the most likely diagnosis had AAS. 2/3319 (0.06%) patients in whom AAS was considered not possible did have AAS. 540 (10%; n=5446) patients underwent CT, of which 407 were CTA (7%). 30-day follow-up did not reveal any missed AAS diagnoses. AUROC curve for ED clinician AAS likelihood rating was 0.958 (95% CI 0.933-0.983, n=4006) and for individual CDTs were: ADD-RS 0.674 (0.508-0.839, n=4989), AORTA 0.689 (0.527-0.852, n=5132), Canadian 0.818 (0.686-0.951, n=5180) and Sheffield 0.628 (0.467-0.788, n=5092).

Conclusion: Only 0.3% of patients presenting with potential AAS symptoms had AAS but 7% underwent CTA. CDTs incorporating clinician gestalt appear to be most promising, but further prospective work is needed, including evaluation of the role of D-dimer.

(294 / 300 words)

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Keywords: Acute Aortic Syndrome, D-dimer, Aorta, Dissection, Emergency, Diagnosis

Key messages:

***What is already known on this topic*:** ED diagnosis of AAS is a substantial challenge and many patients do not receive timely diagnosis and treatment. Over-investigation with too low a threshold for CT scanning of the thoracic aorta cannot be the solution. There is little research in truly undifferentiated ED populations, or in non-North American populations with different thresholds for CT and most previous studies of AAS clinical decision tools have limited inclusion to those patients undergoing CTA.

***What this study adds**:* In this multi-centre observational study including 5548 patients with symptoms potentially attributable to AAS*,* 0.3% of patients presenting with potential AAS symptoms did have AAS and 10% of patients with potential AAS symptoms undergo CT. A third of proven AAS patients still endure a diagnostic delay over 24 hours from time of arrival.

How this study might affect research, practice or policy: We illustrate the diagnostic challenge of AAS and the limitations of methods for selecting patients for CT. The best decision aid to facilitate decision to CT and to outperform ED clinician gestalt is not yet clear. More research is required in truly undifferentiated ED populations such as these.

(192words)

Introduction

Acute aortic syndrome (AAS) could be considered as a wolf in sheep's clothing in our emergency departments (EDs). AAS incorporates aortic dissection, intramural hematoma and penetrating aortic ulcer, and has a "lethal triad"; it is rare, has high mortality, and presents in atypical ways **[1]**. AAS affects approximately 4000 people in the UK per annum **[2]**, many not receiving timely diagnosis and treatment**,** and is responsible for 43-47,000 deaths annually in the United States (US) **[3]**. Population-based studies, suggest the mean annual incidence of AD ranges from 6 **[4]** to 7.2 **[5]** per 100,000 person-years, whilst a US study which included all AAS (AD, IMH and PAU) found an incidence of 7.7 per 100,000 person-years **[6]**. The misdiagnosis rate is estimated to be 33.8% **[7]**, with diagnostic delay of up to 24 hours for 25% of cases **[2]**, and mortality follows a linear increase of 0.5% per hour in the first 48 hours **[8]**.

Chest pain is the most common presenting symptom of AAS (80%) although back and abdominal pain are not uncommon **[9]**. Chest pain is responsible for 7.6 million annual visits to EDs in the United States **[10]** and collectively, chest, back and abdominal pain accounts for over 2 million ED attendances annually in England **[11]** and are overwhelmingly due to causes other than AAS. The estimated incidence of AAS is one in every 980 ED atraumatic chest pain attendances **[12]**, thus creating substantial diagnostic challenge. Too low a threshold for performing a CT aorta angiogram (CTA), the gold standard for diagnosis, would result in low diagnostic yields **[13, 14]**, significant costs and risks of ionising radiation. Clinicians therefore need to use CTA selectively, yet there is no validated clinical decision tool (CDT) for this scenario.

Several CDTS have been proposed. **[15-17]**. However, they have been tested in patients undergoing CTA. Additionally, d dimer has been suggested as a rule-out biomarker in low pre-test probability patients (95-98% sensitivity) **[18, 19]** and has been incorporated into the ADD-RS CDT. No CDT has previously been studied in truly undifferentiated ED populations. It is important to test possible CDTs and biomarkers in undifferentiated ED patients, because ED clinicians are likely to apply them to all patients with possible AAS rather than just those selected for CTA. It is currently unclear whether any AAS CDTs have sufficient sensitivity to be acceptable to clinicians, which is the most accurate, and whether they are likely to lead to

CTA and D-Dimer over-investigation. Assessment of CTA rate vs CTA positivity has not previously been studied in the clinically relevant population.

With these challenges in mind, we aimed to describe the characteristics of ED attendances with possible AAS and to assess existing CDTs and use of CTA in an 'all-comer' cohort of patients.

Methods

This was a multi-centre observational cohort study of ED patients with symptoms potentially attributable to AAS. The primary objective was to establish the characteristics and performance of existing clinical decision tools, including ADD-RS **[15]**, Canadian guideline **[16]**, AORTAs **[17]** and Sheffield [Ben Loryman, personal communication, 30th September 2021], in this cohort of patients. Secondary objectives were to establish patient characteristics, CTA rates and patient enrolment at participating sites.

This study was conducted in 27 EDs in England, Scotland, and Wales. A pragmatic approach to maximise recruitment was taken, with each ED including eligible patients for a consecutive period of between 2-40 days in autumn 2022. Data from each patient attendance was entered onto a standard Case Report Form (CRF), with subsequent 30-day outcome data captured from the Electronic Patient Record (EPR).

People aged 16 years or over, attending the ED with new-onset symptoms of possible AAS were eligible for inclusion. New onset was defined as starting within the past seven days; and possible AAS symptoms included chest, back or abdominal pain, syncope or symptoms related to malperfusion. The only exclusion was the absence of any potential AAS symptoms. Patients transferred from other centres were included. Patients were either identified prospectively by the treating clinician, prospectively by the local study team reviewing real-time ED attendance data to identify presentations of chest, back or abdominal pain, syncope or symptoms related to malperfusion, or retrospectively by the local study team, where local legal and ethical consent processes allowed. Data was collected by either the treating clinicians or the local study team. Where patients were identified prospectively, either the treating clinician commenced the CRF or was approached by the study team as soon after the

consultation as possible, to establish their clinical suspicion of AAS before any confirmatory testing took place. Retrospective patient identification was done from daily searches of the EPR using an ED presenting complaint of chest, back or abdominal pain, syncope or symptoms related to malperfusion, and radiology records of ED-requested CTAs during the study period. This enabled collection of an accurate picture of the epidemiology and management of patients attending the ED with symptoms of AAS, including at weekends and out of hours when research staffing was often reduced relative to daytime hours.

For patients identified prospectively, the treating clinician was also asked about their clinical suspicion of AAS (Yes/No), with likelihood from 0 to 10, and whether they thought AAS was the most likely diagnosis (Yes/No). If the treating clinician thought that there was a negligible likelihood of AAS, the patient was still enrolled to allow us to assess what proportion of presentations with symptoms possibly associated with AAS had no clinical concern for AAS. Clinician impression was recorded by the treating clinician at the time of reviewing the patient to ensure they were not influenced by any laboratory or radiological results. There was no change to usual clinical care and no study specific interventions for participants. A waived consent process was approved by the South-Central Oxford C Research Ethics Committee on 28 June 2022 (REC reference: 22/SC/0219) and by HRA.

Anonymised patient data was uploaded to an electronic Case Report Form (eCRF) **[Appendix 1]**, sited on an online secure database (REDCAP; http://www.project-redcap.org) on a University of Edinburgh server **[20,21]**. No participant identifiable data was entered onto the eCRF, left the local hospital, or was viewed outside of the clinical care team. After eCRFs were completed, hospital/study number linkage was destroyed. Data was recorded for patient demographics (age, sex), attendance date and time, and for all characteristics of the clinical decision tools being evaluated. Clinical data included time of onset and features of any pain, relevant past medical or family history, examination findings, results from investigations and suspected diagnosis. Diagnoses and data were not adjudicated. Data was not validated but was cleaned by the central analysis team with any data queries being addressed where possible by the site study teams.

Study endpoints

- The proportion of patients in whom the ED clinician thought AAS was a possible differential diagnosis, and most likely diagnosis, who had confirmed AAS.
- The proportion of patients in whom the ED clinician thought AAS was not a possible differential diagnosis but had confirmed AAS
- Test characteristics of clinical acumen, ADD-RS, AORTA, Canadian and Sheffield AAS clinical decision tools, and D-dimer (separately and in combination)
- CT/CTA ordering and positivity rate
- Proportion of alternative diagnoses found on CT/CTA and final hospital diagnosis
- Median time from hospital presentation to imaging diagnosis
- Median time from symptom onset to hospital presentation
- 30-day outcome (including 30-day mortality in proven AAS) through EPR

Outcomes

Each local study team kept a record on a password protected NHS computer linking the patient's hospital number with their study number so that 30-day outcome data could be collected from the EPR and entered onto the eCRF noting any diagnosis of AAS, final hospital diagnosis and mortality. Reference standard was radiological or operative confirmation of AAS.

Sample size calculation

The sample size calculation was based on the expected width of 80% confidence intervals. We estimated that approximately 5000 eligible patients would attend during the study period, of whom 125 would undergo CTA and 6 would have confirmed AAS. This would provide sufficient power to estimate key measures with an acceptable degree of precision e.g. 0.12% prevalence of confirmed AAS (80% CI 0.06-0.21%); 2.5% prevalence of CTA use (80% CI 2.2-2.8%). We used 80% confidence intervals for the key proportions so that we were not reporting intervals that were too wide to be informative, while also enabling us to identify the most likely range of values for the true proportion with reasonable certainty. Indeed, 80% confidence intervals are consistent with the intervals that are usually reported in pilot and feasibility studies **[22].** However, for the diagnostic accuracy analysis of CDTs, we used the conventional 95% confidence intervals.

Statistical Analysis

A descriptive analysis was performed. Categorical variables were summarised using frequencies and percentages and continuous variables using medians and interquartile ranges (IQRs). Exact binomial 80% confidence intervals were constructed around key proportions such as the proportion of patients in whom the clinician considered AAS was not a possible differential.

CDTs were assessed for diagnostic accuracy, taking a confirmed AAS diagnosis as the reference standard. Reference standard results were not available to those providing data to derive the CDTs, and conversely, information on decision tools were not readily available to those making a confirmed AAS diagnosis. The following performance indices were calculated (all with exact binomial 95% confidence intervals): sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Total scores were calculated for the CDTs by using the published criteria **[15-17].** If more than 50% of the individual dimensions of the CDT had more than 50% missing data, then a total score was not calculated. Where scores were able to be calculated, any missing data were scored as 0.

The presence of missing data in the total scores and reference standard (confirmed AAS diagnosis) may have caused bias in the performance indices. We therefore calculated the performance indices according to three methods: (i) missing data was excluded and only valid data was analysed, (ii) all missing data in the numerator was assumed to take a value of 0 (indicating a negative result); and (iii) all missing data in the numerator was assumed to take a value of 1 (indicating a positive result). Thus, we were able to assess the dependence of each performance index on our assumptions about the missing data.

ROC curve analysis was performed for the clinical decision tools (and clinical acumen i.e. ED clinician rating as to likelihood of AAS before confirmatory testing) based on their raw ordinal scores, excluding any missing data. The area under the ROC curve was calculated for each decision tool with 95% confidence intervals.

SPSS version 27 [IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp] was used to produce the graphs, and R software version 4.2.1. was used to calculate the exact 80% confidence intervals **[23].** All other analyses, including descriptive analyses were performed using SAS software version 9.4 [SAS Institute Inc., Cary, NC, USA].

Results

Between 26/09/2022 and 30/11/2022, 5548 patients presented to 27 EDs during their recruitment window, with symptoms potentially attributable to AAS **[Supplementary Figure 1a]**. **Figure 1** details participant recruitment and **Supplementary Table 1** details recruitment at each of the participating EDs. Data on ED presentations (excluding minor injuries) over 16 years of age were available for 464 of the 599 (77.5%) recruitment days (60,381 presentations; mean 130.1 presentations per day), meaning there were an estimated total at all sites of 77,949 adult major presentations during the 599 study recruitment days. 2037 (37%) patients were identified prospectively, 2688 (48%) patients were identified retrospectively by study teams through EPRs or other searches, and the method of recruitment was unknown in 823 (15%). **(Supplementary Figure 1b** details the number of patients attending hospital per hour of the day, stratified by type of recruitment). Recruitment was similarly distributed throughout the 24-hour period with a slightly greater proportion of prospective recruitment during 'office' hours **[Supplementary Figure 2]**.

The median age was 55 years (IQR 37-72; n=5539); 2591 (47%) patients were male (**Table 1).** **Table 2** details the clinical findings for the enrolled study population. Pain was described as sudden onset in 743 (15%), severe or worst ever in 1547 (32%), migrating or radiating in 1752 (34%) and 1609 (31%) had hypertension in ED, indicating that CDTs using these criteria will have high rates of positivity when using a low threshold.

Table 3 details the results of investigations and outcome of the study population. Physician gestalt was obtained in 4111 (74%) patients prior to confirmatory testing (i.e. CT/D-Dimer). AAS was considered a possibility by the clinician in 1082 (24%) patients but only 407 underwent CTA. Fourteen patients (0.3%) were confirmed to have AAS: five had a Stanford type A aortic dissection, three had a Stanford type B aortic dissection and six an intramural

haematoma or penetrating ulcer. Median (IQR) time from ED attendance to confirmed AAS was 6 hours (3 to 63; n=13); one patient was diagnosed on CT scan performed prior to their ED attendance for another indication which resulted in their ED attendance and is not included in the analysis of time to diagnosis AAS. A second patient had a CT scan prior to ED attendance which was misreported and was only diagnosed after ED attendance followed by further scan review by radiology and is included. Of note, this is the only patient who was diagnosed with AAS who had no high-risk condition, no high-risk pain feature, no high-risk exam features, and a normal chest x-ray; CT showed metastatic cancer with an incidental mural thrombus and penetrating thoracic aortic ulcer). Four patients had a diagnostic delay over 24 hours from time of ED arrival. This included the patient diagnosed on scan re-review.

33 other patients had alternative aortic pathologies (4 ruptured thoracic aortic aneurysms, 5 ruptured abdominal aortic aneurysms, 21 non-ruptured thoracic or abdominal aortic aneurysms and 3 previously known stable aortic dissection/intramural haematoma or penetrating ulcer). 31 (94%) of these were identified in the ED. This group had a 26% (9/33) 30-day mortality. No patients in our cohort were found to have been discharged with undiagnosed AAS at 30 day follow up.

Table 4 and Figure 2 detail the summary test characteristics of clinical acumen, CDTs, and D-dimer (both separately and in combination (**Supplementary Table 2** also includes sensitivity analyses). Brackets denote the range of possible values of sensitivity and specificity if all data that is currently missing in the test scores had been observed. Area under the Receiver Operating Characteristic (ROC) curve for ED clinician AAS likelihood rating was 0.958 (95% CI 0.933-0.983, n=4006) and for D-dimer was 0.658 (95% CI 0.466-0.850, n=644). Area under ROC for individual CDTs were: ADD-RS 0.674 (0.508-0.839, n=4989), AORTA 0.689 (0.527-0.852, n=5132), Canadian 0.818 (0.686-0.951, n=5180) and Sheffield 0.628 (0.467-0.788, n=5092) [**Supplementary Figure 3]**.

Table 1

Demographics	
Median time in hours (IQR) from symptom onset to hospital presentation (n=4784)	12 (4 to 50)
Male sex (n=5547)	2591 (47%)
Mean age (SD; must be 16 or over; n=5539)	55 (21)
Median age (IQR; must be 16 or over; n=5539)	55 (37 to 72)
History of presenting episode	
Chest pain	2903 (54%; n=5422)
Back pain	1211 (23%; n=5301)
Abdominal pain	2023 (38%; n=5360)
Syncope	665 (13%; n=5258)
Malperfusion / symptoms related to perfusion deficit	543 (11%; n=5120)
Neurology: paraparesis, hemiparesis/acute confusion (can be transient)	399 (8%; n=5226)
Pain severe intensity or worst ever	1547 (32%; n=4865)
Pain thunderclap/abrupt onset (including worst when awoke)	743 (15%; n=4884)
Pain tearing or ripping	124 (3%; n=4810)
Pain migrating or radiating	1752 (34%; n=5086)
Pregnant (if female)	81 (3%; n=2535)
Recent significant trauma / high speed deceleration injury	69 (1%; n=5074)
Recent recreational drugs including cocaine or other sympathomimetics	72 (2%; n=4683)
Past Medical History	
Known Marfan syndrome/connective tissue disease/giant cell arteritis	26 (0.5%; n=4999)
Known or family history of aortic dissection/syndrome/disease/coarctation	70 (2%; n=2979)
Known aortic valve disease (e.g. bicuspid / dilated aortic root)	107 (2%; n=4869)
Recent aortic manipulation / Instrumentation (within last year)	32 (1%; n=4993)
Known thoracic aortic aneurysm	19 (0.4%; n=4987)
Known abdominal aortic aneurysm	52 (1%; n=4992)
Physical examination findings	
Pulse deficit (i.e. absence of one or more upper limb or femoral pulse)	49 (1%; n=3400)
Systolic BP differential (>20mHg at any time during ED stay)	115 (5%; n=2196)
Focal neurological deficit	240 (5%; n=5060)
New aortic regurgitation murmur (i.e. not previously documented)	10 (0.2%; n=4806)
Hypotension (SBP < 90mmHg) or shock or pericardial effusion	143 (3%; n=5192)
Hypertension (SBP >140 and DBP> 90) documented at any point during ED stay	1609 (31%; n=5162)

Data are n (%) unless stated. N=5548 unless stated

Table 2

Investigations		
D-Dimer performed	716 (13%; n=5431)	
D-Dimer raised (>own hospital upper limit of normal; no result available in 41)	272 (40%; n=675)	
CXR performed in ED	2255 (41%; n=5461)	
If so; abnormal mediastinum (no result available in 40)	77 (4%; n=1956)	
CT (any type) chest performed Of these, was this a CTA?	540 (10%; n=5446) 407 (78%; n=525)	
Median (IQR) time from ED attendance to CT (hours)	5 (3 to 9; n=510)	
CT positive for AAS (type A/B aortic dissection, intramural haematoma, or penetrating ulcer)?	12 (2%; n=506) *	
Alternative diagnoses found on CT/CTA	201 (40%; n=503)	
Top 5 alternative diagnoses found on CT/CTA (n)	Pulmonary Embolus	27
	LRTI/pneumonia	26
	Aortic aneurysm (thoracic or abdominal) - non-ruptured	21
	Acute coronary syndrome including STEMI and NSTEMI	15
	Cholecystitis	8
Inpatient / 30 day discharge diagnoses		
Number with confirmed Acute Aortic Syndrome (AAS)	14 (0.25%; Type A Aortic Dissection=5, Type B Aortic Dissection=3, Intramural haematoma /penetrating ulcer=6)	
Median (IQR) time from ED attendance to confirmed AAS	6 (IQR 3 to 63; n=13) hours	
Location of patient when AAS confirmed (n=12)	ED 11 (92%) Ward 1 (8%)	
30-day mortality after AAS confirmed (n=12)	5 (42%; 80% CI 22% to 64%)	
Patients who have confirmed AAS in whom the ED clinician thinks *AAS is a possible differential*	10 (1.0%; 80% CI 0.6% to 1.5%; n=1046)	
Patients who had confirmed AAS in whom clinician considers *AAS is NOT a possible differential*	2(0.06%; 80% CI 0.02% to 0.16%; n=3319)	
Patients who had confirmed AAS in whom the ED clinician thinks *AAS is the most likely diagnosis*	5 (3.4%; 80% CI 1.7% to 6.2%; n=147)	
ED clinician rating as to likelihood of AAS before confirmatory testing in patients with confirmed AAS(n=5353)	ED clinician rating as to likelihood of AAS before confirmatory testing	Number with confirmed AAS
	0	0
	1	0
	2	0
	3	2
	4	1
	5	2
	6	1
	7	1
	8	2
	9	0
	10	2
Number with confirmed AAS in patients in whom AAS a possible diagnosis according to treating clinician		No AAS / Confirmed AAS
	AAS not possible	3317 / 2
	AAS possible	1036 / 10
	Unknown	986 / 2

Data are n (%) unless stated. N=5548 unless stated. LRTI=Lower Respiratory Tract Infection, STEMI=ST Elevation Myocardial Infarction, NSTEMI=Non-ST Elevation Myocardial Infarction.

* Two patients were diagnosed on CT scans performed for another indication prior to attending ED and are not included here. One CT scan then resulted in the ED attendance. The other CT had been misreported and was only diagnosed on review. The two CT scans showed one subacute type B dissection flap, and for the other, a mural thoracic aorta thrombus and penetrating ulcer.

Table 3

ED clinician suspicion of AAS		
AAS/dissection a possible diagnosis according to treating clinician?	Yes 1082 (24%; n=4484)	
ED clinician rating as to likelihood of AAS before confirmatory testing (from 0 = not likely to 10 = almost definitely; n=4111)	0	2315 (56%)
	1	694 (17%)
	2	468 (11%)
	3	272 (7%)
	4	133 (3%)
	5	71 (2%)
	6	56 (1%)
	7	47 (1%)
	8	35 (1%)
	9	11 (0.3%)
	10	9 (0.2%)
Acute aortic syndrome/dissection the most likely diagnosis according to treating clinician?	Yes 151 (3%; n=4574)	
If Acute aortic syndrome/dissection is NOT the most likely diagnosis according to treating clinician, then most likely diagnosis(n=4267)	Acute coronary syndrome	583 (13.7%)
	Musculoskeletal	455 (11%)
	Non-specific chest pain	429 (10%)
	Acute abdomen	399 (9%)
	Non-specific abdominal pain	292 (7%)
	Dyspepsia/Oesophageal spasm	187 (4%)
	Pulmonary Embolus	158 (4%)
	Renal colic	130 (3%)
	Stroke	111 (3%)
	TIA	59 (1%)
	Subarachnoid haemorrhage	12 (0.3%)
	CNS infection	5 (0.1%)
	Other	1447 (34%)

Data are n (%) unless stated

Table 4

	Sensitivity (complete cases)	**Sensitivity** (min)	**Sensitivity** (max)	**Specificity** (complete cases)	**Specificity** (min)	**Specificity** (max)	**PPV** (complete cases)	**PPV** (min)	**PPV** (max)	**NPV** (complete cases)	**NPV** (min)	**NPV** (max)	**AUROC** 95% CI
Clinical Acumen													
ED clinician AAS likelihood rating													0.958 (0.933-0.983)
AAS is a 'possible' diagnosis according to clinician	83% (52%,98%)	71% (42%,92%)	86% (57%,98%)	76% (75%,77%)	62% (61%,63%)	81% (80%,82%)	0.96% (0.46%,1.8%)	0.92% (0.44%,1.7%)	4.3% (3.1%,5.6%)	99.9% (99.8%,100%)	97.5% (96.9%,98%)	99.9% (99.8%,100%)	
AAS is the 'most likely' diagnosis according to clinician	45% (17%,77%)	36% (13%,65%)	57% (29%,82%)	97% (96%,97%)	81% (80%,82%)	97% (97%,98%)	3.4% (1.1%,7.8%)	3.3% (1.1%,7.6%)	6% (2.8%,11%)	99.9% (99.7%,99.9%)	97.3% (96.8%,97.8%)	99.9% (99.7%,100%)	
Likelihood of AAS diagnosis ≥3/10 according to clinician	100% (72%,100%)	79% (49%,95%)	100% (77%,100%)	85% (84%,86%)	64% (62%,65%)	89% (88%,90%)	1.8% (0.9%,3.2%)	1.7% (0.87%,3.1%)	4.9% (3.3%,6.9%)	100% (99.9%,100%)	97.6% (97%,98%)	100% (99.9%,100%)	
Clinical decision tools													
ADD-RS													0.674 (0.508-0.839)
ADD-RS ≥1	69% (39%,91%)	64% (35%,87%)	71% (42%,92%)	55% (53%,56%)	51% (50%,52%)	58% (57%,59%)	0.4% (0.18%,0.76%)	0.39% (0.18%,0.74%)	2.4% (1.8%,3.1%)	99.9% (99.6%,100%)	95.9% (95.1%,96.6%)	99.9% (99.6%,100%)	
AORTA score													0.689 (0.527-0.852)
AORTA score ≥1	69% (39%,91%)	64% (35%,87%)	71% (42%,92%)	59% (58%,60%)	57% (55%,58%)	61% (59%,62%)	0.43% (0.2%,0.81%)	0.42% (0.19%,0.79%)	2.6% (2%,3.4%)	99.9% (99.7%,100%)	95.9% (95.2%,96.6%)	99.9% (99.7%,100%)	
Canadian score													0.818 (0.686-0.951
Canadian score ≥1 (no d-dimer)	77% (46%,95%)	71% (42%,92%)	79% (49%,95%)	76% (75%,78%)	74% (73%,75%)	77% (76%,78%)	0.82% (0.39%,1.5%)	0.79% (0.38%,1.4%)	4.6% (3.5%,5.9%)	99.9% (99.8%,100%)	96.9% (96.3%,97.4%)	99.9% (99.8%,100%)	

Sheffield score													0.628 (0.467-0.788)
Sheffield score ≥2	36% (13%,65%)	36% (13%,65%)	36% (13%,65%)	82% (81%,83%)	78% (77%,79%)	83% (82%,84%)	0.54% (0.18%,1.3%)	0.53% (0.17%,1.2%)	3.2% (2.1%,4.5%)	99.8% (99.6%,99.9%)	96.4% (95.8%,97%)	99.8% (99.6%,99.9%)	
Raised D-dimer alone													
D-dimer alone													0.658 (0.466-0.850)
D-dimer alone (local cut off)	71% (29%,96%)	36% (13%,65%)	86% (57%,98%)	59% (56%,63%)	7% (6%,8%)	95% (95%,96%)	1.9% (0.62%,4.4%)	1.8% (0.6%,4.2%)	5.1% (2.8%,8.5%)	99.5% (98.1%,99.9%)	94% (91.3%,96.1%)	99.5% (98.2%,99.9%)	
D-dimer alone (fixed 500ng/mL cut-off)	57% (18%,90%)	29% (8.4%,58%)	79% (49%,95%)	61% (57%,65%)	7% (7%,8%)	95% (95%,96%)	1.59% (0.43%,4.01%)	1.54% (0.42%,3.89%)	4.62% (2.41%,7.92%)	99.2% (97.8%,99.8%)	93.7% (91%,95.9%)	99.3% (97.9%,99.9%)	
Raised D-dimer based on hospital-specific upper limit of normal with….													
D-dimer with clinical acumen (AAS is a possible diagnosis)	91% (59%,100%)	71% (42%,92%)	93% (66%,100%)	18% (16%,20%)	4.9% (4.4%,5.5%)	78% (76%,79%)	0.83% (0.4%,1.5%)	0.8% (0.38%,1.5%)	4.1%(3.1%, 5.3%)	99.6% (97.9%,100%)	93.6%(90.1%,96.2%)	99.6% (98%,100%)	
ADD-RS ≥1 or raised d-dimer	100% (69%,100%)	71% (42%,92%)	100% (77%,100%)	8% (7%,9%)	3.8% (3.3%,4.4%)	56% (54%,57%)	0.42% (0.2%,0.77%)	0.41% (0.2%,0.76%)	2.5% (1.9%,3.2%)	100% (98.2%,100%)	93.6% (89.5%,96.5%)	100% (98.3%,100%)	
ADD-RS ≥2 or raised d-dimer	78% (40%,97%)	50% (23%,77%)	86% (57%,98%)	43% (40%,47%)	6.6% (5.9%,7.3%)	91% (91%,92%)	1.5% (0.61%,3.1%)	1.5% (0.59%,3%)	4.4% (2.7%,6.6%)	99.4% (98%,99.9%)	94.1%(91.2%, 96.3%)	99.5% (98.1%,99.9%)	
Canadian score≥1 or raised d-dimer	100% (74%,100%)	86% (57%,98%)	100% (77%,100%)	17% (15%,19%)	5.2% (4.7%,5.9%)	74% (73%,75%)	0.86% (0.44%,1.5%)	0.83% (0.43%,1.4%)	4.6% (3.5%,5.8%)	100% (98.7%,100%)	94.3% (91%,96.6%)	100% (98.8%,100%)	
Canadian score≥2 or raised d-dimer	92% (62%,100%)	79% (49%,95%)	93% (66%,100%)	35% (32%,38%)	6.3% (5.7%,7%)	88% (88%,89%)	1.7% (0.88%,3.1%)	1.7% (0.85%,3%)	4.9% (3.4%,6.9%)	99.7% (98.4%,100%)	94.1% (91.2%,96.3%)	99.7% (98.5%,100%)	

95% confidence intervals are reported. Exclusion of unknowns and missing values from the clinical tests *and* the reference standard outcome in a complete cases analysis may cause a small bias in the performance indices. Therefore, missing data sensitivity analyses were performed assuming missing data belongs to each category: "min" indicates the minimum possible values of the point estimates and confidence intervals, whereas "max" indicates the maximum possible values of the point estimates and confidence intervals based on the configuration of missing data. If there is considerable variation in the point estimates and confidence intervals, this indicates that the performance indices are highly dependent on the missing data and results should be interpreted with caution.

Discussion

This study illustrates current real-world management of AAS in EDs, and highlights the diagnostic difficulty facing ED clinicians and the limitations of methods for selecting patients for CT. Most striking is the number of patients presenting with potential AAS symptoms, who did not have AAS (99.7%). Despite the low AAS prevalence, 10% with potential AAS symptoms underwent CT and 7% underwent CTA. The median time from ED arrival to confirmed AAS diagnosis was 6 hours but ranged from just over 2 hours to almost 11 days. A third of proven AAS patients endured a diagnostic delay over 24 hours from time of ED arrival, more than the 25% reported in the literature **[2]**. With mortality increasing per hour of delay **[8]**, there is room for improvement in the management of potential AAS in the ED.

10% of patients with potential AAS symptoms underwent CT with 2% of scans being positive. This is at the lower end of previous reported figures; a North American retrospective series of patients undergoing CTA for suspected AAS, reported a prevalence rate of AAS on CTA of around 3% **[24]**. All ED requested CT scans diagnosing AAS were CT angiograms of the aorta (CTA). It should be noted that 40% of all CT scans detected alternative diagnoses (201 of 503), the commonest are detailed in Table 2. Clinicians need to use CT selectively yet be comfortable deciding which patients presenting with AAS symptoms do not require further investigation with CTA.

It may be that CTA rate was increased (407/5446; 7%) from that anticipated in the power calculation (125/5000; 2.5%) due to the presence of this study in the ED biasing ED clinicians to over investigate for AAS. However, this increased CTA rate may also reflect a more widespread generalised change in usual care towards more ED clinicians investigating potential AAS symptoms with CTA. This study shows the potential implications of over-interpreting the recommendation that all patients presenting with potential AAS symptoms should undergo CTA. A literal interpretation could have led to 5008 further patients undergoing CT scan in our study. The ASES study, an evidence synthesis and value of information analysis is currently underway, determining what CT positivity rate would represent a cost-effective use of resources **[25]**.

Whilst clinician gestalt appears to perform well, a sensitivity of 45% when an ED clinician rates AAS as the most likely diagnosis, suggests additional help to stratify who should undergo CT is required. Whilst our low AAS prevalence means we must be cautious about comparing the performance of different clinical decision tools, the Sheffield score (sensitivity of 36%) is probably not suitable for clinical use, with too many missed AAS cases. The other clinical decision tools performed better, but alone did not reach sufficient sensitivity for clinical use in our cohort. **Table 2** potentially explains the poor specificity of the CDTs. The ADD-RS and Canadian tools both include 'Pain severe intensity or worst ever' and 'migrating or radiating pain'. These characteristics are present in 32% and 34% of people with potential AAS symptoms in our cohort, yet not all underwent CT. This suggests that clinicians are choosing not to CT all patients with these symptoms, and that CDTs need to better differentiate which patients with severe intensity, worst ever, migrating or radiating pain should undergo CT.

Whilst the area under the ROC (AUROC) for ED clinician AAS likelihood rating was impressive compared to individual CDTs, this must be interpreted with caution. AUROC for clinician likelihood was based on an ordinal score with wider range than for all the CDTs. The clinician likelihood also had a much higher proportion of missing data (26% compared to 4-7% in the other decision tools). Finally, the study taking place in the ED with ongoing recruitment of allcomers with potential AAS symptoms may have biased towards a higher accuracy of clinical gestalt and may have reduced the risk of ED clinicians missing AAS. Nevertheless, the finding that an ED clinician AAS likelihood of 3/10 or greater detected all AAS cases, suggests that ED clinician gestalt could be a useful addition to any AAS CDT. Currently only the Canadian clinical practice guideline includes any measure of ED clinician gestalt, and this clinical decision tool performed well in our evaluation.

In our study around half of patients could not be recruited prospectively despite extensive advertisement, excellent site engagement, and acceptance amongst the ED community that AAS is a top emergency medicine research priority **[26,27]**. Conducting research in this area in challenging. Some AAS patients are missed because the diagnosis is not considered. These patients' care will not be improved by prospective ED research studies as they will not be included. Our data is limited by the fact that it is not possible to capture patients with AAS where the diagnosis was not considered, who subsequently died without imaging or post-

mortem. If a diagnostic intervention is researched in those whom the ED clinician suspects AAS, this risks the Hawthorne effect **[28]**.

This study has limitations. Retrospective recruitment of around half of patients led to missing clinician gestalt data. D-dimer and CT scans were only available if they were ordered by the treating clinician. Generating accurate test characteristics of decision tools was therefore difficult, especially around D-dimer estimation. Here, exclusion of unknown and missing values may have led to bias in the test characteristics. However, in our analyses we carefully considered the dependence of the test characteristics on the missing data and created ranges to show the possible range of test characteristics depending on the unobserved data.
The strength of this study is the recruitment of a clinically relevant cohort. However, 90% of participants did not undergo CTA and it is possible that there were missed cases of AAS. Many patients who had D-dimer and CT were being primarily investigated for pulmonary embolism. Because of a likely higher prevalence of AAS in this group, the test characteristics of D-dimer may not reflect their performance in the entire cohort. Whilst the CDT variables were collected prospectively where possible, the overall score was determined during analysis. Any definite study of CDT performance would need to apply the CDT at the time of ED clinician decision making.

Previous studies of AAS clinical decision tools have included a very different population to the one we have looked at. All studies previously evaluating the accuracy of ADD-RS for identifying AAS have restricted inclusion to those patients undergoing CTA, using CTA as the reference standard **[29-36].** We have included everyone presenting with potential AAS symptoms, illustrating the current real-world management of AAS in EDs, the diagnostic difficulty facing ED clinicians and the limitations of methods for selecting patients for CT. Despite the difficulties conducting research in such a difficult environment at a time of the most extreme pressures on the clinical service **[37]**, we have maximised recruitment and produced a study with maximal generalisability with the ability to shape ED research and improve patient care in this area in future. The best decision aid to facilitate decision to CT and to outperform ED clinician gestalt in AAS is not yet clear. Further research is required in truly undifferentiated ED populations such as these.

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Conflict of interest: No authors have any conflicts of interest to declare.

Data availability statement: All study data and metadata will be available upon reasonable request to dashedstudy@gmail.com.

Patient and Public Involvement statement: Patient organisations have been involved from the outset of this project. The Aortic Dissection Charitable Trust (TADCT) Research Advisory Group were involved in the RCEM grant application and in designing the protocol. Two representatives from TADCT were grant co-applicants.

Ethics approval statement: DAShED was approved by the South-Central Oxford C Research Ethics Committee on 28 June 2022 (REC reference: 22/SC/0219) and by HRA.

Contributorship Statement: RML, MJR, NF, RAP, SW, SG, AC, JB, BC and EC conceived the study and were involved in study design and study delivery; MJR and RAP performed data analysis; RML, MJR, NF, RAP, SW, SG, AC, JB, BC and EC were involved in data interpretation and RML, MJR, NF, RAP, SW, SG, AC and EC prepared the manuscript. RML, MJR, NF, RAP, SW, SG, AC, JB, BC, and EC contributed to its revision. MJR takes responsibility for the paper as a whole. The DAShED investigators were involved the acquisition of data for the work.

Table and Figure legends:

Figure 1: DAShED participant recruitment.

Figure 2: Stacked bar chart showing percentages for each rating score of the likelihood of AAS, stratified by confirmed AAS.

Table 1: Baseline characteristics of study population including history, past medical history, and physical examination findings of study population.

Table 2: Results of investigations and outcome of study population.

Table 3: Clinician impression of AAS.

Table 4: Summary test characteristics of clinical acumen, clinical decision tools, and d-dimer (separately and in combination). For full test characteristic analysis including sensitivity analyses, see **Supplementary Table 2**.

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Appendices/ Supplementary files

Appendix 1: Study Case Report Form

Supplementary Table and Figure legends:

Supplementary Figure 1a: Stacked bar chart of numbers per day of study (stratified by prospective/retrospective recruitment)

Supplementary Figure 1b: Stacked bar chart of numbers attending hospital per hour of day (stratified by prospective/retrospective recruitment)

Supplementary Figure 2: Stacked bar chart of numbers attending hospital per day of week (stratified by prospective/retrospective recruitment)

Supplementary Figure 3: ROC curve of clinical acumen, ADD-RS, AORTA, Canadian and Sheffield AAS clinical decision tools, and D-dimer (separately and in combination)

Supplementary Table 1: Site profile data

Supplementary Table 2: Full test characteristics of clinical acumen, ADD-RS, AORTA, Canadian and Sheffield clinical decision tools, and D-dimer (separately and in combination)

Case Report Form

Please complete the DAShED Case Report Form, thanks.

Study Site

- ◯ Edinburgh RIE
- ◯ Royal Alexander Hospital, Paisley
- ◯ QUEH, Glasgow
- ◯ Queen Elizabeth Hospital, King's Lynn
- ◯ Kirkcaldy, Fife
- ◯ Wythenshawe
- ◯ James Paget Hospital, Great Yarmouth
- ◯ Raigmore, Inverness
- ◯ Harrogate
- ◯ John Radcliffe, Oxford
- ◯ Frimley
- ◯ Wexham Park
- ◯ Royal Berkshire, Reading
- ◯ Bristol Royal Infirmary
- ◯ Luton and Dunstable
- ◯ Sheffield Northern General
- ◯ Milton Keynes
- ◯ Manchester Royal Infirmary
- ◯ Addenbrookes Hospital, Cambridge
- ◯ Royal Glamorgan
- ◯ Hywel Dda (Withybush)
- ◯ Hywel Dda (Glangwili)
- ◯ Hywel Dda (Bronglais)
- ◯ Derby
- ◯ Horton Hospital, Banbury
- ◯ Southmead, North Bristol NHS Trust
- ◯ Kettering

Please confirm the patient meets study Inclusion criteria i.e. Attended the ED with new-onset chest, back or abdominal pain, syncope, symptoms related to malperfusion or any other symptom of Acute Aortic Syndrome?

- ◯ Yes
- ◯ No

At least SECTIONS A and B to be collected by treating clinician preferably at time of enrolment

SECTIONS C-F must completed even if AAS not suspected, but may be completed at time of enrolment or at a later date using the 'Saved and Return Later' button at the bottom of CRF, or through Redcap by study team

SECTION A: Demographics (MUST BE COMPLETED BY TREATING CLINICIAN)

Recruiting ED Clinician name

_____

Date and time of ED attendance

_____

Symptom onset date and time (nearest hour)

_____

Sex

- ◯ Male
- ◯ Female
- ◯ Other

Age (must be 16 or over)

_____

SECTION B: ED clinician suspicion of AAS (MUST BE COMPLETED BY TREATING CLINICIAN)

Acute aortic syndrome/dissection a possible diagnosis according to treating clinician?

- ◯ Yes
- ◯ No
- ◯ Unknown

ED clinician rating as to likelihood of AAS before confirmatory testing
(from 0=not likely to 10=almost definitely)

- ◯ 0
- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ 6
- ◯ 7
- ◯ 8
- ◯ 9
- ◯ 10
- ◯ unknown

Acute aortic syndrome/dissection the most likely diagnosis according to treating clinician?

- ◯ Yes
- ◯ No
- ◯ Unknown

If not then most likely diagnosis?

- ◯ Acute coronary syndrome
- ◯ Pulmonary Embolus
- ◯ Stroke
- ◯ TIA
- ◯ Subarachnoid haemorrhage
- ◯ CNS infection
- ◯ Renal colic
- ◯ Dyspepsia / Oesophageal spasm
- ◯ Acute abdomen
- ◯ Musculoskeletal
- ◯ Non specific chest pain
- ◯ Non specific abdominal pain
- ◯ Other
- ◯ Unknown

SECTION C: History of presenting episode

Must completed even if AAS not suspected, but may be completed at time of enrolment or at a later date using the 'Saved and Return Later' button at the bottom of CRF, or through Redcap by study team

Chest pain?

- ◯ Yes
- ◯ No
- ◯ Unknown

Back pain?

- ◯ Yes
- ◯ No
- ◯ Unknown

Abdominal pain?	◯ Yes ◯ No ◯ Unknown
Syncope?	◯ Yes ◯ No ◯ Unknown
Malperfusion / symptoms related to perfusion deficit? (examples: CNS=stroke or TIA, cardiac=STEMI, mesenteric=ischemic bowel, limb=acute embolic limb etc)	◯ Yes ◯ No ◯ Unknown
Neurology: paraparesis, hemiparesis/acute confusion (can be transient)?	◯ Yes ◯ No ◯ Unknown
Pain severe intensity or worst ever?	◯ Yes ◯ No (or no pain) ◯ Unknown
Pain thunderclap/abrupt onset (including worst when awoke)?	◯ Yes ◯ No (or no pain) ◯ Unknown
Pain tearing or ripping?	◯ Yes ◯ No (or no pain) ◯ Unknown
Pain migrating or radiating?	◯ Yes ◯ No (or no pain) ◯ Unknown
Pregnant?	◯ Yes ◯ No ◯ Unknown
Recent significant trauma / high speed deceleration injury?	◯ Yes ◯ No ◯ Unknown
Recent recreational drugs including cocaine or other sympathomimetics?	◯ Yes ◯ No ◯ Unknown

SECTION D: Past Medical History

Known Marfan syndrome/connective tissue disease / Ehler Danlos / giant cell arteritis?	◯ Yes ◯ No ◯ Unknown
Known or family history of aortic dissection/syndrome, aortic disease/coarcation?	◯ Yes ◯ No ◯ Unknown

Known aortic valve disease (e.g. bicuspid / dilated aortic root)?	◯ Yes ◯ No ◯ Unknown
Recent aortic manipulation / Instrumentation (within last year)?	◯ Yes ◯ No ◯ Unknown
Known thoracic aortic aneurysm?	◯ Yes ◯ No ◯ Unknown
Known abdominal aortic aneurysm?	◯ Yes ◯ No ◯ Unknown

SECTION E: Physical examination findings

Pulse deficit (i.e. absence of one or more upper limb or femoral pulse)?	◯ Yes ◯ No ◯ Unknown
Systolic BP differential (>20mHg difference in SBP between arms at anytime during ED stay)?	◯ Yes ◯ No ◯ Unknown
Focal neurological deficit?	◯ Yes ◯ No ◯ Unknown
New aortic regurgitation murmur (i.e. not previously documented)?	◯ Yes ◯ No ◯ Unknown
Hypotension (SBP < 90mmHg) or shock or pericardial effusion?	◯ Yes ◯ No ◯ Unknown
Hypertension (SBP >140 and DBP> 90) documented at any point during ED stay	◯ Yes ◯ No ◯ Unknown

SECTION F: Investigations

D-Dimer performed?	◯ Yes ◯ No ◯ Unknown
Result in ng/mL (if reported as < 150 for example then please put 1 in this box)	_____
D-Dimer upper limit of normal in your hospital for detection of PE in a patient of this age	◯ 250 ng/ml ◯ 500 ng/ml ◯ other
D-Dimer upper limit of normal in your hospital for detection of PE in a patient of this age/ ng/ml?	_____

CXR performed in ED?	◯ Yes ◯ No ◯ Unknown
If so; abnormal mediastinum? (if available from either treating clinician or formal radiology report)	◯ Yes ◯ No ◯ Unknown
CT chest performed?	◯ Yes ◯ No ◯ Unknown
Was this a CT angiogram?	◯ Yes ◯ No ◯ Unknown
Date and time of CT	_____
CT positive for AAS (Type A or B Aortic Dissection, Intramural haematoma/thrombus or Penetrating ulcer)?	◯ Yes ◯ No ◯ Unknown
Alternative diagnoses found on CT/CTA?	◯ Yes ◯ No ◯ Unknown

SECTION G: Follow up to be completed at 30 days

Confirmed Acute Aortic Syndrome?	◯ Yes (Type A or B Aortic Dissection, Intramural haematoma/thrombus or Penetrating ulcer) ◯ Thoracic or Abdominal Aneurysm (in aneurysmal aorta, not 2 dissection) ◯ Previously known stable Aortic Dissection/Intramural haematoma/thrombus/Penetrating ulcer ◯ No (Neither of above) ◯ Unknown
Date and time of confirmed Acute Aortic Syndrome?	_____
Type of Acute Aortic Syndrome	◯ Type A Aortic Dissection ◯ Type B Aortic Dissection ◯ Intramural haematoma/thrombus/penetrating ulcer ◯ Ruptured Thoracic aortic aneurysm ◯ Ruptured Abdominal aortic aneurysm ◯ Non ruptured Thoracic or Abdominal aortic aneurysm ◯ Previously known stable Aortic Dissection/Intramural haematoma/thrombus/Penetrating ulcer
Further details about AAS diagnosis if available e.g. CT report/brief description of case/outcome (KEEP ANONYMISED)	_____

Location of patient when AAS confirmed?	◯ ED ◯ Medical receiving ◯ Ward ◯ ITU/HDU ◯ Unknown
Alive at 30-days according to EPR?	◯ Yes ◯ No ◯ Unknown
Final hospital discharge diagnosis (99 if unknown)	_____
How was this case IDENTIFIED? (we realise that most cases will have some retrospective data entry but here we want to know specifically about initial case IDENTIFICATION)	◯ Prospectively by treating clinician ◯ Retrospectively by study team through Electronic Patient Records or other searches

Supplementary Table 1:

Study Site	Days recruiting to study *	N	% of total study participants
Addenbrookes Hospital, Cambridge	10	200	3.6
Bristol Royal Infirmary	24	550	9.9
Derby	17	678	12.2
Edinburgh RIE	37	422	7.6
Frimley Park	15	303	5.5
Harrogate	16	30	0.5
Horton Hospital, Banbury	2	17	0.3
Hywel Dda (Bronglais)	30	157	2.8
Hywel Dda (Glangwili)	8	64	1.2
Hywel Dda (Withybush)	28	50	0.9
James Paget Hospital, Great Yarmouth	17	299	5.4
John Radcliffe, Oxford	31	282	5.1
Kettering	14	50	0.9
Kirkcaldy, Fife	15	348	6.3
Luton and Dunstable	30	57	1.0
Manchester Royal Infirmary	19	50	0.9
Milton Keynes	17	117	2.1
Queen Elizabeth Hospital, King's Lynn	55	133	2.4
QEUH, Glasgow	16	109	2.0
Raigmore, Inverness	22	52	0.9
Royal Alexander Hospital, Paisley	25	51	0.9
Royal Berkshire, Reading	31	584	10.5
Royal Glamorgan	28	40	0.7
Sheffield Northern General	35	211	3.8
Southmead, North Bristol NHS Trust	15	37	0.7
Wexham Park	16	644	11.6
Wythenshawe	5	13	0.2

* Days from date of first patient recruited to date of last patient recruited (inclusive)

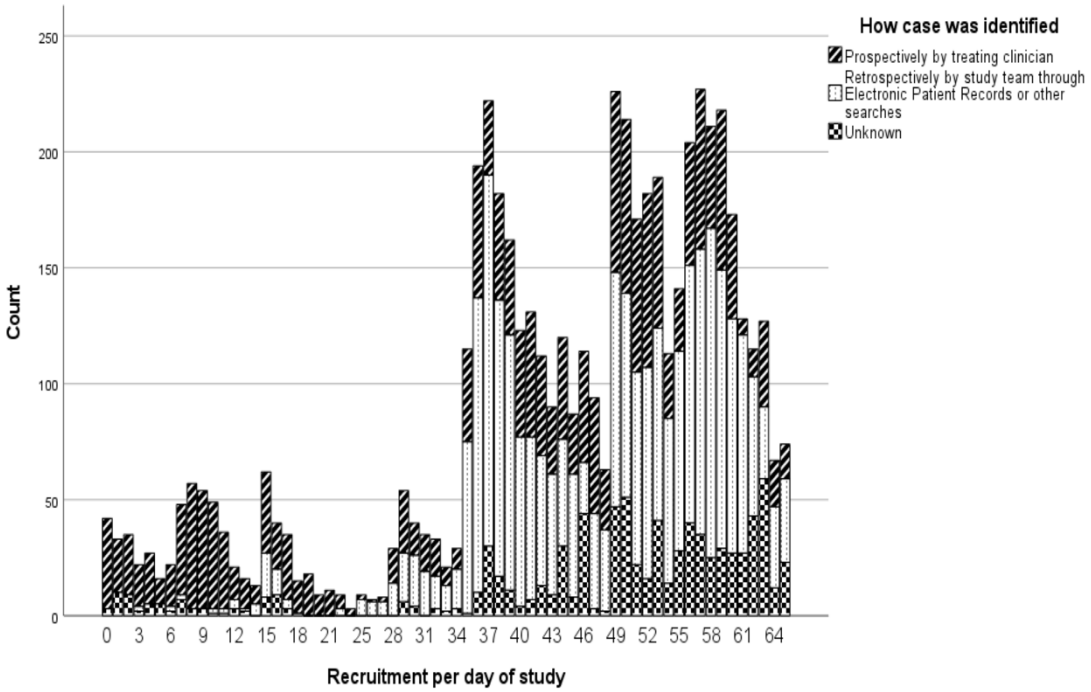
Supplementary Table 2

	Sensitivity (complete cases)	**Sensitivity** (min)	**Sensitivity** (max)	**Specificity** (complete cases)	**Specificity** (min)	**Specificity** (max)	**PPV** (complete cases)	**PPV** (min)	**PPV** (max)	**NPV** (complete cases)	**NPV** (min)	**NPV** (max)
Clinical decision tools												
ADD-RS ≥2	30.8% (9.09%,61.4%)	28.6% (8.39%,58.1%)	35.7% (12.8%,64.9%)	95.5% (94.9%,96%)	89% (88.1%,89.8%)	95.8% (95.2%,96.3%)	1.75% (0.478%,4.41%)	1.7% (0.466%,4.3%)	4.26% (2.06%,7.69%)	99.8% (99.6%,99.9%)	96.7% (96.1%,97.1%)	99.8% (99.7%,99.9%)
AORTA score ≥2	69% (39%,91%)	64% (35%,87%)	71% (42%,92%)	59% (58%,60%)	57% (55%,58%)	61% (59%,62%)	0.43% (0.2%,0.81%)	0.42% (0.19%,0.79%)	2.6% (2%,3.4%)	99.9% (99.7%,100%)	95.9% (95.2%,96.6%)	99.9% (99.7%,100%)
Canadian score ≥2 (no d-dimer)	54% (25%,81%)	50% (23%,77%)	57% (29%,82%)	92% (91%,93%)	89% (88%,90%)	92% (92%,93%)	1.7% (0.69%,3.5%)	1.6% (0.66%,3.4%)	4.9% (3.1%,7.5%)	99.9% (99.7%,100%)	96.7% (96.1%,97.1%)	99.9% (99.7%,100%)
Canadian score ≥2 or {=1 with raised d-dimer}	69% (39%,91%)	64% (35%,87%)	71% (42%,92%)	90% (89%,91%)	75% (74%,76%)	92% (91%,92%)	2% (0.9%,3.7%)	1.9% (0.87%,3.6%)	5.1% (3.3%,7.5%)	99.9% (99.7%,100%)	96.8% (96.2%,97.3%)	99.9% (99.8%,100%)
Raised D-dimer based on hospital-specific upper limit of normal with….												
D-dimer with clinical acumen (AAS is the most likely diagnosis)	90% (55%,100%)	64% (35%,87%)	93% (66%,100%)	49% (45%,53%)	6.8% (6.2%,7.5%)	93% (92%,94%)	2.3% (1.1%,4.3%)	2.2% (1%,4.2%)	5.2% (3.3%,7.9%)	99.7% (98.5%,100%)	94.1% (91.2%,96.2%)	99.7% (98.6%,100%)
AORTA score ≥1 or raised d-dimer	91% (59%,100%)	71% (42%,92%)	93% (66%,100%)	9.2% (8.1%,10%)	4.2% (3.7%,4.8%)	58% (57%,60%)	0.45% (0.21%,0.82%)	0.44% (0.21%,0.8%)	2.7% (2.1%,3.5%)	99.6% (97.6%,100%)	93.4% (89.4%,96.2%)	99.6% (97.7%,100%)
AORTA score ≥2 or raised d-dimer	90% (55%,100%)	64% (35%,87%)	93% (66%,100%)	29% (26%,32%)	6.1% (5.5%,6.8%)	85% (84%,86%)	1.1% (0.51%,2.1%)	1.1% (0.5%,2%)	3.5% (2.3%,5%)	99.7% (98.3%,100%)	93.9% (90.9%,96.2%)	99.7% (98.4%,100%)
Sheffield ≥2 or raised d-dimer	90% (55%,100%)	64% (35%,87%)	93% (66%,100%)	22% (20%,24%)	5.8% (5.2%,6.5%)	79% (78%,80%)	0.81% (0.37%,1.5%)	0.79% (0.36%,1.5%)	3.5% (2.5%,4.7%)	99.7% (98.2%,100%)	93.7% (90.5%,96.1%)	99.7% (98.3%,100%)
Raised D-dimer based on fixed 500ng/mL cut-off with….												
D-dimer (fixed cut-off) with clinical acumen (AAS is a possible diagnosis)	91% (59%,100%)	71% (42%,92%)	93% (66%,100%)	18% (16%,20%)	5% (4.5%,5.7%)	78% (76%,79%)	0.83% (0.4%,1.5%)	0.8% (0.39%,1.5%)	4.1% (3.1%,5.4%)	99.6% (98%,100%)	93.7% (90.3%,96.2%)	99.7% (98.1%,100%)
D-dimer (fixed cut-off) with clinical acumen (AAS is the most likely diagnosis)	80% (44%,97%)	57% (29%,82%)	86% (57%,98%)	50% (46%,54%)	7% (6.3%,7.7%)	93% (92%,94%)	2.1% (0.91%,4.1%)	2% (0.88%,4%)	4.8% (2.9%,7.4%)	99.5% (98.1%,99.9%)	93.7% (90.8%,95.9%)	99.5% (98.2%,99.9%)
ADD-RS ≥1 or raised d-dimer (fixed cut-off)	100% (69%,100%)	71% (42%,92%)	100% (77%,100%)	7.9% (6.9%,9%)	3.8% (3.3%,4.4%)	56% (54%,57%)	0.42% (0.2%,0.77%)	0.41% (0.2%,0.76%)	2.5% (1.9%,3.2%)	100% (98.2%,100%)	93.6% (89.5%,96.4%)	100% (98.3%,100%)

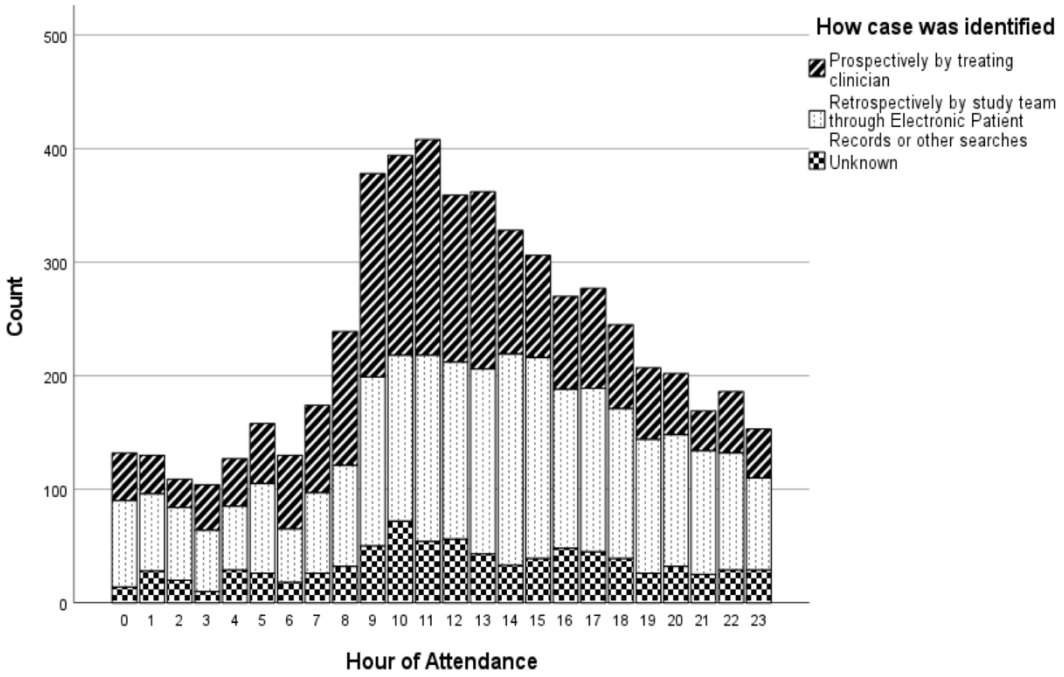
ADD-RS ≥2 or raised d-dimer (fixed cut-off)	78% (40%,97%)	50% (23%,77%)	86% (57%,98%)	44% (40%,47%)	6.6% (6%,7.4%)	91% (91%,92%)	1.5% (0.61%,3.1%)	1.5% (0.59%,3%)	4.2% (2.6%,6.4%)	99.4% (98%,99.9%)	93.9% (91%,96.1%)	99.5% (98.1%,99.9%)
AORTA score ≥1 or raised d-dimer (fixed cut-off)	91% (59%,100%)	71% (42%,92%)	93% (66%,100%)	9.2% (8.1%,10%)	4.2% (3.7%,4.8%)	58% (57%,60%)	0.45% (0.21%,0.82%)	0.44% (0.21%,0.8%)	2.7% (2.1%,3.5%)	99.6% (97.6%,100%)	93.4% (89.4%,96.2%)	99.6% (97.7%,100%)
AORTA score ≥2 or raised d-dimer (fixed cut-off)	80% (44%,97%)	57% (29%,82%)	86% (57%,98%)	29% (26%,31%)	6% (5.4%,6.7%)	85% (84%,86%)	0.98% (0.43%,1.9%)	0.96% (0.42%,1.9%)	3.2% (2.1%,4.7%)	99.4% (97.8%,99.9%)	93.3% (90.2%,95.7%)	99.4% (97.9%,99.9%)
Canadian score≥1 or raised d-dimer (fixed cut-off)	100% (74%,100%)	86% (57%,98%)	100% (77%,100%)	17% (15%,18%)	5.2% (4.6%,5.8%)	74% (73%,75%)	0.86% (0.44%,1.5%)	0.82% (0.43%,1.4%)	4.5% (3.5%,5.7%)	100% (98.7%,100%)	94.2% (90.8%,96.6%)	100% (98.7%,100%)
Canadian score≥2 or raised d-dimer (fixed cut-off)	83% (52%,98%)	71% (42%,92%)	86% (57%,98%)	35% (32%,39%)	6.3% (5.7%,7%)	88% (88%,89%)	1.6% (0.77%,2.9%)	1.5% (0.74%,2.8%)	4.6% (3.1%,6.6%)	99.4% (97.9%,99.9%)	93.6% (90.6%,95.9%)	99.4% (98%,99.9%)
Sheffield≥2 or raised d-dimer (fixed cut-off)	80% (44%,97%)	57% (29%,82%)	86% (57%,98%)	22% (20%,24%)	5.9% (5.2%,6.5%)	79% (78%,80%)	0.72% (0.31%,1.4%)	0.7% (0.3%,1.4%)	3.3% (2.4%,4.5%)	99.4% (97.7%,99.9%)	93.2% (89.9%,95.6%)	99.4% (97.9%,99.9%)

95% confidence intervals are reported. Exclusion of unknowns and missing values from the clinical tests *and* the reference standard outcome in a complete cases analysis may cause a small bias in the performance indices. Therefore, missing data sensitivity analyses were performed assuming missing data belongs to each category: “min” indicates the minimum possible values of the point estimates and confidence intervals, whereas “max” indicates the maximum possible values of the point estimates and confidence intervals based on the configuration of missing data. If there is considerable variation in the point estimates and confidence intervals, this indicates that the performance indices are highly dependent on the missing data and results should be interpreted with caution.

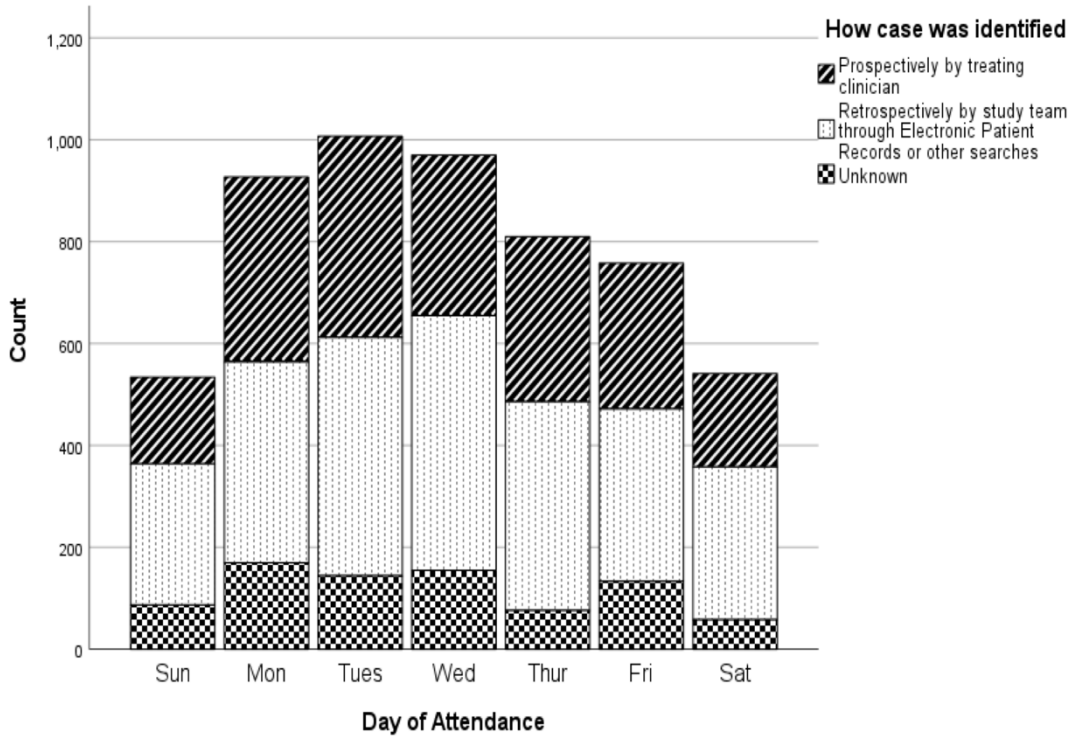
Supplementary Figure 1a



Supplementary Figure 1b



Supplementary Figure 2



Supplementary Figure 3