

CME What Is the Specificity of the Aortic Dissection Detection Risk Score in a Low-prevalence Population?

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ABSTRACT

Background: Acute aortic syndrome (AAS) is a time-sensitive and difficult-to-diagnose aortic emergency. The American Heart Association (AHA) proposed the acute aortic dissection detection risk score (ADD-RS) as a means to reduce miss rate and improve time to diagnosis. Previous validation studies were performed in a high prevalence population of patients. We do not know how the rule will perform in a lower-prevalence population. This is important because application of a rule with low specificity would increase imaging rates and complications. Our goal was to assess if the diagnostic accuracy of the score would be maintained in a low-prevalence population that we are attempting to risk stratify in the emergency department (ED).

Methods: Retrospective cohort of patients age 18 years old and older who presented to two tertiary care EDs from January 1, 2015, to December 31, 2015, and underwent a computed tomographic angiography to rule out AAS. Two trained reviewers extracted data using a standardized data collection form. AAS was defined according to accepted radiologic standards. The components of the AHA risk score were defined a priori. Agreement was measured using kappa statistic. Sensitivity, specificity, and positive and negative likelihood ratios with 95% confidence intervals (CIs) were calculated. Analysis was performed using SAS 9.4 University Edition.

Results: A total 370 patients underwent computed tomography for suspected AAS. Chief presenting symptoms were chest pain (207, 58%), back pain (26, 7%), abdominal pain (32, 8.6%), syncope (7, 2.6%), and symptoms of stroke (6, 1.6%). AAS was finally diagnosed in 12 (3.2%) patients: five (1.4%) type A aortic dissection, four (1%) type B aortic dissection, two (0.5%) an aortic intramural hematoma, no penetrating aortic ulcer, and one a ruptured abdominal aortic aneurysm. The presence of one or more ADD risk markers ($\text{ADD-RS} \geq 1$) was associated with a sensitivity of 100% (95% CI = 73.5%–100%) and a specificity of 12.3% (95% CI = 9.1%–16.2%) for the diagnosis of AAS. The negative likelihood ratio was 0 and the positive likelihood ratio was 1.14 (95% CI = 1.1–1.2).

Conclusions: Our study confirms that in North America the prevalence of AAS in those undergoing advanced imaging is low. The ADD-RS in this population has a low specificity. A lack of defined inclusion criteria and a low specificity limits the application of this rule in practice.

Acute aortic syndrome (AAS) refers to a spectrum of aortic catastrophes. It includes acute aortic dissection, intramural hematoma, penetrating atherosclerotic ulcer, and ruptured abdominal aortic aneurysms.¹ It is the great masquerader, often presenting like more common conditions such as pulmonary embolism, acute coronary syndrome, or stroke. Therefore, it is not surprising that one in every five cases is missed.^{2–6}

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professional societies published the 2010 thoracic aortic disease guidelines to improve the missed or delayed treatment of AAS. They developed an expert consensus risk stratification tool that has been modified to create the aortic dissection detection risk score (ADD-RS). This score uses predisposing conditions, pain features, and physical findings to stratify patients into low (0) medium (1) or high risk (>1).⁷

Previous studies validating the ADD-RS were conducted in a population with a high prevalence of AAS (13%–22.6%; see Data Supplement S1, available as supporting information in the online version of this paper, which is available at <http://onlinelibrary.wiley.com/doi/10.1111/acem.13634/full>).^{8,9} The population that we are attempting to risk stratify likely has a much lower prevalence.^{10,11} We do not know how the ADD-RS will perform in a low-risk population. This is important as implementation of a rule with a low specificity could lead to an increase in imaging rates with an associated increase in radiation exposure, cost, time in the emergency department (ED), contrast-induced nephropathy, and incidental findings. Our objective was to assess the diagnostic accuracy of the ADD-RS in a low-prevalence population to address the spectrum bias of previous studies and improve generalizability.

METHODS

Study Population

We included patients > 18 years old who presented to two tertiary care EDs from January 1, 2015, to December 31, 2015, who underwent a computed tomographic angiography (CTA) to rule out AAS. Two trained researchers reviewed all CT thorax and/or abdomen ordered in the ED during the study period. Indications for CTA were recorded from electronic radiology requisitions (“OASIS” electronic medical record system). We included all those who included any variation of “rule out acute aortic dissection or ruptured abdominal aortic aneurysm.” The kappa statistic for interobserver agreement was calculated.

We then reviewed included patients’ charts. Data were extracted as per guidelines put forward by Jansen et al.¹² Data extracted were verified in multiple sources: ED record of treatment, consultant notes, and integrated progress notes. Two trained reviewers extracted data by a standardized electronic data form. The data form was trialed on a random selection of 20 patient charts, refined, and trialed on a further 20

charts. Training included 20 chart data extractions by each reviewer, data were compared and kappa was calculated with clarification and oversight provided by a third reviewer (RO). For calculating the kappa, the data extraction form was considered as a single variable. If extraction of any variable on the form varied between reviewers then it was counted as a disagreement, if all variables on the form were identically extracted that data form was counted as agreement. Reviewers were blinded to the CT reports during chart review.

Outcome Measures

Acute aortic syndrome was defined by radiologic evidence of aortic dissection, intramural hematoma, penetrating atherosclerotic ulcer, or ruptured abdominal aortic aneurysm on CTA. We also reviewed all ICD-10 discharge codes related to AAS for missed cases. A missed case of AAS was defined by failure to diagnose within the ED or treatment for an alternative diagnosis (i.e., anticoagulation for a pulmonary embolism) within the ED or representation within 14 days of initial visit with a new diagnosis of AAS. An incidental finding was defined as any previously unknown finding that was identified in the radiologist’s final report that did not lead to an alternative diagnosis or change in management in the ED.

ADD-RS Classification

The data not reported in the charts were defaulted to negative, as previously performed in the IRAD (International Registry for Acute Aortic Dissection).¹³ The ADD-RS was calculated according to the presence or absence of 12 risk markers classified in three ADD risk categories (predisposing conditions, pain features and physical findings), as suggested by the 2010 AHA guidelines.^{4,7} ADD predisposing conditions were: 1) history of Marfan syndrome or of other connective tissue disease, 2) family history of aortic disease, 3) history of known aortic valve disease, 4) history of recent aortic manipulation, and 5) history of known thoracic aortic aneurysm. ADD pain features were: 1) abrupt onset of pain, 2) severe pain intensity, and 3) ripping or tearing quality of pain. ADD physical findings were the following: 1) pulse asymmetry or systolic blood pressure differential (>20 mm Hg) between extremities, 2) focal neurologic deficit, 3) new murmur of aortic insufficiency, and 4) shock state or hypotension (systolic blood pressure ≤ 90 mm Hg). The ADD-RS was calculated based on the number of categories

where at least one risk marker was present. Patients were divided into low-risk (ADD-RS 0, zero risk markers), intermediate-risk (ADD-RS 1, at least one risk marker in one ADD risk category) and high-risk (ADD risk > 1, at least one risk marker in more than one ADD risk categories). There are no definitions provided by the AHA to define the variables that make up the ADD-RS. We defined the variables as follows: aortic valve disease included bicuspid aortic valve, any previous surgical/endovascular repair, or graft replacement for aortic valve disease. Thoracic aortic aneurysm was defined as known aortic enlargement (>3 cm). Recent aortic manipulation was defined as coronary or aortic angiography, intra-aortic balloon pump, aortic surgery, coronary artery bypass surgery, or aortic valve surgery performed within the past month. Acute-onset pain was defined as acute, sudden, or starting at a defined time and reaching maximal intensity at onset. Pleuritic pain was any pain that was worse with inspiration. Neurologic deficits were defined as any reported sensory or motor deficit on physical examination, in addition to a decreased level of consciousness below a Glasgow Coma Scale score of 8. Bilateral systolic blood pressure differential measurements were recorded if measurements occurred directly after one another without any intervention between. Nursing staff at our institution perform blood pressure measurements with an automated blood pressure machine. If multiple measurements were recorded the first bilateral measurement was extracted. Hypotension (<90 mm Hg) was defined as a sustained systolic blood pressure < 90 mm Hg for greater than 10 minutes or with signs of hypoperfusion (decreased level of consciousness, chest/abdominal pain, mottled limbs, weak peripheral pulses). Pulse deficit/differential was defined as any recorded difference in volume/force or difference in obvious signs of malperfusion (cold, blue, mottled) between right and left extremity.

Data Analysis

We used descriptive statistics including means, medians, and standard deviation for continuous variables and percentages for dichotomous variables. Variables were assessed for association with AAS with univariate analysis followed by a Bonferonni correction for multiple comparisons ($m = 21$ with an $\alpha = 0.05$, Bonferonni correction tests each variable at $\alpha = 0.001$). Therefore a variable is said to be significantly associated with AAS if $p < 0.001$.

The continuous variables were compared using the two-sided Student's *t*-test for normal distributions and the Mann-Whitney U-test for nonnormal distributions. The categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate.

Sensitivity, specificity, and positive and negative likelihood ratios with 95% confidence intervals (CIs) were calculated. Analysis was performed using SAS 9.4 University Edition. The results were reported according to the STARD (Standards for Reporting of Diagnostic Accuracy Studies) criteria.¹⁴ This retrospective observational study was approved by the institutional ethics review board.

Sample Size

Sample size was calculated based on an expected prevalence of 5% with an 80% power to detect an alpha of 0.05 with a required 12 cases of AAS and a total number of 240 CTA procedures. This was based on a previous study of CT to rule out acute aortic dissection.¹¹

RESULTS

During the study period, 9,389 CT scans (7,354 CT abdomen, 2,827 CT thorax, 714 CT thorax and abdomen) were performed. A total of 370 unique patients underwent CT for suspected AAS (Figure 1). The kappa for data extraction was 0.91 (95% CI = 0.83–1). The chief presenting symptoms were chest pain (207, 58%), back pain (26, 7%), abdominal pain (32, 8.6%), syncope (7, 2.6%), and symptoms of stroke (6, 1.6%). AAS was finally diagnosed in 12 (3.2%) patients: five (1.4%) type A aortic dissection, four (1%) type B aortic dissection, two (0.5%) aortic intramural hematoma, zero penetrating aortic ulcer, and one ruptured abdominal aortic aneurysm. AAS was ruled out in 358 (97%) patients; the alternative diagnoses were undifferentiated chest/abdominal/back pain (283, 76.5%), stable abdominal aortic aneurysm (38, 10.3%), and stable chronic aortic dissection (8, 2.2%; Table 1). The time interval between index test (i.e., variables in the ADD-RS) and CTA was not accurately recorded on charts and is therefore not reported. No adverse events were reported from assessment of the index tests. The number of incidental findings in our population was 17.5%.

The clinical characteristics and prevalence of ADD-RS risk markers in patients with AAS and in patients

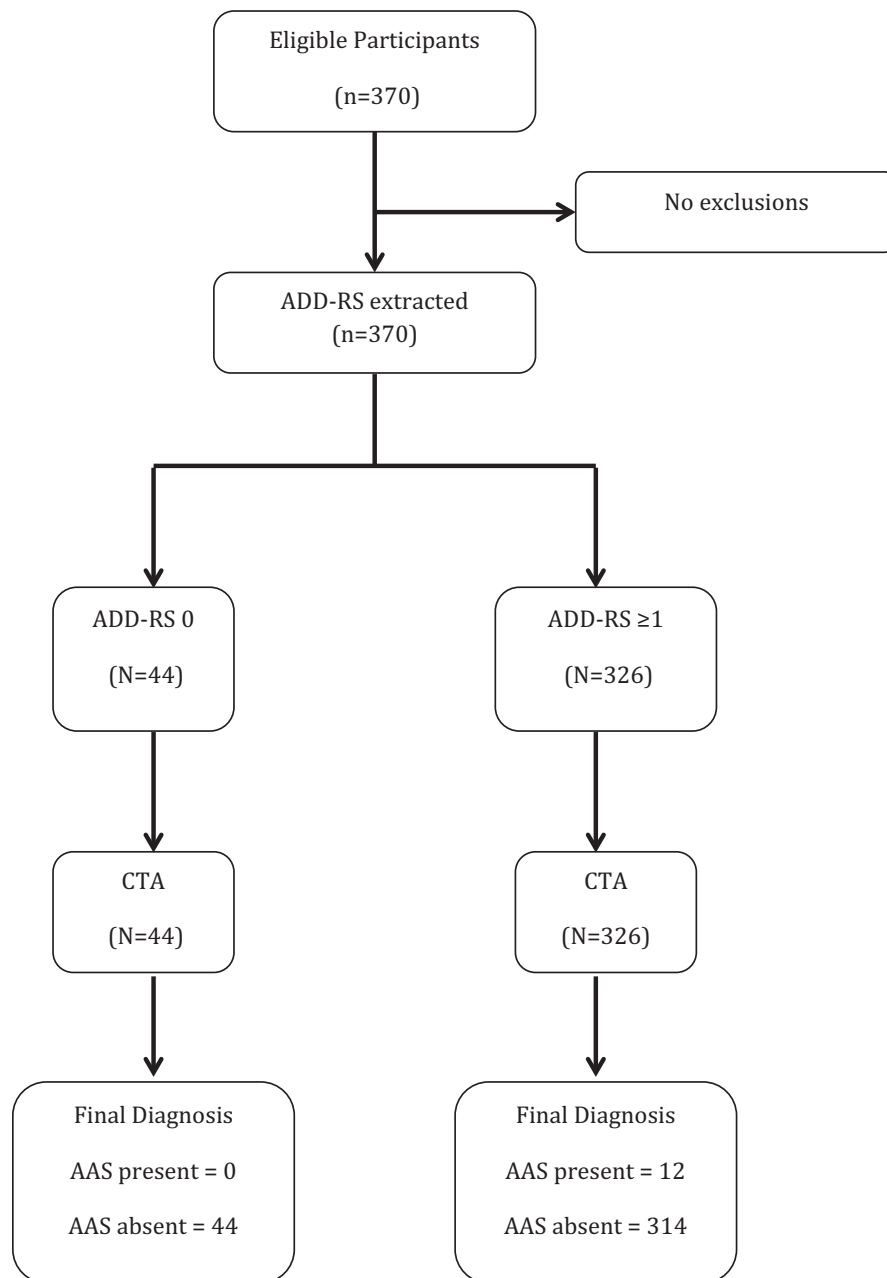


Figure 1. Flow diagram for patients. AAS = acute aortic syndrome; ADD-RS = aortic dissection detection risk score; CTA = computed tomographic angiography.

with alternative diagnoses are presented in Table 2. The prevalence of AAS was 0% among patients at low risk of AD (ADD-RS = 0), 0.5% among patients at intermediate risk of AD (ADD-RS = 1), and 8.6% among patients at high risk of AD (ADD-RS > 1; Table 3). Presence of one or more ADD risk markers (ADD-RS ≥ 1) was associated with a sensitivity of 100% (95% CI = 73.5%–100%) and a specificity of 12.3% (95% CI = 9.1%–16.2%) for the diagnosis of AAS (Table 4). The negative likelihood ratio was 0 and the positive likelihood ratio was 1.14 (95% CI = 1.1–1.2).

DISCUSSION

This is the first study to explore the accuracy of ADD-RS in a population that represents the low prevalence we see in everyday practice. We found a specificity that was significantly lower than all previous validation studies. This may limit the generalizability of these studies in a population with a low prevalence.

We found a larger number of patients falsely classified as positive than in previous validation studies. In our study a higher proportion of patients had high-risk pain features. Characteristics of pain deemed high risk by the ADD-RS are common in patients presenting to

Table 1
Final Diagnosis of Included Patients

Diagnosis	N (370)	%
AAS	9	2.43
• Type A		
• Type B		
• Intramural hematoma		
• Penetrating atherosclerotic ulcer		
• Ruptured AAA		
Ruptured AAA	1	0.27
Intramural hematoma	2	0.54
Pain NYD	283	76.49
Stable abdominal aortic aneurysm	38	10.27
Stable chronic aortic dissection	8	2.16
Pneumonia	7	2
Biliary disease (cholecystitis, cholithiasis, cholangitis, cholelithiasis)	4	1.08
Thrombus (iliac artery/SMV/aortic arch)	3	0.81
Colitis/diverticulitis	2	0.54
Pleural disease (effusion)	2	0.54
Perforated viscus	2	0.54
Nephrolithiasis	1	0.27
Pancreatic disease (pancreatitis, abscess, pseudocyst)	1	0.27
Hernia (inguinal, incisional, femoral, umbilical, hiatal)	1	0.27
Lung cancer	1	0.27
Gastrointestinal malignancy	1	0.27
Peptic ulcer disease	1	0.27
Fracture	1	0.27
Incidental findings	65	17.5

AAA = acute aortic aneurysm; AAS = acute aortic syndrome; NYD = not yet diagnosed; SMV = superior mesenteric vein.

the ED. Two of every three patients presenting with pain will describe it as severe.¹⁵ Application of the rule to a large number of undifferentiated patients will result in a large number of false-positives. Patients included in our study were those that physicians felt were at risk for AAS and thus required a CTA to rule out the diagnosis. In the prospective trial by Nazerian et al.⁸ conducted in Italy, patients were included if they had a suspicion for AAS and pain or perfusion deficit. They have a similar entry criterion but vastly different prevalence of AAS. It would seem in North America there is a lower threshold for considering AAS in one's differential. Clinical suspicion varies between physicians and there is a significant practice variation on who requires advanced imaging.¹¹ This variation is based on the difficult-to-define clinical suspicion for AAS. The AHA guidelines suggest that anyone without a clear diagnosis and chest pain should be investigated for AAS, if up to 65% of these

Table 2
Characteristics of Included Patients

Variable	AAS	No AAS	p-value
Sex: female	6 (50)	166 (46.3)	0.73
CTAS			
1	1 (8.3)	8 (2.2)	0.57
2	8 (66.7)	259 (72.3)	
3	3 (25)	86 (24)	
4	0	5 (1.4)	
Incidental findings	0	64 (18.1)	
Widened mediastinum	2 (66.7)	27 (14.7)	0.015
Abrupt-onset pain	7 (70)	158 (44.1)	0.1
Severe	11 (91.7)	229 (64)	0.048
Tearing	0	20 (5.6)	0.39
Ongoing pain	10 (83.3)	280 (78.2)	0.67
Neurologic deficit	7 (58.3)	108 (30.2)	0.04
Marfan syndrome	0	3 (0.8)	0.75
Aortic valve disease	0	7 (1.96)	0.62
Family history of aortic disease	1 (8.3)	6 (1.68)	0.09
Recent aortic manipulation	0	4 (1.12)	0.7
Aortic aneurysm	3 (25)	61 (17)	0.47
Hypertension	9 (75)	207 (57.8)	0.23
Diabetes	3 (25)	67 (18.7)	0.58
Ischemic heart disease	2 (2.2)	89 (24.86)	0.52
Hypotension	4 (22.2)	4 (1.1)	<0.0001
Pulse deficit	2 (16.7)	5 (1.4)	0.0001
Bilateral systolic blood pressure differential (>20 mm Hg)	1 (8.3)	32 (11.72)	0.07
New murmur	1 (8.3)	5 (1.4)	0.06
Aortic insufficiency	1 (8.3)	1 (0.28)	0.0009
Focal neurologic deficit	7 (58.3)	67 (18.82)	0.0008
Troponin elevated	1/12 (8.3)	33/354 (9.3)	0.91
Lactate > 3	3/7 (42.9)	4/93 (4.3)	0.0001
D-dimer elevated (>500 ng/dL)		39/81 (48.2)	

Data are reported as n (%).

AAS = acute aortic syndrome; CTAS = Canadian Triage Assessment Score.

*Not all patients underwent laboratory testing.

patients report pain as severe, a significant number of patients will have a risk score of 1.¹⁵ The issue with a risk score that has a large number of false-positives is the harm of over investigation. An increase in imaging rates will increase radiation exposure, cost, time in the ED, and incidental findings.^{16,17} The number of incidental findings in our population was 17.5%.

We found an excellent sensitivity for the risk score, with an ADD-RS of 0 missing no cases and a score of 1 missing only one case. However, given the low number of cases, the lower end of the CI for sensitivity was 74%. Nazerian et al.^{8,9} found a sensitivity of 91%

Table 3
Number (%) of Patients With and Without AAS at Each Score Level

ADD-RS	AAS	No AAS	Total
0	0	44 (12.3)	44 (11.9)
1	1 (8.3)	197 (55)	198 (53.5)
2	11 (91.7)	107 (29.9)	118 (31.9)
3	0	10 (2.8)	10 (2.7)
Total	12	358	370

Table 4
Diagnostic Accuracy of the ADD-RS at a Cut Point of 0 or >1

	ADD-RS > 0	ADD-RS > 1
Sensitivity	100 (73.5–100)	91.7 (61.5–99.8)
Specificity	12.29 (9.1–16.2)	67.3 (62.2–72.2)
Negative likelihood ratio	0	0.12 (0.02–0.81)
Positive likelihood ratio	1.14 (1.1–1.2)	2.8 (2.24–3.52)
Number of CT reduced	44 (11.9)	242 (65.4)
Number (%) of AAS missed	0	1 (8.3%)

AAS = acute aortic syndrome; ADD-RS = aortic dissection detection risk score.

in a retrospective study and 95% in a prospective study of all those presenting to the ED with a suspicion for AAS. Rogers et al.¹⁸ tested the ADD-RS in the IRAD (International Registry of Acute Aortic Dissection) database. This is a massive database including thousands of cases of AAS. They found a sensitivity of 96%. An ADD-RS of 0 has an AAS prevalence of 2.8% to 6.2%; therefore, it is likely not sufficient to rule out AAS.^{8,9,18,19} To improve sensitivity Nazerian et al, derived a diagnostic algorithm with the use of D-dimer for all patients with an ADD-RS ≤ 1 . In this prospective derivation study only 0.6% of cases were missed if ADD-RS ≤ 1 and the D-dimer was negative. The major drawback of this algorithm is that even a patient with an ADD-RS of 0 still requires a D-dimer to rule out AAS. Therefore, any patient with pain and/or perfusion deficit with a clinical suspicion for AAS and no high-risk features present (ADD-RS 0) require a D-dimer to rule out AAS. The use of this algorithm does not provide any guidance on who is at such a low risk that they do not even need a D-dimer. A large number of patients are likely to meet the inclusion criteria of the diagnostic algorithm (chest abdominal back pain and/or perfusion deficit and a clinical suspicion for AAS). The concern in applying a rule with a specificity of 12% and inclusion criteria including a hard to define “clinical suspicion for AAS” is that it will increase imaging. In addition there is a large variation in physician threshold for considering AAS, this is apparent in the difference in our study

population with a prevalence of 3% compared with 13% to 25% in other studies.

LIMITATIONS

The data collected were retrospective in nature. This could potentially lead to misclassification bias with each physician defining the clinical variables according to their own criteria. However, in prospective studies examining historical and physical examination findings, inter-rater reliability is often reported as only fair to moderate. We used strict definitions for our data extraction so as to not further introduce bias. Our inter-rater reliability for data extraction was excellent.²⁰ Misclassification is also a potential issue in defining cases of AAS. However, it is unlikely that any case was misclassified as we reviewed the radiology report generated by a board-certified radiologist and also confirmed the documentation of an assessment by consult service in regard to the new diagnosis of AAS. Our case population contains only patients in whom AAS was identified at some point during their evaluation. Patients with unrecognized AAS do not appear in our study, and because these patients may in fact be unrecognized as a result of atypical presentations, our estimate of sensitivity of classic features may be inflated. In addition this study was conducted at an academic tertiary care center, which may be subject to referral bias.

Finally, documentation in the medical record is often done at the conclusion of an emergency visit when the diagnosis is known. Knowing that a patient has AAS may impact the variables documented—for instance, a clinician may be more likely to characterize the pain as sudden onset or tearing. This recall bias could artificially inflate the specificity of these classic variables.

Clinical and Research Implications

The next step in improving accuracy of diagnosis and rational resource utilization is to standardize clinical suspicion for AAS. With such a rare diagnosis, the application of any rule to a low-risk population will likely increase testing without any guaranteed reduction in missed cases. Future research should focus on defining realistic expected diagnostic accuracy of any score or algorithm to help rule out AAS. Two previous studies have attempted to define the test–no test threshold and they have significantly different acceptable miss rates of 0.3% to 3%.^{21,22} It is unlikely that we will be able to reduce our miss rate to the industry standard of pulmonary embolism or acute coronary

syndrome without a significant increase in cost. However, any algorithm or rule that improves our current miss rate with minimal increase in resource utilization will likely have positive impact on patient care.

CONCLUSION

Our study confirms that in North America the prevalence of acute aortic syndrome in those undergoing advanced imaging is low. The aortic dissection detection risk score in this population has a low specificity. A lack of defined inclusion criteria and a low specificity limits the application of this rule in practice.

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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.13634/full>

Data Supplement S1. Prevalence of high-risk pain features in current study versus two previous validation studies.