REUE | Review Article

Value of D-dimer concentration for ruling out a diagnosis of acute aortic syndrome

Valor del Dímero-D en el diagnóstico de exclusión del síndrome aórtico agudo

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Introduction

The acute aortic syndrome (AAS) is a clinical entity that encompasses several conditions sharing a common element: the loss of integrity of the wall of the aortic artery.[1] The three most prominent are aortic dissection, penetrating ulcer, and intramural hematoma, all of which pose a potential life-threatening risk due to the possibility of rupture and the development of other complications.

The incidence rate of AAS ranges from 6 to 7.7 cases per 100,000 patients/year. The most frequent presentation (4.4 per 100,000 patients/year) is aortic dissection, followed by penetrating ulcer and intramural hematoma (2.1 and 1.2 per 100,000 patients/year, respectively). Aortic dissection primarily affects the ascending aorta (58.2%), while intramural hematoma predominantly involves the descending aorta (76.2%).[2,3] It is more common in men and increases with age, although in women, aortic dissection tends to present differently, leading them to seek care later and often with more severe clinical pictures.[4,5] The true incidence of acute aortic dissection is likely underestimated, as an unknown number of individuals die before reaching the hospital, and the cause of death is often attributed to another cardiovascular event.[6] A systematic review indicated that type A aortic dissection may account for up to 7% of out-of-hospital cardiac arrests, and type B for up to 0.5%. Mortality rate after an out-of-hospital cardiac arrest due to acute aortic dissection was 100%.[7,8] Since it is an uncommon but potentially lethal condition, establishing an accurate diagnosis in emergency departments is of paramount importance.

AAS shares signs and symptoms with other conditions that commonly present in emergency settings. Its presentation varies widely from one patient to another, making diagnosis a real challenge. The most frequent clinical signs is sudden-onset, intense chest pain accompanied by diaphoresis. The pain is located on the anterior or posterior chest wall, often interscapular, and may radiate to the lower limbs or neck depending on the propagation of the dissection. Depending on the structures affected and the location of the aortic lesion, clinical signs may include hyper- or hypotension, acute pulmonary edema, absence of peripheral pulses, focal neurological deficits due to carotid obstruction or spinal cord ischemia. When major arteries are occluded, intestinal ischemia, myocardial ischemia, or hematuria may occur. If compression of adjacent structures arises from aneurysmal dilation of the dissection, it can result in Horner's syndrome, hoarseness, airway compromise, dysphagia, or even superior vena cava syndrome. In cases of proximal dissection, aortic insufficiency, hemopericardium, and cardiac tamponade may develop. Other signs may include fever (aortitis), hemoptysis, GI bleeding, nausea, vomiting, diarrhea, or paralytic ileus.[9-11]

In more than 30% of patients ultimately diagnosed with AAS, the initial suspicion corresponded to other diseases with similar presentations — such as myocardial ischemia, pericarditis, pulmonary thromboembolism, musculoskeletal pain, or even cholecystitis.[12] One condition in which a differential diagnosis is particularly crucial is acute coronary syndrome, especially if thrombolytic therapy is being considered.

Beyond its variable clinical presentation, another challenge in the emergency setting is the lack of uniform diagnostic strategies and protocols.[13] For emergency medicine, achieving an accurate and rapid diagnosis is essential, and this would be greatly aided by specific biomarkers and simple, standardized diagnostic protocols.

In the latest guidelines from the American College of Cardiology (ACC) and the American Heart Association (AHA) on the management of aortic disease,[11] the use of the Aortic Dissection Detection Risk Score (ADD-RS) is recommended. This score classifies patients into three risk levels — low risk if

ADD-RS = 0, intermediate risk if ADD-RS = 1, and high risk if ADD-RS > 1 — based on the presence of high-risk factors, high-risk pain features, and high-risk examination findings, thereby establishing the pre-test probability of aortic dissection (Table 1). However, its use is not yet widespread in suspected cases of this condition.

Vilacosta *et al.*[14] proposed a three-step diagnostic algorithm to achieve this goal:

a) First step: establish clinical suspicion based on risk factors (including hypertension), suggestive chest pain, and physical examination findings using the ADD-RS scale.

b) Second step: perform an electrocardiogram (ECG), chest X-ray, and laboratory tests including D-dimer and troponin.

c) Third step: in patients with intermediate risk (ADD-RS ≥ 1) and elevated D-dimer, a computed tomography (CT) scan of the aorta should be performed — particularly if troponin is normal and no ECG changes are observed.

Biomarkers of acute aortic syndrome

In recent decades, biomarkers have assumed a fundamental role in both the diagnosis and prognosis of various cardiovascular diseases, such as heart failure, venous thromboembolic disease, and acute coronary syndrome.

Although the definitive diagnosis of AAS must be made using CT of the aorta,[2] having a biomarker capable of either excluding or confirming the diagnosis would be extremely useful — improving diagnostic times and optimizing the use of healthcare resources. Throughout history, several biomarkers have been investigated for their potential utility in diagnosing AAS (Table 2):

Markers of smooth muscle damage

– Smooth Muscle Myosin Heavy Chain (smMHC): this molecule is released following an injury to the medial layer of the aortic wall. It rises and falls very rapidly, limiting its diagnostic window to 3–6 hours.[15,16]

– Creatine Kinase Isoenzyme-BB (CK-BB): elevated in patients with acute aortic dissection due to smooth muscle damage, reaching approximately eight times normal levels.[17]

– Calponin: this protein has 3 isoforms — acidic, basic, and neutral. The basic calponin (h1) is the most abundant and specific form found in smooth muscle tissue, while the acidic and neutral forms (h2) are less abundant and not considered smooth muscle-specific. Therefore, basic calponin is often used as a marker of differentiation and smooth muscle injury in various pathological conditions. Patients with aortic dissection show elevations of both acidic and basic calponin within the first 24 hours following aortic injury, with reported sensitivities of around 50% and specificities of 73–87%, but with low positive predictive values.[18] More studies are needed to demonstrate the clinical utility of this biomarker in practice.

– Endothelins: Endothelins are a family of peptides that include endothelin-1 (ET-1), endothelin-2 (ET-2), and endothelin-3 (ET-3). Elevated concentrations of ET-1/2 have been found in dissections or ruptured aneurysms, especially among non-surviving patients, which gives them potential prognostic value.[19]

Table 1. Aortic dissection detection risk score (ADD-RS) (used to rule out aortic dissection)

	No (0 points)	Yes (1 point)
Any high-risk condition:		
Marfan syndrome, family history of aortic disease, known aortic valve disease, recent aortic manipulation, or known thoracic aortic aneurysm.		
Any high-risk pain feature:		
Chest, back, or abdominal pain described as abrupt in onset, severe in intensity, or tearing/ripping in nature.		
Any high-risk examination finding:		
Evidence of perfusion deficit (pulse deficit, systolic BP differential, or focal neurological deficit with pain), new aortic regurgitation murmur (with pain), or hypotension/shock.		
– For ADD-RS > 1, consider proceeding directly to CTA or another conclusive imaging modality. – For ADD-RS ≤ 1, proceed with D-dimer testing: • If D-dimer < 500 ng/mL, consider stopping further dissection evaluation. • If D-dimer ≥ 500 ng/mL, consider CTA.		

BP: blood pressure; ADD-RS: aortic dissection detection risk score; CTA: computed tomography angiography.

Markers of vascular interstitial damage

– Matrix metalloproteinases (MMPs): matrix metalloproteinases are a family of endopeptidases involved in the process of aortic remodeling. An increase in MMP-9 levels has been observed within the first hour after symptom onset, remaining elevated during the subacute phase (up to two months after hospital discharge) in patients under medical treatment.[20] In this context, Vianello *et al.*[21] suggest the potential usefulness of the simultaneous evaluation of circulating levels of CD40 ligand (CD40L), myeloperoxidase (MPO), MMP-1, and tissue inhibitor of metalloproteinase-1 (TIMP-1) as a promising diagnostic tool for clinical assessment in the early phase of acute aortic syndrome.

Table 2. Biomarkers of acute aortic syndrome

Smooth muscle damage markers:
Smooth muscle myosin heavy chain (smMHC)
Creatine kinase isoenzyme-BB (CK-BB)
Calponin
Endothelins
Vascular interstitial damage markers:
Matrix metalloproteinases (MMP)
Soluble elastin fragments (sELAF)
Transforming growth factor-beta (TGF-β)
Markers related to inflammation, immune cell activation, tissue damage, and remodeling:
C-reactive protein (CRP)
Tenascin-C (TN-C)
Natriuretic peptides
Soluble ST2 (suppression of tumorigenicity 2)
Non-coding RNAs (ncRNAs)
MicroRNAs (miRNAs)
Thrombosis markers
D-dimer

– Soluble elastin fragments (sELAF): these substances could be considered an early diagnostic marker, since their levels increase within the first hour after symptom onset. Interestingly, patients with thrombosis in the false lumen did not show an increase in sELAF levels, whereas in cases of false lumen without thrombosis, levels remained elevated for more than 72 hours.[22]

– Transforming growth factor beta (TGF-β): in patients with Marfan syndrome, there is a fibrillin-1 deficiency leading to TGF-β overactivation. However, elevated TGF-β levels have also been observed in patients with aortic dissection, particularly in type A and in those with larger aortic diameters, suggesting potential usefulness in patients not affected by Marfan syndrome.[23]

Markers related to inflammation, immune cell activation, tissue damage, and remodeling

– C-reactive protein (CRP): CRP is produced in response to the stimulation of several cytokines during the acute phase of inflammation; therefore, it is a marker of the presence and extent of the inflammatory response but not specific for vascular inflammation. In aortic dissection, there seems to be a correlation between CRP levels and long-term adverse events,[24] although its clinical value in patients with aortic syndrome remains unclear.

– Tenascin-C (TN-C): this adhesive glycoprotein is part of the extracellular matrix and may play a role in vascular remodeling. It has been observed that in patients with type B aortic dissection, elevated TN-C levels are associated with higher mortality,[25] suggesting a possible prognostic role.

– Natriuretic peptides: these are circulating hormones secreted mainly by cardiac tissues, whose diagnostic and prognostic utility in heart failure is already well established. Moreover, elevated NT-proBNP levels appear to be independently associated with mortality in type A aortic dissection.[26]

– Soluble ST2 (suppression of tumorigenicity 2): ST2 is a member of the interleukin-1 receptor family, involved in regulating immune responses. Soluble ST2 (sST2), a truncated form of the transmembrane ST2, is secreted into the circulation and acts as a receptor for interleukin-33. It is currently a recognized marker of cardiac remodeling, and it has been suggested that the levels of this protein may be elevated due to vascular injury and smooth muscle cell stretch, although these findings have not yet been experimentally confirmed. Results suggest that sST2 levels could be useful as an exclusion marker, possibly even slightly superior to D-dimer.[27,28]

Non-coding RNAs (ncRNAs)

Non-coding RNAs are single-stranded RNA molecules that negatively regulate gene expression through mRNA degradation. ncRNAs include long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), and microRNAs (miRNAs). ncRNAs can influence biological processes through post-transcriptional regulation and are differentially expressed in various cell or tissue states. However, to date, only limited studies have correlated deregulated miRNA expression with acute aortic syndrome. Wang *et al*.[29] analyzed miRNA expression in aortic tissue and plasma samples from patients with aortic dissection and control groups. They found that four miRNAs (miR-4313, -933, -1281, and -1238) were upregulated both in aortic tissue and plasma, concluding that these selected molecules could be potential diagnostic biomarkers. Nevertheless, at present, testing remains costly, slow, and not widely accessible, and clinical studies are still insufficient.[30]

Markers of thrombosis

– D-dimer: D-dimer is a fibrin degradation product (protein fragment) detectable in the blood during active fibrinolysis. It is widely used as a diagnostic and prognostic marker in venous thromboembolism and disseminated intravascular coagulation. The IRAD-Bio study demonstrated that D-dimer has high sensitivity and a low negative likelihood ratio, making it suitable for ruling out AAS.[18]

An additional issue is that many of the above-mentioned biomarkers are not available for urgent testing, as they have only been used in research settings. In contrast, D-dimer is easily measurable and widely available in emergency clinical practice, being one of the few biomarkers included in diagnostic protocols and with proven usefulness in suspected AAS diagnosis in hospital emergency departments.[1,11]

Importance of D-dimer in the diagnosis of acute aortic syndrome

As previously mentioned, AAS presents with non-specific symptoms that overlap with other common conditions in emergency departments, making it difficult to differentiate without an imaging study such as a thoracic CT angiography (CTA). It is essential to properly select patients who require this imaging test — balancing the risk of underdiagnosis against the cost, radiation exposure, and contrast-induced nephropathy associated with performing excessive imaging studies.[31,32]

Plasma D-dimer, being a degradation product of cross-linked fibrin, becomes elevated when an active clot is present, reflecting simultaneous activation of coagulation and fibrinolysis. It is important to note that D-dimer levels increase with age, approximately by 100 ng/mL per decade after age 50. Thus, normal values are around 500 ng/mL for individuals younger than 50 years, 600 ng/mL at 60, 700 ng/mL at 70, and so on. D-dimer is most useful in the diagnosis of venous thromboembolic disease, where it has a very high negative predictive value (NPV).[33] Because it is highly specific to fibrin, which is produced in various processes (e.g., cancer, inflammation, infection, necrosis, or aortic dissection), D-dimer can also assist in the diagnostic evaluation of other entities.

Several recent studies have evaluated the usefulness of D-dimer in AAS screening prior to CTA, identifying it as an important diagnostic tool in emergency settings.[34] These studies have assessed sensitivity, specificity, predictive values, and likelihood ratios (Table 3).

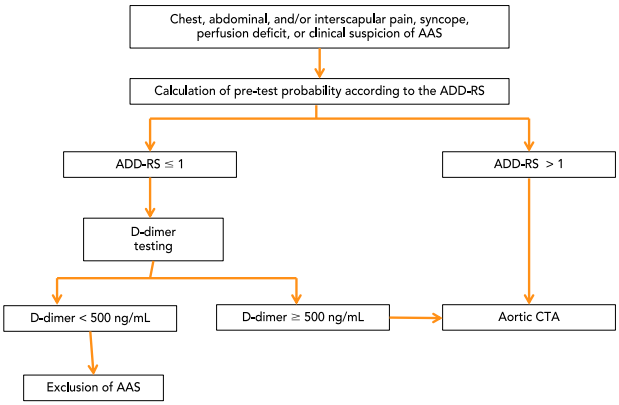

Figure 1. Proposed diagnostic algorithm based on the pre-test probability of acute aortic syndrome (AAS) according to the Aortic Dissection Detection Risk Score (ADD-RS) and D-dimer, adapted from Nazerian *et al.*[1]

In 2015 and 2016, two systematic reviews and meta-analyses summarized the evidence available at that time regarding D-dimer's effectiveness in AAS diagnosis. In the first,[35] the authors reviewed studies published up to 2014 that examined D-dimer for ruling out AAS. Out of 30 potentially relevant studies, only 5 (totaling 1,600 patients) met inclusion criteria. All used a cutoff value of 500 ng/mL (not age-adjusted). The sensitivity and specificity were 98% (95% CI, 96–99) and 42% (95% CI, 39–45), respectively. In 2016, Watanabe *et al.*[36] conducted another systematic review including case-control and cohort studies that provided data on D-dimer's diagnostic accuracy. Among 22 studies, 12 (2,827 participants) used the 500 ng/mL cutoff, yielding sensitivity 95.2% (95% CI, 90.1–97.8) and specificity 60.4% (95% CI, 48.5–71.2). Both analyses concluded that D-dimer is useful for excluding AAS, particularly in low-risk patients.

Following these two reviews, several studies were published with the aim of generating stronger evidence to support the use of D-dimer in the diagnostic management of AAS. Kotani *et al.*[34] conducted an observational study in patients evaluated in the emergency department of a tertiary hospital who underwent D-dimer testing due to chest pain. A total of 887 patients were included, of whom 123 were diagnosed with AAS, 29 with pulmonary embolism, and 735 with other conditions. Patients with AAS had significantly higher D-dimer values than those in the control group, although lower than in patients with pulmonary embolism. The area under the ROC curve (AUC) for AAS diagnosis was 0.87, which was lower than that for pulmonary embolism (0.94). A cutoff point of 500 ng/mL showed high sensitivity (97%), similar to that observed in pulmonary embolism patients, with a specificity of 44%. When age-adjusted cutoffs were used, sensitivity decreased only slightly to 96%. These results led the authors to conclude that D-dimer is useful to differentiate AAS and pulmonary embolism from other diagnoses in patients presenting to the emergency department with chest pain. The 500 ng/mL cutoff can be used as an exclusion criterion for either diagnosis with high sensitivity, and using an age-adjusted cutoff helps reduce false positives. Lee *et al.*[37] evaluated the diagnostic performance of age-adjusted D-dimer values compared to standard fixed cutoffs. They analyzed 301 emergency patients in whom AAS was suspected and thoracic CT angiography was performed. D-dimer levels were significantly higher in the confirmed AAS group (10.85 µg/mL vs. 0.40 µg/mL in non-AAS patients; $P < .001$), with an AUC of 0.915 (95% CI: 0.873–0.956). They concluded that the use of age-adjusted D-dimer values provides the same sensitivity as the traditional 500 ng/mL cutoff but with greater specificity (65.57% vs. 59.84%).

More recently, another study analyzed the ability of D-dimer to predict the diagnosis of AAS, comparing the conventional cutoff value with the ADD-RS and plain chest radiography in an emergency department setting.[38] The sensitivity and specificity values for D-dimer were similar to those reported in the two previous studies, with higher specificity when age-adjusted levels were used — an important consideration in elderly patients, who represent the majority of those treated for this condition in emergency departments in our country. However, the main finding was that the combination of the three diagnostic strategies resulted in fewer than 3% diagnostic errors and a 7.6% reduction in false positives.

Zhang *et al.*[39] also conducted a retrospective study including patients who presented with symptoms suggestive of AAS and a group of patients in whom AAS-like findings were discovered incidentally during follow-up imaging for other conditions. Their goal was to compare D-dimer values with the neutrophil-to-lymphocyte ratio (NLR) in this cohort. D-dimer showed a sensitivity of 74%, a specificity of 76%, and a negative predictive value (NPV) of 90%. When comparing both biomarkers, D-dimer and NLR had similar areas under the ROC curve (AUC), although NLR showed slightly superior discriminative capacity.

Another important aspect of D-dimer in the diagnostic suspicion of AAS is its early elevation, which can occur within the first hour after symptom onset.[40]

These studies, however, were not without limitations, the most significant being their retrospective and single-center design. This led to the need for a prospective study to validate the findings. Nazerian *et al.*[41] conducted a multicenter prospective study including 1,850 emergency department patients with symptoms suggestive of AAS, aiming to evaluate the diagnostic accuracy of the ADD-RS combined with D-dimer. Of these patients, 13% were ultimately diagnosed with AAS, and 5% had an ADD-RS of 0. D-dimer levels were significantly higher in AAS patients (5,810 ng/mL vs. 370 ng/mL in those without aortic disease; $P < .001$). Using a cutoff of 500 ng/mL, D-dimer demonstrated a sensitivity of 96.7%, specificity of 64%, PPV of 28.7%, and NPV of 99.2%. When combining D-dimer with ADD-RS, patients with ADD-RS = 0 or ≤ 1 and D-dimer < 500 ng/mL had an NPV of 99.7%. Based on these results, the authors proposed a diagnostic algorithm in which patients with ADD-RS > 1 should undergo aortic CTA, whereas those with ADD-RS ≤ 1 should first have a D-dimer test. If D-dimer < 500 ng/mL,

Table 3. Sensitivity, specificity, positive and negative predictive values, and likelihood ratios of major studies on the usefulness of D-dimer for diagnosing acute aortic syndrome (AAS)

Study	Type of study	Target population	S (95% CI)	Sp (95% CI)	PPV (95% CI)	LR+ (95% CI)	NPV (95% CI)	LR– (95% CI)	AUC (95% CI)
Asha *et al.* Ann Emerg Med 2015; 66:368-78.	Systematic review and meta-analysis	5 studies (N = 1600)	98 (96-99)	42 (39-45)		2.11 (1.46-3.05)		0.05 (0.02-0.09)	
Watanabe *et al.* Sci Rep 2016;6:26893.	Systematic review and meta-analysis	12 studies (N = 2827)	95.2 (90.1-97.8)	60.4 (48.5-71.2)		2.4 (2.8-3.3)		0.079 (0.036-0.172)	
Zhang *et al.* Am J Emerg Med. 2023;69:44-51.	Retrospective	Symptomatic AAS patients and incidental cases when studying other conditions (N = 697)	AAS: 74 (69-79) AD: 79 (73-84) Acute AD: 81 (75-85)	AAS: 76 (72-80) AD: 71 (67-76) Acute AD: 73 (69-77)	AAS: 51 (46-56) DA 48 (44-52) Acute AD: 50 (46-54)	AAS: 3.1 (2.6-3.8) DA 2.7 (2.3-3.2) Acute AD: 3.0 (2.5-3.5)	AAS: 90 (88-92) DA 91 (89-93) Acute AD: 92 (90-94)	AAS: 0.34 (0.3-0.4) DA 0.3 (0.2-0.4) Acute AD: 0.27 (0.2-0.4)	AAS: 0.882 (0.792-0.850) DA 0.827 (0.797-0.855) Acute AD: 0.844 (0.815-0.870)
Nazerian *et al.* Circulation. 2018; 137:250-8.	Prospective. multicenter	ED patients with suspected AAS (N = 1.850)	D-dimer only 96.7 (93.6-98.6) ADD-RS = 0 + D-dimer < 500 ng/mL 99.6 (97.7-100) ADD-RS ≤ 1 + D-dimer < 500 ng/mL 98.8 (96.4-99.7)	D-dimer only 64 (61.6-66.4) ADD-RS = 0 + D-dimer < 500 ng/mL 18.2 (16.4-20.2) ADD-RS ≤ 1 + D-dimer < 500 ng/mL 57.3 (54.9-59.7)	D-dimer only 28.7 (25.6-32) ADD-RS = 0 + D-dimer < 500 ng/mL 15.4 (13.7-17.3) ADD-RS ≤ 1 + D-dimer < 500 ng/mL 25.8 (23-28.7)	D-dimer only 2.69 (2.51-2.88) ADD-RS = 0 más D-dimer < 500 ng/mL 1.22 (1.19-1.25) ADD-RS ≤ 1 más D-dimer < 5 00 ng/mL 2.31 (2.18-2.45)	D-dimer only 99.2 (98.5-99.7) ADD-RS = 0 más D-dimer < 500 ng/mL 99.7 (98.1-100) ADD-RS ≤ 1 más D-dimer < 500 ng/mL 99.7 (99.1-99.9)	D-dimer only 0.05 (0.03-0.1) ADD-RS = 0 más D-dimer < 500 ng/mL 0.02 (0.003-0.16) ADD-RS ≤ 1 más D-dimer < 500 ng/mL 0.02 (0.01-0.07)	
Kotani *et al.* Eur Heart J Acute Cardiovasc Care. 2017;6:223-31.	Retrospective	ED patients with chest pain who ended up being hospitalized (N = 887)	D-dimer (unadjusted): 97 (92-99) D-dimer (age-adjusted): 96 (91-99)	D-dimer (unadjusted): 44 (41-48) D-dimer (age-adjusted): 58 (54-61)		D-dimer (unadjusted): 1.74 (1.62-1.87) D-dimer (age-adjusted): 2.26 (2.06-2.48)		D-dimer (unadjusted): 0.07 (0.03-0.19) D-dimer (age-adjusted): 0.07 (0.03-0.17)	0.87
Morello *et al.* J Am Heart Assoc. 2021;10:e018425.	Retrospective cohort	ED patients with AAS-suggestive symptoms and no alternative diagnosis	ADD-RS ≤ 1 + D-dimer < 500 98.8 (96.4-99.7)	ADD-RS ≤ 1 + Dimero-D < 500 57.3 (54.9-59.8)		ADD-RS ≤ 1 + D-dimer < 500 2.31 (2.18-2.45)		ADD-RS ≤ 1 + D-dimer < 500 0.02 (0.01-0.07)	
Morello *et al.* J Am Heart Assoc. 2021;10:e018425.	Prospective cohort	ED patients with suspected AAS	ADD-RS ≤ 1 + D-dimer < 500 99.1 (96.9-99.95)	ADD-RS ≤ 1 + D-dimer < 500 30.2 (27-33.5		ADD-RS ≤ 1 + D-dimer < 500 1.42 (1.35-1.49)		ADD-RS ≤ 1 + D-dimer < 500 0.03 (0.01-0.11)	

ADD-RS: aortic dissection detection risk score; AUC: area under the curve; AD: aortic dissection; AAS: acute aortic syndrome; S: Sensitivity; Sp: Specificity; VPP: Positive predictive value; VPN: Negative predictive value; LR+: Positive likelihood ratio; LR–: Negative likelihood ratio.

AAS can be safely ruled out; if D-dimer ≥ 500 ng/mL, imaging should be performed (see Table 1). Morello *et al.*[42] obtained similar findings in a study designed to validate a new AAS suspicion score, concluding that the combination of D-dimer and clinical probability scores constitutes the best diagnostic approach for AAS in emergency departments.

Recently, the combination of D-dimer with other biomarkers has been explored to improve AAS diagnosis. A recent study evaluated the ability of the D-dimer/high-sensitivity troponin ratio (D/T ratio) to differentiate AAS from non-ST-elevation acute coronary syndrome (NSTEACS) in patients presenting to the emergency department with chest pain, since both entities often share similar symptoms. Results showed that the D/T ratio had an AUC of 0.973 (95% CI, 0.930–0.998), with an optimal cutoff of 81.3, yielding 91.4% sensitivity and 96.2% specificity. By comparison, D-dimer alone had an AUC of 0.943 (95% CI, 0.910–0.984), with 94.2% sensitivity and 91.8% specificity at a cutoff of 1.185 µg/mL.[43]

Conclusions

Efforts to develop useful biomarkers for the diagnosis of AAS have been numerous. As discussed, some may have prognostic utility, but to date, no biomarker has proven sufficiently effective to warrant widespread clinical implementation. D-dimer has demonstrated good discriminatory ability, particularly for the exclusion of AAS, based on consistently high sensitivity values across studies and high NPV. However, as with many other conditions, the greatest clinical usefulness arises from its combined use with the ADD-RS.[44] Thus, in patients with ADD-RS ≤ 1 and normal age-adjusted D-dimer levels, the diagnosis of AAS can be reliably excluded.[41] Conversely, in patients with ADD-RS > 1 or positive D-dimer results, additional imaging modalities should be performed.[23]

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