D-dimer measurements in acute aortic dissection

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Abstract

Acute aortic dissection (AAD) is a medical emergency with significant morbidity and mortality. The diagnosis can be challenging due to the wide array of presenting symptoms and a broad differential diagnosis. Computed tomographic angiography is currently the gold standard for diagnosis of AAD. However, it carries the risk of contrast and radiation exposure and has a financial burden for patients. Multiple biomarkers have been evaluated as a screening tool for AAD. D-dimer has previously been suggested as a sole rule-out test for AAD. It is rapid and inexpensive, is widely available in the emergency rooms, and is highly sensitive for any thrombotic event. This review article evaluates the evidence for the use of D-dimer assays in the diagnosis of AAD, in differentiation of AAD from acute coronary syndromes, and in risk stratification of AAD patients.

Key words: aortic dissection, D-dimer, diagnosis

Introduction

Acute aortic dissection (AAD), although uncommon, is a medical emergency with significant morbidity and mortality if not promptly treated. The initial presentation of AAD can range from an array of common and nonspecific symptoms to a dramatic presentation of cardiovascular collapse.[1-3] After the diagnosis of AAD is suspected, it is confirmed by imaging modalities. [4] These imaging studies, although frequently used, are not without flaws; they have high costs and might not be available in small rural hospitals. The most common imaging study is computed tomographic angiography (CTA), which is usually diagnostic of AAD. However, this imaging modality exposes patients to radiation and may produce contrast nephropathy or cause allergic reactions with anaphylaxis as the most extreme adverse effect.[5-6] As a result, the 2010 AHA guidelines for diagnosis and management of thoracic aortic disease proposed a risk score for use at the bedside as a clinical tool to estimate the risk of AAD.[7] This has been shown to be effective in subsequent studies.[8]

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Multiple studies have been conducted to identify a biomarker suitable for AAD screening. A desirable biomarker needs to be accurate, rapid, and relatively inexpensive. Unfortunately, no biomarker currently provides a gold standard.[4,9-13] Another possibility is to use a combination of biomarkers, but according to Peng et al an effective combination has not yet been identified. [9]

This review evaluates the evidence for the use of D-dimer assays in the diagnosis of AAD. D-dimer is a degradation product of crosslinked fibrin. It is widely used in emergency departments as a screening tool for deep veins thrombosis and pulmonary thromboembolism due to its high sensitivity and negative predictive value.[14-15] D-dimer assays are both rapid and inexpensive, and this adds to their value as a screening test. A number of studies have evaluated this test as a potential biomarker for the diagnosis of AAD.

Methods

An extensive Medline search was performed using the following text words: “acute aortic dissection”, “D-dimer”, “biomarkers”. The articles related to the topic were initially selected based on their titles. Then irrelevant articles were excluded based on their abstracts. The remaining articles were used to develop this review.

Results

We identified 17 original studies that addressed the utility of D-dimer levels in the diagnosis of AAD (Table 1).[8,16-31] Most studies used proven AAD patients as a study group. The control group consisted of patients who were suspected to have AAD but were subsequently ruled out by imaging studies. Suggested D-dimer cut-off levels varied from 0.1 to 0.626 μg/ml; the most common threshold level used was 0.5 μg/ml. The sensitivity was as high as 96.6-100%, and the specificity varied from 30.9 to 73%.

Four studies did not include a control group and, therefore, were able to evaluate sensitivity but not specificity.[16-19] They all used a D-dimer cut-off of 0.5 μg/ml, and the sensitivity reported was 88-100%.

Meta-analysis

We identified four meta-analysis studies that assessed the diagnostic performance of D-dimer tests (Table 2).[17,32-34] The pooled sensitivity was between 94-97%. The pooled specificity was reported in only two studies and was 56% and 59%. [33-34]

D-dimer in combination with other diagnostic tests

Several studies also analyzed the ability of D-dimer to reliably exclude AAD when used in combination with other diagnostic tests. Giachino et al reported an negative predictive value of 100% for the diagnosis of AAD when using matrix metalloproteinase 8 (MMP8) levels above 0.11 ng/ml and D-dimer levels above any of the following cut-offs: 0.5, 1, or 2 μg/ml. However, the combination of D-dimer tests with MPP8 levels decreased the already low specificity of D-dimer tests from 32.8% to 16.4%.[26]

Hazui et al studied the diagnostic value of D-dimer levels in combination with the M-ratio (ratio of the maximum upper mediastinal diameter to the maximum upper thoracic diameter on plain chest radiograph). They showed that D-dimer plasma concentrations above 0.8-0.9 μg/ml with an M-ratio of >0.309 can distinguish AAD from AMI with a sensitivity of 100%. However, the study sample was rather small and consisted of 78 patients (29 were subsequently diagnosed with AAD and 49 with ACS).[27]

Nazerian et al assessed D-dimer performance in combination with the aortic dissection detection (ADD) risk score (Table 3). They demonstrated better performance of D-dimer in the low risk group compared to the high risk group.[8]

Can D-dimer differentiate between AAD and CAD?

Four studies were identified that tried answer this question (Table1). One of them showed significant differences between patients with AAD, aortic aneurysm (AA), and coronary artery disease (CAD).[31]

Table 1 Original articles that evaluated the performance of D-dimer in diagnosis of acute aortic dissection

Name, year	Study group/N of patients	Control group/N of patients	Sensitivity, %	Specificity, %	D-dimer cut-off value, µg/ml	Additional findings
Perez, 2004[16]	AAD/7	N/A	100	N/A	0.5	
Sodeck, 2007[17]	AAD/65	N/A	100 98 86	N/A	0.1 0.5 0.9	
Wiegand, 2007[18]	AAD/25	N/A	88	N/A	0.5	No association was found between D-dimer level and the time from symptoms onset and the extend of the dissection.
Weber, 2006[19]	AAD/27	N/A	100	N/A	0.5	D-dimer was the only independent predictor of in-hospital mortality
Weber, 2003[20]	AAD/64	Chest pain patients/35	100	68.6	0.5	
Eggebrecht , 2004[21]	AAD/16	Chest pain syndromes/48	100	73	0.626	D-dimer failed to be statistically significant predictor of in-hospital mortality of AAD patients.
Akutsu, 2005[22]	AAD/30	Suspected but ruled out AAD/48	100	54	0.5	No correlation was found between D-dimer levels and time from symptoms onset or type of AAD (type A or B, with thrombosed or patent false lumen). Combination of D-dimer level with SBP at admission >180 mmHg increased PPV but decreased sensitivity compared to D-dimer level alone.
Ohlmann, 2006[23]	AAD/94	Suspected but ruled out AAD/94	99	34	0.4	Statistically significant correlation was found between D-dimer levels of patients with intramural hematoma and in patients with patent false lumen. No significant difference was found between D-dimer levels in patients with Stanford A and B ADD. D-dimer levels were significantly higher DeBakey I compared to DeBakey II or III AAD patients. D-dimer was a significant predictor of in-hospital mortality.
Suzuki, 2009[24]	AAD/87	Suspected but ruled out AAD/133	96.6	46.6	0.5	Sensitivity and specificity of D-dimer for AAD detection was 95.7% and 61.3% respectively within the first 6 hours after presentation. The difference between D-dimer levels in AAD with false and patent lumen was not statistically significant.
Fan, 2010[25]	AAD/107	Suspected but ruled out AAD/260	99.2	30.9	0.17	
Giachino, 2013[26]	AAD/52	Suspected but ruled out AAD/74	97.6	32.8	0.5	Diagnostic performances of MMP8 and MMP9 were inferior to that of D-dimer. Combination of MMP8 at cut-off of 0.11 ng/ml and D-dimer at any cut-off level (0.5, 1 or 2 µg/ml) had NPV of 100% for detecting of AAD. However, combination of D-dimer with MPP8 had lower specificity compared to D-dimer alone (16.4 vs. 32.8% correspondingly).

Table 1 Original articles that evaluated the performance of D-dimer in diagnosis of acute aortic dissection (continued)

Name, year	Study group/N of patients	Control group/N of patients	Sensitivity, %	Specificity, %	D-dimer cut-off value, µg/ml	Additional findings
Nazerian, 2014[8]	AAD/233	Suspected but ruled out AAD/802	98.3	35.9	0.5	Aortic dissection detection (ADD) risk score ≥1 had sensitivity of 91.9% and specificity of 37.8% for detection of AAD. D-dimer levels had better diagnostic performance in patients with low ADD risk score than in patients with high ADD risk score.
Hazuil, 2005[27]	AAD/29	AMI/49	93.1	91.8	0.8-0.9	Significant difference between D-dimer levels was found in patients with a thrombosed false lumen and with a patent false lumen; in patients with DeBakey type I and II AAD. Combination of D-dimer level over specified cut-off value with M-ratio >0.309 yielded sensitivity of 100%.
Sakamoto, 2011[28]	AAD+PE/57	AMI/206	68.4	90.3	5	
Sbarouni, 2006[29]	AAD/18	Normal subjects+chronic aortic aneurysm/29	94	59	0.7	D-dimer was not shown to be a significant predictor of mortality or type of AAD. There were no correlation between D-dimer and time from symptoms onset.
Tokital, 2009[30]	Large vessel disease/15	Suspected but ruled out ACVD/204	87	99	5	D-dimer levels at cut-off of 5 µg/ml were able to discriminate between ACS patients (N=60) and large vessel disease patients with sensitivity of 87% and specificity of 98%. D-dimer levels at cut-off of 0.5 µg/ml were able to discriminate between ACVD and non-ACVD with sensitivity of 92% and specificity of 27%
Yuan, 2011[31]	AAD type A/20 AA/9 CAD/20	Healthy volunteers/ unknown number	No significant difference was found between D-dimer levels of AAD and AA groups. D-dimer levels were significantly different between AAD+AA and CAD, AAD+AA and healthy volunteers groups. D-dimer was undetectable in supernatant of aortic tissue of CAD patients, as opposed to AAD+AA group.			

AA – aortic aneurysm, ACVD – acute cardiovascular disease, ADD – acute aortic dissection; AMI – acute myocardial infarction, CAD – coronary artery disease; MMP – matrix metalloproteinases; NPV – negative predictive value; PPV – positive predictive value; PE – pulmonary embolism; SBP-systolic blood pressure

Table 2 Meta-analysis studies that evaluate diagnostic performance of D-dimer levels

Study	N of studies included	N of AAD patients analyzed	D-dimer cut-off value, µg/ml	Pooled sensitivity	Pooled specificity
Sodeck, 2007[17]	16	437	0.1-0.9	97	N/A
Marill, 2008[32]	11	349	0.5	94	N/A
Shimony, 2011[33]	7	298	0.5	97	56
Cui, 2015[34]	5	274	Variable	94.5	69

Table 3 Aortic dissection detection risk score

Low risk (score 0): No high risk features present **Intermediate risk (score 1):** Any single high risk feature present **High risk (score > 1):** Two or more high risk features present	
High risk features	
High risk conditions	☐ Marfan syndrome ☐ Connective tissue disease ☐ Family history of aortic disease ☐ Known aortic valve disease ☐ Recent aortic manipulation ☐ Known thoracic aortic aneurism
High risk pain features	☐ Chest, back, or abdominal pain described as: ▪ Abrupt in onset/severe in intensity **and** ▪ Ripping/tearing/sharp or stabbing quality
High risk exam features	☐ Evidence of perfusion deficit: pulse deficit, systolic BP differential, focal neurologic deficit (in conjunction with pain) ☐ Murmur of aortic insufficiency (new or not known to be old and in conjunction with pain) ☐ Hypotension or shock state

Two other studies evaluated the ability of D-dimer levels to discriminate between AAD and acute myocardial infarction (AMI) 27 or combined AAD and pulmonary embolus (PE) group and AMI.28 They reported that D-dimer cut-of values of 0.8-0.9 and 5 µg/ml were able to differentiate between AAD and AMI or AAD+PE and AMI with sensitivity of 93.1% and 68.4% and specificity of 91.8% and 90.3%, respectively. Mean D-dimer levels reported by these studies were 32.9-45.3 µg/ml for AAD group and 0.4-2.1 µg/ml for AMI group. Tokita et al showed that at a level of 5 µg/ml the D-dimer was able to discriminate between ACS and large vessel disease with sensitivity of 87% and specificity of 98%.[30]

Can D-dimer differentiate between different types of AAD?

Studies answering this question have had equivocal results. In relation to Stanford classification, one study found statistical significance in D-dimer levels (6.51±4.11 µg/ml for type A vs 4.87±2.29 µg/ml for type B, p=0.013) 35 and two studies did not. [22-23] Two studies measured differences in D-dimer levels between patients with DeBakey Type I and DeBakey Type II or III AAD; they both reported statistical significance (15.7 µg/ml for DeBakey Type I vs 3.1-4.0 µg/ml for DeBakey Type II-III, p<0.05; 23 56.6 µg/ml for DeBakey Type I vs 2.0 µg/ml for DeBakey Type II, p=0.004 27). Two studies reported significant differences in D-dimer levels in patients with thrombosed false lumens vs. patent false lumens (9.3 vs 1.2 µg/ml respectively, p=0.0001; 23 73.9 vs 10.1 µg/ml respectively; p=0.001 27), but two other studies failed to identify any difference. [22,24]

Can D-dimer be used for prognosis determination?

Several studies have tried to identify significant predictors of in-hospital mortality for patients with proven AAD. Eggbrecht et al and Sbarouni et al reported no significant difference in D-dimer levels between patients who died and those who survived.[21,29] However, their samples included only 16 and 18 patients with 50 and 72% survival rates, respectively. Ohlmann et al evaluated the differences in D-dimer levels between survivors and non-survivors and found a significant positive relationship between D-dimer levels and in-hospital mortality. [23]

Two studies specifically evaluated predictors of in-hospital mortality in AAD patients. [19,35] Both of them showed D-dimer levels to be independent significant predictors of mortality (Table 4). Wen et al showed that AAD patients with abnormal D-dimer levels (>0.5 µg/ml) are three times more likely to die in the hospital compared to those with normal levels. They also determined a cut-off value that provides the best sensitivity and specificity for predicting mortality (>5.67 µg/ml, 90.3%, 75.9%, respectively).[35]

Discussion

The D-dimer is an easy to perform, inexpensive, and safe test that has been suggested as a rule out test for AAD. Its sensitivity for AAD detection was as high as 94-97% with the most commonly accepted cut-off value of 0.5 µg/ml in a number of meta-analysis studies, but it is very non-specific. The cost-effectiveness of D-dimer was demonstrated by a German study performed in 2011, which showed that the cost of emergency medical care for patients who presented with chest pain can be reduced by almost 2.5 fold if CT scanning is performed only for patients with elevated D-dimer levels. [36]

It is commonly accepted in clinical practice that D-dimer has a value in patients with high pre-test probability for AAD as opposed to patients with low pre-test probability. Nazerian et al assessed D-dimer performance in combination with the ADD risk score and demonstrated better performance of D-dimer in the low risk group compared to the high-risk group.8 However, AAD is a critical cardiovascular emergency in which mistakes cost lives. As shown above, every negative D-dimer value carries a risk of approximately 5% to miss the diagnosis of AAD. Therefore, in our opinion, D-dimer can be used to support a clinical suspicion but should not be used as a sole rule-out test.

D-dimer levels can provide some assistance in differentiating AAD from AMI and other ACSs. How-

ever, it cannot serve as a primary tool in differential diagnosis and is secondary to gold standard tests. There is not enough evidence to demonstrate that D-dimer levels can differentiate AAD with false thrombosis from AAD with a patent lumen. There has been no cut-off level suggested to differentiate DeBakey Type I from DeBakey Type II and III AADs even though its level correlates significantly with the extent of aortic involvement. Moreover, this information is readily available from CT readings; therefore D-dimer measurement does not add any practical benefit. Studies show D-dimer to be a useful tool in predicting in-hospital mortality. At a cut-off level of 5.67 μg/ml its sensitivity and specificity are 90.3 and 75.9%, respectively. These results are interesting but need to be validated in large sample size and in prospective clinical trials.

Table 4. Original articles that evaluate risk factors for in-hospital mortality of acute aortic dissection patients.

Study	N of AAD patients analyzed	Mortality,%	Predictors of death in univariate logistic regression	Predictors of death in multivariate logistic regression
Weber, 2006[19]	27	51.9	D-dimer Lower diastolic BP on admission Conservative management	D-dimer
Wen, 2013[35]	114	73	Type of AD Aortic diameter D-dimer CRP	Type of AD D-dimer CRP

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