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Application of D-dimer to Aid in Diagnosis of Acute Aortic Dissection

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Abstract:

Introduction: Acute aortic dissection (AAD) is an emergent, relatively uncommon condition that typically presents with sudden onset severe chest or back pain.¹ Advanced imaging, such as computerized tomography, is currently the gold standard to diagnose AAD; this can be expensive and unavailable at all health care centers. D-dimer is a blood test that has been shown in recent studies to be elevated in acute aortic dissection. This may be a more cost-effective way to help the clinician “rule-out” an acute aortic dissection.¹

Objective: The purpose of this research was to determine if there is significant data regarding the sensitivity and specificity of a D-dimer in the use of diagnosing an acute aortic dissection.

Methods: A PubMed search was conducted utilizing the following terms and filters: “aortic dissection” and “D-dimer.” Articles were screened and assessed for eligibility based on sample size, evaluation of sensitivity and specificity of d-dimer, and if D-dimer was the only independent factor being examined in diagnosis of an AAD.

Results: Our search resulted in one retrospective observational study, one prospective observational study, and one meta-analysis.

Conclusion: In a patient presenting to the Emergency Department with symptoms suspicious of an acute aortic dissection, a D-dimer level less than 500ng/ml may be a useful tool to decrease the likelihood of the disease and reduce the need for advanced imaging. The D-dimer is not shown to be specific for acute aortic dissection. The addition of a D-dimer as a first line test may be a quick tool to help a clinician adjust their differential diagnoses to determine the need for imaging.¹

Introduction

Acute Aortic Dissection (AAD) is a tear in the wall of the aorta.² As the tear extends, blood can flow in between the layers of the blood vessel wall, which leads to ischemia to nearby organs or aortic rupture; both abrupt and lethal. AAD often presents with severe chest pain and acute hemodynamic compromise; however, the symptoms can be vague, making the disease privy for misdiagnosis and malpractice.³

Currently, the gold standard to diagnose AAD is the use of imaging which includes the following methods: computed tomography (CT), magnetic resonance angiography (MRA), and transesophageal echocardiogram (TEE). Each of these imaging techniques has its own risk associated with them for the patient. CT exposes patients to radiation and also uses contrast dye which is harmful to the kidneys. MRA also uses contrast dye meaning patients with renal disease may not be able to undergo the test. TEE is a moderately invasive procedure which includes the risk of esophageal perforation, and the patient is also under conscious sedation. Due to the lethality of AAD, most patients presenting with chest pain will undergo imaging to rule out AAD; however, due to the rarity of AAD, most of the imaging is negative as the prevalence/incidence of AAD is 3.5 per 100,000 person per year³, which uses time, resources, and money. It is difficult to perform imaging as the initial diagnostic test due to high cost, radiation exposure, and the high volume of patients who present with a chief complaint of “chest pain.”⁴

D-dimer is degradation product of fibrin, whose serum level is elevated in AAD, venous thromboembolism (VTE), and other conditions.³ Collecting a quick, serum blood D-dimer would be a faster, more cost-efficient method to rule out AAD. In the past 20 years, increased research has displayed diagnostic accuracy of D-dimer for AAD, with a sensitivity at 0.97 and sensitivity of 0.64.² The high sensitivity indicates a negative D-dimer which could theoretically rule out AAD. Using the cutoff value of 500ng/ml, the same value used to rule out venous pulmonary embolism (PE), has been repeatedly used with consistent results.¹ We analyzed three studies to assess the role of a negative D-dimer in the workup in patients suspected of an AAD to eliminate the use of unnecessary imaging.

Case:

CB is a 68 year old Caucasian male who presents to a busy ER with abrupt chest pain, beginning one hour prior to arrival. He has a history of hypertension and high cholesterol. Upon arrival, his clinician is considering both myocardial infarction and acute aortic dissection based on his clinical appearance and physical exam findings. We are interested to see if performing a D-dimer assay will assist the clinician in their diagnosis and help determine the need for advanced imaging.

PICO Criteria:

Population: Patients with Acute Aortic Dissection

Intervention: D-dimer assay

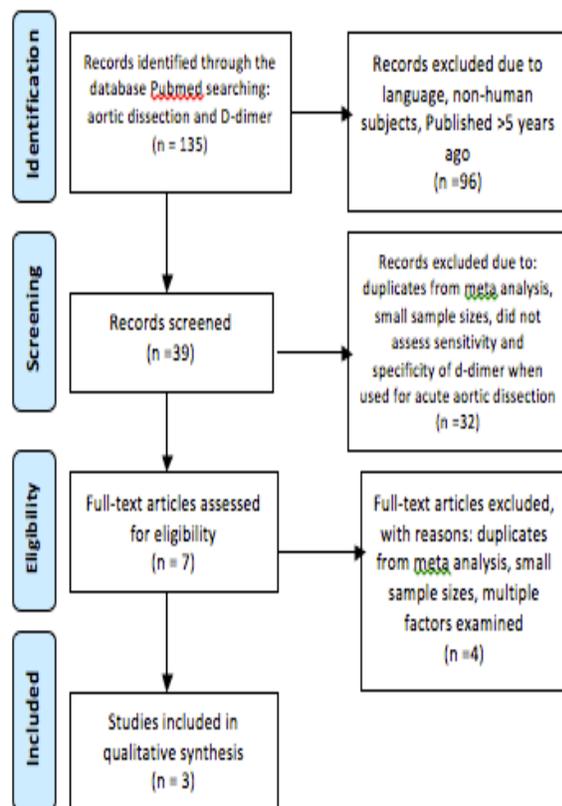
Comparison: Imaging (including CT, MRA, TEE)

Outcome: Accurate Diagnosis

Clinical Question: In patients presenting with symptoms of an acute aortic dissection, can a D-dimer assay be used to help determine the need for advanced imaging?

Methods:

An initial PubMed search was conducted in September of 2015 using the search terms, “aortic dissection” and “D-dimer.” 135 articles were found and screened for their eligibility. Ninety-six articles were excluded due to non-human subjects, non-English language, or if they were published before 2009. The remaining 39 articles were further screened, and 32 were excluded if they were duplicates used within the selected meta-analysis, had a small sample size less than 100, or did not assess both sensitivity and specificity of a D-dimer used in the evaluation



of an acute aortic dissection. Seven full text articles were assessed for eligibility and four were excluded due to including statistics other than sensitivity and specificity. Three articles qualified for this research, including one meta-analysis, one prospective original research article, and one retrospective observational original research article.

Results:

Study 1: *Validation of the diagnostic utility of D-dimer measurement in patients with acute aortic syndrome* by Kotani et al.

Objective:

Evaluated the validity of D-dimer for the diagnosis of acute aortic syndrome (AAS) in patients that were admitted to the hospital with acute chest pain.⁵

Design:

A retrospective observational study from 2011-2014 assessed D-dimer values from corresponding medical records. Patients referred from the emergency room (ER) with acute chest pain were admitted (N=887) to the tertiary hospital; of those admitted, 123 patients were diagnosed with acute aortic syndrome. Twenty-nine patients were diagnosed with acute pulmonary embolism(APE); 735 patients had other diagnoses, which served as the

control. Outpatients from the hospital were included if they were admitted for acute chest pain.⁵ Exclusion Criteria is shown in Table 1.

Table 1. Study #1 Exclusion Criteria

Exclusion Criteria
Discharged from ER with a lack of confirmation about final diagnosis and insufficient follow up instructions
Died in the emergency room before admission
Referred from another hospital
D-dimer analysis was not available on admission

This article used the terminology, acute aortic syndrome (AAS), which is an umbrella term that included all subtypes of acute aortic emergencies, including aortic dissection, intramural hematoma, penetrations ulceration of aorta, aortic aneurysm leak, aortic aneurism rupture, and

traumatic aortic transection.⁴ For purposes of uniformity, we referred to all the results in terms of AAD with associated subtypes since the other two articles use the terminology of AAD.

D-dimers were routinely drawn immediately in the (ER) for any patient with acute chest pain using the commercially available latex agglutination tests. Based on the 2010 AHA Guideline for the Diagnosis and Management of Patients with Thoracic Aortic Disease, the probability of risk was determined from the patient's history, physical exam, and chest pain characteristics to categorize the patients at low (score 0-1) or high (score 2-3) risk of AAD.⁵

The threshold above 500ng/ml was used to define a positive D-dimer assay. The final diagnosis was made based on computed tomography (CT) scan, which was also used to classify the types of AAD into the following subtypes: classic intimal flap type, intramural hematoma (IMH), penetrating aortic ulcer (PAU), ruptured aortic aneurysm, impending rupture of aortic aneurysm, or infectious aortic aneurysm.⁵

A Wilcoxon rank test, used to evaluate the difference between two tests which in this case are D-dimer level and imaging, established counts and percentages that were compared to the chi-square test, which is used to see the relationship between two variables. To assess the diagnostic ability of D-dimer assays, a Receiver-Operator Characteristic (ROC) curve was calculated that compared patients with AAS with the control group. Sensitivities, specificities, and likelihood ratios using a cutoff D-dimer value of 500ng/ml were evaluated; p values < 0.05 were considered significant.⁵

Results:

D-dimer levels in AAD and APE were both compared to the control group. D-dimer levels were significantly increased in patients with acute aortic dissection (AAD) ($p < 0.001$) compared to the control group. The area under the ROC curve was 0.87. An area under the ROC curve of 1 would represent a diagnostic test with perfect accuracy. This implies that the D-dimer has moderate to high accuracy in diagnosing an AAD because area is between 0.80-0.90.⁵

The age-adjusted formula was used in patients over 50 years old. If the patient's D-dimer level was greater than or equal to the patient's age divided by two, it was considered a positive test.⁵ When the positive age-adjusted D-dimer level was used for patients above 50 years old, the

results decreased four false positive down to two false positive results. For AAD, using this formula decreased the sensitivity to 0.9 (0.91-0.99) and specificity to 0.58 (0.54-0.61). The positive likelihood ratio increased to 2.26 (2.06-2.48) and the negative likelihood ratio stayed relatively the same at 0.07 (0.03-0.17). Although the formula improves a few unaccounted data points, the D-dimer assay missed two acute aortic dissection diagnosis subtypes: one intramural hematoma and one penetrated aortic ulceration.⁵

The study showed that D-dimer can distinguish AAD from other diseases that present with acute chest pain with high sensitivity and modest specificity.⁵ When separated into low and high risk probabilities, the sensitivity of D-dimer diagnosing AAD was 0.98 and the specificity of 0.51, compared to the high-risk sensitivity of 0.88 and specificity of 0.45; meaning the sensitivity is significantly stronger in patients with a lower probability risk of AAD.⁵ See Table 2.

The biggest limitation of this study was that high D-dimer levels were not seen in all subtypes of AAD; intramural hematoma and penetrated aortic ulceration in particular.

Table 2. Diagnostic utility of D-dimer in Acute Aortic Syndrome in Patients with Low Risk Probability Using Cut Off Level of the D-dimer Age-Adjusted Model.

LOW probability (score 0-1) n=474	Total	Positive age-adjusted D-dimer	Negative age-adjusted D-dimer	Sensitivity	Specificity	Negative Likelihood Ratio	Positive Likelihood Ratio
Acute Aortic Dissection	92	90	2	0.98 (0.92-0.99)	0.51 (0.46-0.56)	0.04 (0.01-0.17)	2.00 (1.80-2.22)
Other Disease	382	187	195	-	-	-	

Critique:

The strength of this study was that it included an adequate control group (n=735). The comparison of D-dimer values of AAD compared to APE and the control signified that a negative D-dimer may be applicable in ruling out AAD in patients with a low probability risk.

The paper included vital signs, including mean heart rates, systolic and diastolic blood pressures, and presence of arrhythmias; however, there was no mention if there were discrepancies in bilateral blood pressures, which can be a sign of acute aortic dissection, but also skew the means of the blood pressure results.⁶

The high sensitivity and modest specificity of D-dimers ability to diagnose AAS matches previous research. However, “acute” chest pain was not defined in terms of time, which could influence the results by allowing bias in which patients were chosen for the study. Another limitation of the study was that it was retrospective. This makes it difficult to know all the confounding variables each patient had and the reliance on records to have been kept with all the pertinent information may limit the study in who they could have chosen to be included. A retrospective study also not fully represent the general population in that each patient that presents with chest pain suspected of an AAD may not have gotten a D-dimer and those patients would not be included in the patient population.

Only initials were displayed accrediting the radiologist and physician who interpreted all the CT results, which matched the initials of some of the authors, which would indicate bias; however, speculation is high.

Study 2: *Diagnosis of Acute Aortic Dissection by D-dimer*⁷

Objective:

To determine the diagnostic capability of a D-dimer assay in patients with an acute aortic dissection.

Design:

Data was collected in this prospective study at 14 centers located in Europe, the United States, and Japan. Patients were included in the study if they presented to one of the centers within 24 hours of symptom onset and if consent was given. The evaluating physician must have ordered imaging due to suspected aortic dissection for the results to be included. D-dimer levels were measured using the triage D-dimer assay at the time the patient presented to the center.

Analyze-It software was used to examine the diagnostic performance, sensitivity, specificity, likelihood ratios, and predictive values using designated cutoff levels. The D-dimer levels were compared between patients with confirmed cases of aortic dissection and patients with other final diagnoses using the Nonparametric Mann-Whitney tests. The nonparametric Mann-Whitney test was used because it compares two independent groups, those with ADD and those without, with a dependent variable that is continuous, which is the D-dimer level.⁷

Results:

Two hundred and twenty patients were included in the study. Eighty-seven patients had confirmed acute aortic dissection, which was determined by imaging. The other 133 patients were used as a control group; their results were grouped into the following categories: myocardial infarction, angina, PE, or other uncertain diagnoses. Within the acute aortic dissection cases, 64 were Type A dissections that occur in the ascending aorta, and 23 were Type B dissections that occur in the descending aorta.⁷

In the acute aortic dissection Type A cases, the mean D-dimer was 3213 +/- 1465.⁷ For acute aortic dissection Type B cases the mean was 3574 +/- 1430.⁷ The D-dimer levels were elevated when compared to the mean D-dimer level for each of the control groups. These results can be seen in Table 1. A receiver-operating characteristics (ROC) curve analysis was performed and the area under the curve was 0.84 for all the patients presenting with acute aortic dissection compared to all the control subjects. The area under the curve of 0.84 implies that the D-dimer has moderate to high accuracy as a diagnostic test. A score of 1 would mean the diagnostic test has perfect accuracy.⁷ See Table 3.

Table 3. Patient Demographics and Baseline Data for Patients Presenting Within the First 24 Hours⁷

Diagnosis	Cases (Male), n	Age, y	Mean \pm SD	D-Dimer, ng/mL			
				25th Percentile	50th Percentile	75th Percentile	99th Percentile
Type A AD	64 (39)	60.6 \pm 14.8	3213 \pm 1465	2083	3310	5000	5000
Type B AD	23 (14)	60.2 \pm 12.4	3574 \pm 1430	2265	3902	5000	5000
MI	46 (36)	65.2 \pm 15.0	1459 \pm 1650	325	694	2216	5000
Angina pectoris	37 (28)	61.7 \pm 13.2	760 \pm 974	250	319	250	4337
PE	5 (2)	50.0 \pm 32.0	2452 \pm 1891	776	2765	3931	4515
Other uncertain diagnoses	45 (26)	62.2 \pm 15.4	1399 \pm 1511	250	676	2252	5000

MI: myocardial infarction, PE: pulmonary embolism

The D-dimer cutoff value in this study was 500ng/ml and was evaluated for its diagnostic performance. The sensitivity was 96.6% and specificity was 46.6% for acute aortic dissection compared to all controls. Predictive values were examined and the population prevalence used was an estimated 25% of patients would present with acute aortic dissection. The positive likelihood ratio was 1.81. The negative likelihood ratio was 0.07. Results of the diagnostic performance of the D-dimer compared to all controls and compared to controls based on different final diagnoses can be seen in Table 4.⁷

Table 4. Diagnostic Performance of D-dimer for Patients Presenting Within the First 24 Hours at the Cutoff of 500 ng/ml⁷

AD and Control	Sensitivity, %	Sensitivity 95% CI	Specificity, %	Specificity 95% CI	PLR	NLR	PPV	NPV
A and B	96.6	90.3-99.3						
All			46.6	37.9-55.5	1.81	0.07	37.6	97.6
MI only			39.1	25.1-54.6	1.59	0.09	34.6	97.1
Angina only			62.2	44.8-77.5	2.55	0.06	46	98.2
PE only			20	0.5-71.6	1.21	0.17	28.7	94.6
Other only			44.4	29.6-60.0	1.74	0.08	36.7	97.5
A only	96.9	89.2-99.6						
All			46.6	37.9-55.5	1.81	0.07	37.7	97.8
MI only			39.1	25.1-54.6	1.59	0.08	34.7	97.4
Angina only			62.2	44.8-77.5	2.56	0.05	46	98.4
PE only			20	0.5-71.6	1.21	0.16	28.8	95
Other only			44.4	29.60.0	1.74	0.07	36.8	97.7
B only	95.7	78.1-99.9						
All			46.6	37.9-55.5	1.79	0.09	37.4	97
MI only			39.1	25.1-54.6	1.57	0.11	34.3	96.4
Angina only			62.2	44.8-77.5	2.53	0.07	45.7	97.7
PE only			20	0.5-71.6	1.2	0.22	28.5	93.2
Other only			44.4	29.6-60.0	1.72	0.1	36.5	96.8

PLR indicated positive likelihood ratio; NLR, negative likelihood ratio; PPV, positive predictive value; and NPV, negative predictive value.

With the results, the authors concluded that the use of a D-dimer assay with a cutoff value of 500ng/ml for patients presenting with symptoms of an acute aortic dissection may be useful as a tool to “rule out” the disease.

Further analysis was performed on the data according to dissection type and time related to symptom onset. The 64 type A dissection cases were compared to all control subjects, which produced an area under the curve of 0.83. The 23 type B dissection cases were compared to all control subjects, which produced an area under the curve of 0.85.⁷

Time was also analyzed and broken into symptom onset of 0 to 6 hours, 6 to 12 hours, and 12 to 24 hours. In the 0 to 6 hour group there were 23 cases of aortic dissection and 31 control cases. The performance of the D-dimer assay within the first six hours showed an area under the curve of 0.94.⁷

Critique:

A disadvantage of this study was sample size. A total of 220 patients were enrolled in study and of those only 87 were diagnosed with an acute aortic dissection. Within the 133 other patients with different final diagnoses they were subdivided even further into cohorts and compared to the 87 patients with acute aortic dissection. The lower sample size limited the statistical power by which diagnoses, such as myocardial infarction, were compared to acute aortic dissection. The study also examines the D-dimer levels by time at presentation and presents the data they collected on how D-dimer may change over time at presentation. The authors present data on the patients with symptoms onset from 0 to 6 hours, but this again further limits the sample size they are working with. The authors also do not discuss their results on groups from 6-12 hours and 12-24 hours.

Another disadvantage of this study is that patients were enrolled only if diagnostic imaging was ordered for the clinical suspicion of an acute aortic dissection. The application of a D-dimer assay may benefit from getting more samples of those with a more common complaint where aortic dissection is on the differential problem list, but the imaging was not ordered.

Study 3: *Diagnostic test accuracy of D-dimer for acute aortic syndrome: systematic review and meta-analysis of 22 studies with 5000 subjects* by Watanabe et al**Objective:**

Conducted a thorough, systematic review search strategy and meta-analysis using hierarchical model for diagnostic accuracy of D-dimer for AAD.¹

Design:

The meta-analysis was registered at the international prospective register of systematic reviews (PROSPERO) and Cochrane Review for Diagnostic Testing. Four electronic databases were searched, which included: PubMed, EMBASE, Cochrane Library advanced search, and Web of Science Core Collection. The following are the Inclusion Criteria for choosing the original studies to include in the meta-analysis:

- Case control and cohort studies that included substantial data regarding both sensitivity and specific of D-dimer assays for the diagnosis of AAD; defined AAD included:
 - Classic AAD
 - Intramural hematoma (IMH)
 - Penetrating aortic ulcer (PAU)
- Language: English and non-English
- Conference abstracts
- The reference imaging modality needed to be clearly identified, which include:
 - Angiography
 - Enhanced computed tomography (CT)
 - Computed tomography angiography (CTA)
 - Magnetic resonance imaging (MRI)
 - Transesophageal echocardiogram (TEE)
 - Diagnosis by autopsy¹

Exclusion Criteria is shown in Table 5.

Two investigators independently screened articles via title and abstract. If an article was chosen by at least one investigator, a full-length text investigation was done by the second investigator. Discrepancies were discussed between the two investigators and final decisions were made about inclusion and exclusion criteria.¹

Table 5. Study #1 Exclusion Criteria

Exclusion Criteria
AAD subtypes that include:
<ul style="list-style-type: none"> • Aortic aneurism rupture • Aortic aneurism pending rupture • Chronic dissection

For each study selected, a 2x2 contingency table with true positives (TP), false negatives (FN), false positives (FP), and true negatives (TN) was constructed. For each 2x2 table, the investigators calculated the diagnostic odds ratio (DOR) and area under hierarchical summary receiver operating characteristics (HSROC) curve (AUC) to calculate the overall diagnostic accuracy of D-dimer for AAD per study. Positive likelihood ratio (PLR), negative likelihood ratio (NLH), positive predictive value (PPV), and negative predictive value (NPV) were also

calculated. The investigators obtained a paired forest plot, HSROC curve, and summary estimates of sensitivity and specificity using the bivariate model, which compares two variables in a study.⁷

The two investigators evaluated each study using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) evaluation sheet (See Appendix). This evaluation deemed each original study a “high quality report” if the study showed no high risk nor high applicability concerns with a cut off D-dimer value of 500nl/ml. The use of plain computed tomography or trans-thoracic echocardiogram(TTE) as the imaging reference test rendered the study to have high applicability concern, and therefore, was noted in the analysis. Inconsistencies were resolved through discussion. A high-quality report subgroup was used for sensitivity analyses.¹

Results:

After searching, 557 articles were found to meet preliminary criteria and 22 of those were chosen as eligible and were included in this study. 21 of the studies were in English and one in German. Most of the studies were from Asian and European countries. There were 5,000 subjects total and of those 1,140 had an acute aortic dissection, the remainder 3,860 subjects were used as the control. Three of the studies were determined to be high-quality reports while the remaining nineteen studies contained at least one high risk of bias or concern.¹

With data from all 22 studies being used, the diagnostic odds ratio was 28.5 and the area under the curve was 0.946. The study looked at a sensitivity analysis from the 12 studies which used a D-dimer cutoff value of 500ng/ml and found the diagnostic odds ratio was 30.7, and the area under the curve was 0.95. A second sensitivity analysis was performed on the three studies considered high quality and resulted in a diagnostic odds ratio of 30.4 and an area under the curve of 0.954.¹ The authors state that this suggests the overall diagnostic accuracy did not change through sensitivity analysis.

Sensitivity across the 22 studies ranged from 0.52-1.0 with a median of 0.97. The specificity of the 22 studies ranged from 0.25 to 0.98 with a median of 0.64. The subjects from the 12 studies which used the cutoff value of 500ng/ml were combined and the sensitivity was 0.952 and the

specificity was 0.604. The subjects from the three high quality reports were used for an analysis and the sensitivity was 0.971 and the specificity was 0.532.¹

A positive likelihood ratio and negative likelihood ratio were estimated using the 12 studies which had a cutoff value of 500ng/ml. The positive likelihood ratio was 2.4 and the negative likelihood ratio was 0.079.¹ The results are summarized in Table 6.

Table 6. Summary of diagnostic accuracy by D-dimer for acute aortic dissection. Brackets indicate 95% confidence interval. High-quality reports: A study that had neither a high risk of bias nor a high concern regarding applicability and that used a cutoff value of 500 ng/ml was regarded as a high-quality report. AUC: area under hierarchical summary receiver operating characteristics curve.¹

	All Studies regardless of the cutoff value	Studies with the cutoff value of 500 ng/ml	High-quality reports
Studies	22	12	2
Acute aortic dissection	1140	833	402
Controls	3860	1994	11079
Diagnostic odds ratio	28.5(17.6-46.3) I ² =17.4%	30.7(17.0-55.2) I ² =7.7%	30.4(17.2-53.7) I ² =0%
AUC	0.946(0.903-0.994)	0.950 (0.847-1.000)	0.954 (0.909-1.000)
Sensitivity	Not available	0.952 (0.901-0.978)	0.971 (0.919-0.990)
Specificity	Not available	0.604 (0.485-0.712)	0.532 (0.297-0.753)
Positive likelihood ratio	Not available	2.4 (1.8-3.3)	2.1 (1.4-3.9)
Negative likelihood ratio	Not available	0.079 (0.036-0.172)	0.055 (0.018-0.177)

Critique:

The strength of the paper was the number of studies and sample size of the meta-analysis. The oldest article was from 2003; the studies were recent. Nearly half of the studies were based in China or Japan, while the remaining 12 studies were conducted in Europe; there is no representation from North America.

In general, the inclusion criteria was vague. There was no mention on date of publications, sex, or age in any criteria of the studies. The study included case control and cohort studies with

“substantial” data regarding sensitivity and specificity of D-dimer assays for the diagnosis of AAD; however, the determination of what was considered “substantial” was not discussed.

The exclusion criteria lacks significant details, or reason for exclusion. Pertaining to the last of the following categories that were excluded: aortic aneurism rupture, aortic aneurysm, and chronic aortic dissection; there is no definition as to what is the determined timeline of “chronic.”

The meta-analysis displayed multiple figures and graphs that summarized most statistics. Figures and tables were easy to analyze the various studies based on country, study design, recruit setting, and reference test used, cutoff value of 500nl/ml, and “high quality” study.

The meta-analysis uses a forest plot to compare D-dimer values for acute aortic dissection 22 studies in an easily visual aid. However, Study #3 does not elaborate on any statistics on regarding the forest plot. For example, there is no review section in the top right hand corner, stating the review, comparison, or outcome. The review addresses the research question. The comparison states the test group versus the control. The outcome states primary outcome in the forest plot.

The study does not define if the forest plot is assessing dichotomous or continuous data. Dichotomous data compares two variables, in this case sensitivity and specificity. We have concluded with weak evidence that Study #3 is assessing dichotomous data as the line of no effect is 1.0. The line of no effect is the determinant to see if there is any difference in the study to warrant significance. Therefore, if a study crosses greater than 1.0, the study shows no difference, making the study not significant. However, this forest plot is ambiguous, as there is also a 0.0 on the forest plot, which could be interpreted as comparing continuous data, which would be the various specificity and sensitivity readings. The forest plot also lacks weight, showing an increased size of the square on the forest plot, indicating a bigger sample size. Therefore, one large square that is significant with a large sample size, would bear more strength than several small squares that are insignificant. There is also no total plot on the forest plot, which would have averaged all the findings at the bottom for a quick generalization of data.

The study mentions that a Cochane Collaboration was used to generate the forest plot, but there is no mention of Cochane Q test, or chi-square data, which is the basis for determining whether or not the study shows heterogeneity. There is no mention of how the authors came to their conclusion based on data from the forest plot. However, the article merely concludes there is weak heterogeneity, meaning the studies compared were not similar. The data was difficult to extrapolate the statistics in the graphs into the conclusion.

Study #3 also uses forest plots to explain the classifications of acute aortic dissections, including classic AAD, intramural hematoma, and penetrating aortic ulcer. The forest plots in this section of the study slightly more complete, showing a line of no effect of 0.0, indicating the data is continuous. These forest plots show weight, total forest plot line, and χ^2 and I^2 statistics for heterogeneity. If the I^2 value is less than 25%, the study is homogeneity, which is preferable. If I^2 is greater than 75%, the study has a high heterogeneity. Although I^2 values were listed in the forest plots, there was no definitions of τ^2 , df, χ^2 , or I^2 values, nor how these values determined the authors' conclusion. Their conclusion was that it is difficult to distinguish these three subtypes of AAD due to their overlapping symptoms; however the endpoints of the forest plot were not discussed or extrapolated clearly.

Although the title and concluding statements declared results with 22 studies with $n=5000$, such as sensitivity 0.952 and specificity 0.604, according to Table 2 in Study #3, those results only include 12 studies with the 500ng/ml with $N=2,827$. This information in the concluding statements is exceptionally misleading.

Discussion:

Acute aortic dissection currently requires imaging as the gold standard for diagnoses and current research is examining if D-dimer assaying could be another tool in aiding the diagnoses.⁶ Our research presents consistent statistics including high sensitivities and moderate specificities across all three studies, indicating that a negative D-dimer assay of below 500ng/ml could assist a clinician in ruling out AAD and eliminate the need for imaging.^{5,8,1} However, all studies addressed the misdiagnoses of subtypes of AAD using D-dimer alone. All studies had variable

patient populations, minor biases, and limitations that require further research before implementation of D-dimer without imaging for the diagnosis of AAD.^{5,7,1}

Limitations

The first limitation of the all studies was a lack of random controlled trials (RCTs). Due to the unethicity associated with this study type given the lethality of AAD, the next best study type that demonstrates clinical applicability is prospective cohort; only Study #2 uses this study type.⁸ Most of the studies used populations outside of the US which shows diversity. However, there may be differences with race association and AAD. Cardiovascular disease, which encompasses AAD, is the number one lethal disease in the US. It is possible that AAD is more prevalent in the US compared to other countries, which could skew the data in the three studies. All three studies used variable D-dimer assays. Study #1 used Liatest D-dimer, and Hexamate D-dimer; Study #2 used Triage D-dimer Test; Study #3 used over 19 different D-dimer assays with three studies having unspecified D-dimer assays (See Appendix B.) All studies used a cutoff D-dimer value of 500ng/ml due to subsequent research and reliability of that value associated with the diagnosis of pulmonary embolism; but there was no further justification for the use of that value.^{5,7,1} In general, there was a lack of explanation regarding risk factors, complexity of symptoms and asymptomatic presentations of AAD. All three studies compared different controls. See Table 7. Across the studies, there is a consensus in the false negatives that arose, which mostly stemmed from subtypes of AAD; including ITH, PAU, non-penetrating ulcer, and false lumens.

Reliability

Study #1 has a reliable control population with chest pain as the most common symptom associated with AAD. As a retrospective observational study, the associated vital signs and detailed diagnoses of all patients were presented.⁵ This was the only study to address a calculation that addressed the benign increase in D-dimer associated with age, which decreased the number of false negatives by 13%. Study #3 mentioned age-adjusted D-dimer calculation in their future recommendations.¹

Study #2 is the most reliable as a prospective cohort study with 14 centers across three continents. The study clearly assessed and analyzed:

- Mean D-dimer levels with demographics
- Sensitivity and Specificity with 95% Confidence Intervals
- Positive and Negative Likelihood Ratios
- Positive and Negative Predictive Values
- Type A and Type B AAD D-dimer values comparing time of onset of symptoms⁸

Study #2 had sufficient figures, and their discussion was thorough that addressed limitations, which included: small sample size, higher prevalence (due to restricted control), complications associated with the subtypes of AAD, bias and funding.⁸ The subtleties of AAD are difficult to analyze in statistical setting as the subtypes have overlapping symptoms, yet most subtypes of AAD have consistently shown that the D-dimer assay misses the AAD diagnoses. The need to distinguish why D-dimer misses the subtypes of AAD is a prominent conundrum that has yet to be determined. The study's conclusion was realistic in that it focused on the complexity of AAD presentations and using D-dimer as a step in the risk stratification rather than ruling out AAD.

At first glance, Study #3 appeared to be reliable with the robust number of studies and subjects. However, the data the authors associated with conclusive findings were based off 12 studies (with cut off levels of 500ng/ml), rather than 22 studies. Only three out of 22 studies were deemed high quality. Instead of N=5,000, based on their conclusion, N=2,827 is used to extract their conclusions.¹ The forest plots were not clear in addressing if the data was measuring dichotomous or continuous data. The study concluded that the meta-analysis showed weak heterogeneity during ROC evaluation, meaning that the studies were not comparing similar variables.¹ There was no discussion about chi-square test or associated statistics regarding the forest plot. Using such discrepancies, this article was not as reliable as originally thought. However, this was the only study that clearly identified the role of each author.¹

When the same D-dimer cut off was used, all three studies showed similar sensitivities, specificities, ROC values, and diagnostic accuracies.^{5,7,1} There are numerous, recent studies

regarding this topic so the amount of data is recent and convincing. However, due to the various presentations and lethality of AAD, there are no discrete rules regarding using D-dimer in replacing imaging to rule out AAD. However, the use of D-dimer in assessing risk stratification in patients with low risk of AAD is more representative of a clinical tool.

Biases

The most profound biases among the three articles regarded authors and funding. Study #2 was funded by Biosite and IRAD. Biosite is the company that provided the Triage D-dimer Test used for the entire study. IRAD is a company that examines and develops biomarkers for AAD.⁸ Study #1 and #3 declared no conflict of interest or funding; however, neither article addressed how the study was funded, leaving index of suspicion high.^{5,1}

Another bias is lack of standardization of protocols or rationale to order the D-dimer assay. Study #2 ordered D-dimer due to the physician's evaluation of the patient, Study #1 used medical records; therefore, the evaluation and management could not be standardized (as a retrospective observational study).⁵ Study #3 did not address rationale for ordering D-dimer assays for the 22 studies.¹

Due to the studies performed in different countries, there are general biases that include language barrier, different healthcare policies and protocols, insurance influences, and varying access to healthcare.

Strength and Weakness of Review

The three articles used in this review were all examining the same outcome: how well can a D-dimer assay diagnose an acute aortic dissection. A strength of this is that there is data from each article on the sensitivity and specificity of a D-dimer at the same cut off value of 500ng/ml creating a larger overall sample size to interpret results. While this is helpful to add to the number of subjects, there is a limitation in that all three articles unique classifications, subdivisions, and entrance criteria for patients with acute aortic dissection. See Table 7.

This review only looked at studies which focused on the D-dimer assay and its usefulness to diagnosing an acute aortic dissection. There may be other literature which exam multiple factors that go into assessing an acute aortic dissection that do not focus solely on the diagnostic capability of the D-dimer assay. These could provide further insight into the usefulness and application of the D-dimer clinically to a patient and how this test may compare to other diagnostic tools currently used for assessing those with the suspicion of an aortic dissection.

Table 7. Comparison of Three Studies

	Study #1	Study #2	Study #3*
Study Type	Retrospective observational	Prospective cohort	Systematic review and meta-analysis
D-dimer Cut Off Value (nl/ml)	500	500	500
Sample Size	887	220	2827
Patients Diagnosed with AAD	123	87	833
Control	735	133	1994
Sensitivity	0.97	0.966	0.952
Specificity	0.44	0.466	0.604
DOR	0.87	0.84	0.954
Positive Likelihood Ratio	1.73	1.81	2.4
Negative Likelihood Ratio	0.07	0.07	0.079
Outcome	D-dimer was significantly increased in pts with AAD compared the patients with acute chest pain and other diagnoses (PE, AMI, and other)	AAD D-dimer levels were 4.9x, 10.7x, 1.2x, and 5.1x higher than D-dimer levels of AMI, angina, PE, and other; respectively	D-dimer has very good overall accuracy over 12 studies with high sensitivity and modest specificity
Recommendation	D-dimer can distinguish AAD with acute chest pain with high sensitivity and modest specificity; age-adjusted formula reduced number of false negatives	D-dimer is useful in risk stratification with suspected AAD to rule out AAD if used within 24 hours of symptom onset	D-dimer <500 largely decreases the possibility of AAD; high quality studies replicated high sensitivity and modest specificity
Limitations	Diagnosing some subtypes of AAD: application of age-adjusted D-dimer formula	Sample size	Weak heterogeneity; only 3/22 studies were "high quality"

PE: pulmonary embolism; AMI: acute myocardial infarction; AAD: acute aortic dissection; IHT: intramural hematoma; *=Used in 12 studies to obtain the sensitivities and specificities based off 12 studies using a D-dimer cutoff at 500ng/ml

Additional Statistics

The overall diagnostic accuracy of using a D-dimer in evaluation for an AAD was the main outcome observed by these results.^{5,8,1} All three studies had similar findings for the applicability

of their research with the sensitivities and specificities similar across the three studies. In Study #1, for all patients with acute aortic syndrome compared to all controls, the sensitivity was 0.97 and the specificity was 0.44.⁵ In Study #2, for all patients with acute aortic dissection compared to all their controls, the sensitivity was 0.966 and specificity was 0.466.⁸ In Study #3 the sensitivity and specificity were determined using twelve of the 22 total studies which used the same D-dimer cut off point of 500ng/ml. The sensitivity was 0.952 and specificity was 0.604.¹ With these findings, all three articles had similar interpretation that a D-dimer with a cut off value at 500ng/ml may be a good test to “rule-out” an aortic dissection based on the high sensitivity. With the low specificity across all three studies they also had a similar interpretation that the D-dimer is not a good diagnostic option to “rule-in” an aortic dissection.

In Study #1, the authors also categorized their patients retrospectively as either high probability or low probability based on three factors; a target history, physical examinations, and pain features. For the low probability group, the sensitivity was 0.98 and specificity was 0.51. For the high probability group, the sensitivity was 0.88 and the specificity was 0.45.⁵ The authors suggest that using a combination of a probability assessment and a D-dimer may further increase accuracy in low-probability patients.

The three articles found similar results when determining positive likelihood ratio and negative likelihood ratio. Positive likelihood ratios for articles #1, #2, and #3 were 1.73, 1.81, and 2.4 respectively.^{5,7,1} The results are consistent that a D-dimer with the cut off value of 500ng/ml may not be a useful test to “rule in” an acute aortic dissection and there would be a low rate of true positive results. The negative likelihood ratios for articles #1, #2, and #3 were 0.07, 0.07, and 0.079 respectively.^{5,7,1} The suggest that the D-dimer is a good tool to “rule-out” an acute aortic dissection and there is a small probability of a false negative finding.

A receiver operator characteristic curve was utilized in all three articles to further determine the use of a D-dimer in diagnosis of an acute aortic dissection. In article #1, the area under the curve was 0.87 for all patients with acute aortic syndrome compared to their control.⁵ In article #2, the area under the curve for all patients with an acute aortic dissection compared to all controls was 0.84.⁸ The Area Under the Curve was also calculated for a type A dissection (0.83) and for a type B dissection (0.85). In Article #2, the authors further analyzed and subgrouped their patients

based on symptom onset, and calculated the area under the curve for those with presenting symptoms between 0-6 hours. The area under the curve was 0.94, with a sensitivity of 0.957 and specificity of 0.631. This data is associated with a small sample size of 23 cases of aortic dissection compared to 31 control cases. However, despite the small sample size, the authors suggest that time of symptom onset could affect the usefulness of a D-dimer with a cutoff level of 500ng/ml.⁸ In article #3, the Area Under the Curve was calculated using all 22 studies, regardless of the D-dimer cutoff value, was 0.946. They also calculated Area Under the Curve to be 0.954 using the 12 studies which had a cutoff value of 500ng/ml.¹ These results mean suggest clinically significant as AUC >0.75.

Nomograms

We created nomograms for each of the studies to further examine the clinical usefulness of using a D-dimer assay to assist in diagnosing an acute aortic dissection. Due to the high sensitivities found consistently throughout the studies, we looked at the negative likelihood ratios to determine the post-test probability of having an acute aortic dissection with a D-dimer <500ng/ml. The positive likelihood ratios were used to look at the D-dimer assay's post test probability with a level >500ng/ml.

In Study #1, patients were included into the study if they were admitted to the ER with chest pain. For our nomogram, we suggest a 0.3% pre-test probability for patients presenting to the ER with chest pain based on the results from the von Kodolitsch's study.⁶ The study determined that an estimated 0.3% of patients presenting to the ER with chest pain had an etiology of aortic dissection. Using the negative likelihood ratio from study #1 of 0.07⁵ and a pre-test probability of 0.3%⁶, the post-test probability was <0.1%. Clinically, this suggests that with a D-dimer less than 500ng/ml there is a less than 1% chance of this patient having an acute aortic dissection. The positive likelihood ratio from study #1 was 1.73, and was used to create a nomogram using the 0.3% pre-test probability. See Figure 2. This showed a post-test probability of 0.48%, which suggests that a D-dimer >500 ng/ml may have a high rate of false positives and is not a good predictive tool of an acute aortic dissection.

In Study #2, patients were included if the clinician ordered imaging due to a suspected acute aortic dissection.⁸ The authors of this study estimated that 1 in 4 patients would present with acute aortic dissection within this population.⁸ For our nomogram, we used the authors suspected pre-test probability of 25%.⁸ Using this, along with Study #2's negative likelihood ratio of 0.07, the post-test probability was 0.35. This provides less convincing results compared to study #1 suggesting that there is a less than 2.5% chance of a patient having an acute aortic dissection with a d-dimer less than 500ng/ml. The positive likelihood ratio for Study #2 was 1.81. Using a 25% pre-test probability, the resulting post-test probability was 29%. In this study, a positive D-dimer test indicates 30% will have AAD. The pre-test probability of AAD of 25%, which is far higher than the two other studies, reveals skewed data since the prevalence in AAD is so low in the general population.

In Study #3, the negative likelihood ratio of 0.07 was created using 12 of the studies within their meta-analysis which all used the cutoff of 500ng/ml. While not all of their admitting criteria was stated for each of the studies, the majority included chest pain.¹ For this reason, we chose to use 0.3% as our pre-test probability.⁶ The negative likelihood ratio for study #3 was 0.079 which produced a post-test probability of 0.01%. The positive likelihood ratio was 2.4 which produced a post-test probability of 0.95%.

The nomograms produced similar results on the nomograms show by Figure 2. All three studies show <0.3% post-test probability with a negative D-dimer assay at 500ng/ml cutoff. This indicating if a patient presents with chest pain, a negative D-dimer would indicate AAD in less than .3%.

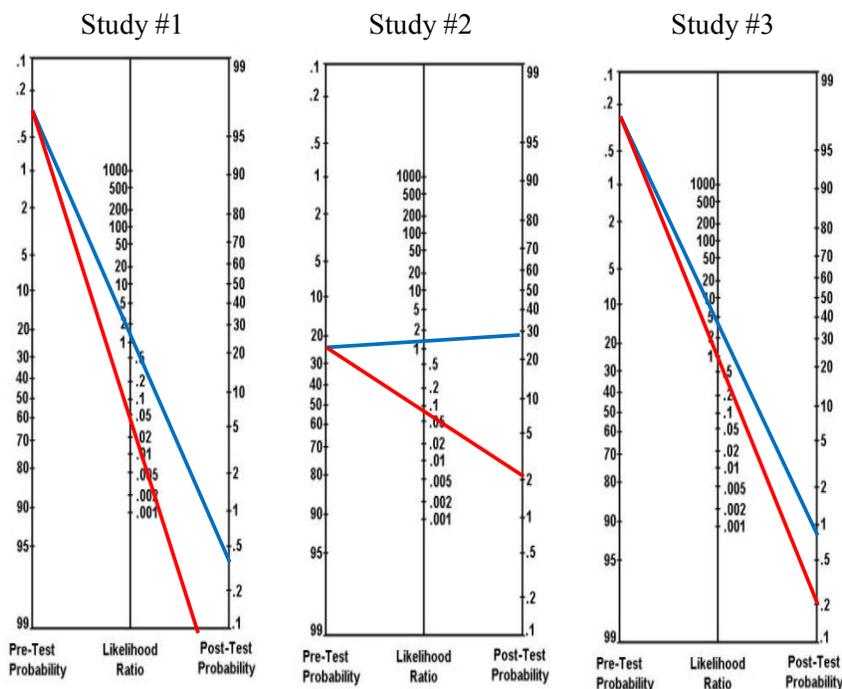


Figure 2. Nomograms for Study #1, #2, and #3; blue lines extrapolated from Positive Likelihood Ratio; red lines extrapolated from Negative Likelihood Ratio

Case Follow Up

After CB was admitted to the ER, a D-dimer assay was obtained along with an EKG, chest x-ray and cardiac enzymes. The EKG and cardiac enzymes were not consistent with an MI and the chest x-ray did not confirm a diagnosis. D-dimer came back at 1320ng/ml. CB’s clinician now has an acute aortic dissection higher on their differential, and decided to send CB for a CT to make the diagnosis.

Conclusion:

There is sufficient data that repeatedly confirms that D-dimer is an accurate test to rule out AAD in low risk patients. Consistent high sensitivity (0.96) and modest specificity (0.5) is repeatedly shown in all studies. However, due to the high lethality and rarity of the disease, various presentations of AAD, providers are hesitant to set protocols regarding D-dimer and excluding AAD without imaging.

We believe that due to the various presentations with AAD and subtypes that still cause false negatives, we recommend that further research needs to be fulfilled. The subtypes of AAD, including intramural hematoma (IMH), penetrating aortic ulceration (PAU), ruptured aortic aneurysm (RAA), impending rupture of aortic aneurysm (IRA), or infectious aortic aneurysm (IAA); all have been misdiagnosed with D-dimer in the proposed articles. The age-adjusted D-dimer calculation also needs additional research. Study #1 showed positive results, but use of this calculation needs verification via larger sample size and reproducibility.

Once more research is completed, due to similarity in sensitivity, specificity, and negative likelihood ratios in diagnosing AAD, compared to PE, a similar follow up AAD protocol should be explored. In the work up for PE, high suspicion despite a negative D-dimer warrants the patient to return for a follow up D-dimer in one week. Similarly, if a patient presents with AAD, with negative D-dimer with high suspicion, the patients should return in x number of hours/days for a repeat D-dimer. The timeline of redraw is an area that could also be further researched. Like PE, AAD has various presentations, and high lethality; however, AAD is much less prevalent.

In conclusion, we suggest utilizing D-dimer would be an additional blood test in the initial work up of AAD prior to imaging. However, due to the high lethality of AAD and misdiagnoses of the subtypes, if the clinician has high suspicion of AAD or its subtypes, regardless of a negative D-dimer, we recommend continued use of imaging.

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Appendix

A. D-dimer tests used in Study #3:

1. Roche
2. Cardiac D-dimer system
3. Dade Behring
4. D-dimer plus
5. Quantitative Immunoturbidimetric assay
6. Tina-quant
7. STA LIATEST D-DI
8. Innovance D-dimer
9. Latex agglutination
10. Liatest D-dimer
11. Coamatic D-dimer
12. D-dimer Plus
13. Hemosil D-dimer HS
14. LIAS Auto D-dimer
15. ELISA (SPELL OUT)*
16. LIAS Auto D-dimer Neo
17. Vidas
18. Automated chemical analysis
19. Sekisui

Three studies did not specify the D-dimer test utilized.

B

QUADAS-2 Evaluation Form

Domain/question	Yes/No/Unclear	Comments
Patient Selection		
1. Was a consecutive or random sample of patients enrolled?		
2. Was a case-control design avoided?		
3. Did the study avoid inappropriate exclusions?		
Index Test		
4. Were the index test results interpreted without knowledge of the results of the reference standard?		
5. If a threshold was used, was it pre-specified?		
Reference Standard		
6. Is the reference standard likely to correctly classify the target condition?		
7. Were the reference standard results interpreted without knowledge of the results of the index test?		
Flow and Timing		
8. Was there an appropriate interval between index tests and reference standard?		
9. Did all patients receive a reference standard?		
10. Did all patients receive the same reference standard?		
11. Were all patients included in the analysis?		

Comments