Original Article

Impact of a negative D-dimer result on the initial assessment of acute aortic dissection

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Abstract

Background: D-dimer shows high sensitivity but low specificity for the diagnosis of acute aortic dissection (AAD). Previous reports indicated that a small number of AAD patients have negative D-dimer results and negative D-dimer patients have shorter dissection length. However, whether patients with negative D-dimer results have a good prognosis is unknown. This study aimed to elucidate the clinical characteristics and implications of a negative D-dimer result on AAD diagnosis.

Methods: The study group comprised 126 patients (71 males, 55 females; mean age, 69 ± 11 years) with AAD admitted to our hospital between April 2009 and March 2015. Blood samples on presentation were used for D-dimer measurement. Clinical characteristics and outcomes were assessed.

Results: Nine patients (7.1%) exhibited a negative D-dimer result (negative group) and 117 patients had a positive D-dimer result (positive group). The negative group showed a significantly lower extension score (3(2-3) vs. 4(2-6), p = 0.008) and a higher platelet count (22.2 ± 3.7 vs. 16.6 ± 4.6 × 10^4/μl, p = 0.0005) than the positive group. Multivariate analysis demonstrated that platelet count (odds ratio, 1.31 (1.09-1.58), p = 0.003) and extension score (odds ratio, 0.56 (0.33-0.96), p = 0.03) were significantly related to a negative result. Notably, 44% of patients in the negative group had type A

dissection and 33% underwent an emergency operation due to cardiac tamponade.

Conclusion: We found that high platelet count and low extension score were independent factors related to a negative D-dimer result. Even if the length of the dissection is short, not a little patients with a negative D-dimer result necessitate an emergency operation. Physicians should recognize that a negative D-dimer result alone cannot exclude patients with fatal AAD conditions.

Key words: acute aortic dissection, negative D-dimer result, emergency operation, platelet count, extension score

Abbreviations: AAD, acute aortic dissection; ADD, aortic dissection detection; CI, confidence interval; CT, computed tomography; ED, emergency department; OR, odds ratio; SD, standard deviation

1. INTRODUCTION

Acute aortic dissection (AAD) is the most common fatal condition that involves the aorta. Rapid diagnosis is essential to improve prognosis. However, diagnosis of AAD can be sometimes difficult, because AAD is clinically heterogeneous at presentation [1-3]. Thus, validated clinical strategies beyond subjective clinical judgment are necessary to assist physicians in the approach to suspected AAD. A rapid and accessible biomarker used as a screening test for AAD could shorten the time for diagnosis and limit the number of patients without AAD undergoing urgent aortic imaging [4].

D-dimer is a thrombosis/fibrinolytic by-product and widely available worldwide to emergency departments (EDs). Several studies evaluated D-dimer as a biomarker of AAD regardless of its type, either type A or B dissection, and D-dimer shows a pooled diagnostic sensitivity of 97% for AAD [5-7]. However, a negative D-dimer per se is considered to be insufficient to rule out AAD in unselected patients [8]. The clinical characteristics and prognosis of patients with AAD and a negative D-dimer result have not been sufficiently elucidated. The objective of this study was to elucidate the diagnostic and prognostic implications of D-dimer on the assessment of AAD.

2. METHODS

2.1 Study setting and patients

This was a single-center retrospective observational study. Our hospital has an advanced emergency and critical care center. Patients with AAD have been transferred from the scene and other hospitals in the Nagano prefecture (area: 13,562 km^2, population: approximately 2,075,000).

2.2 Selection of participants

This single-center, retrospective study comprised consecutive patients with AAD who were admitted to the advanced emergency and critical care center of Shinshu University Hospital between April 2009 and March 2015. Patients with cardiac arrest on arrival, presentation later than 24 h after the onset of AAD, and unavailability of D-dimer value at the time of AAD diagnosis were excluded. For patients with multiple episodes of AAD, only the first episode registered was included in the analysis. Definite diagnosis of AAD was made using thoracic and abdominal contrast-enhanced computed tomography (CT).

2.3 Study protocol

The study was approved by the Shinshu University School of Medicine Institutional Review Board. It was conducted in accordance with the amended Declaration of Helsinki. We retrospectively reviewed the medical records of the patients. Blood samples were obtained in the ED at the time of routine clinical evaluation. In case of

patients referred from another hospital, clinical findings and laboratory data at the time of the first ED visit were used. D-dimer value was considered negative if it was lower than the normal range of each D-dimer kit (Supplement 1). Patients who had a negative D-dimer result (negative group) were compared with those who had a positive D-dimer result (positive group) for each of the following factors: age, gender, Stanford classification, time from the onset of symptoms to admission, past histories, presenting symptoms, laboratory results, extension score, and physical, radiographic, electrocardiographic, echocardiographic, and CT findings. The extension score of AAD was determined in each patient by considering dissection occurring in the following segments: ascending aorta, aortic arch, thoracic descending aorta, suprarenal abdominal aorta, infrarenal abdominal aorta, and iliac arteries. Six categories were then established depending on the number of segments that were affected (one to six) [9]. The aortic dissection detection (ADD) risk score was calculated retrospectively, which encompassed 12 clinical risk markers classified into three categories (predisposing conditions, pain features, and physical findings). The score was calculated based on the number of categories where at least one risk marker was present [10]. Patients were divided according to ADD risk score: 0, 1, 2, or 3. Type A dissection was defined as any dissection involving the ascending aorta or the arch (proximal to the left subclavian

artery), and Type B dissection was defined as dissection limited to the descending aorta [11]. The indication of operation for AAD was based on the guideline for Diagnosis and Treatment of Aortic Aneurysm and Aortic Dissection issued by the Japanese Circulation Society in 2010 [12]. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic pressure ≥90 mmHg or use of antihypertensive medication on admission. Diabetes mellitus was indicated if the patient had a fasting blood glucose level greater than 120 mg/dl or was receiving antidiabetic therapy. Otherwise, the results of a 75-g oral glucose tolerance test were used to diagnose diabetes mellitus. Blood pressure on admission was recorded as hypotensive, normotensive, or hypertensive when systolic blood pressure was <90 mmHg, 90-139 mmHg, or ≥140 mmHg, respectively. Cardiac tamponade was defined as hypotension accompanied by pericardial fluid and typical echocardiographic findings consistent with tamponade physiology. The imaging study results were interpreted by experienced radiologists and cardiologists. All patients underwent urgent CT scan for the final diagnosis. The urgent CT had plain CT, as well as early and late contrast-enhanced images. Late contrast-enhanced images were obtained because the blood flow in the false lumen is so slow that the false lumen cannot be visualized in the early-phase contrast in some patients. The inflow of the contrast agent is observed in the late-phase contrast in all

patients with partially thrombosed false lumen and patent false lumen [12].

2.4 D-dimer testing

D-dimer levels were assayed on venous samples drawn from patients in the ED at the time of routine clinical evaluation. D-dimer assay was performed in each hospital which the patient visited first. Thus, D-dimer assays were performed in 32 hospitals with five kinds of D-dimer kit (Supplement 1). The laboratory technicians were unaware of the clinical data.

2.5 Data analysis

For continuous variables, mean ± standard deviation (SD) or median, and the 25% and 75% percentile values were calculated. Comparison between the 2 groups was performed using the Mann-Whitney U-test. Univariate and multivariate logistic regression analyses were performed to identify independent factors related to the negative group. The threshold for entry of variables into the multivariate models was $p < 0.2$. Odds ratio (OR) and 95% confidence interval (CI) were also calculated. A p value of <0.05 was considered statistically significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0) [13]. EZR is a modified version of the R commander (version 1.6-3) that includes statistical

functions that are frequently used in biostatistics.

3. RESULTS

A total of 217 patients with AAD were admitted to our hospital between April 2009 and March 2015. Ninety-one patients were excluded from the study based on the aforementioned criteria (Supplement 2). Finally, 126 patients were investigated. Among them, 77 patients were transferred from 31 hospitals. In this cohort, 9 patients had a negative D-dimer result (negative group), and 117 patients had a positive D-dimer result (positive group). The positive group had a median D-dimer value of 11.1 μg/ml (interquartile range, 3.7-37.2 μg/ml). The demographic and clinical characteristics of patients in each group are presented in Table 1. No significant difference was found between the two groups. Forty-four percent of patients in the negative group were type A dissection. No patient with ADD risk score 0 was noted in the negative group. Thirty-three percent and sixty-seven percent of patients in the negative group had ADD risk scores of 1 and > 1, respectively. Significant difference was not found in the ADD risk score between the 2 groups. Results of the examinations on admission of each group are presented in Table 2. The negative group had significantly higher platelet count than the positive group ($p = 0.0005$). False lumen was completely and partially thrombosed in 67% and 33% of patients in the negative group. No patient had patent

false lumen in the negative group. The negative group had a significantly lower extension score than the positive group (p = 0.008). Table 3 shows the treatment of the patients. Thirty-three percent of the patients in the negative group were managed surgically. All patients undergoing operation in the negative group had type A dissection, pericardial effusion, and partially thrombosed false lumen. Emergency operation was performed due to cardiac tamponade in these patients. No significant difference was noted in the treatment between the 2 groups.

3.1 Factors related to a negative D-dimer result

The results of the univariate analysis were showed in Table 4. Factors associated with negative results were platelet count, completely thrombosed false lumen, and extension score. Platelet count (OR, 1.31; CI, 1.09-1.58; p = 0.003) and extension score (OR, 0.56; CI, 0.33-0.96; p = 0.03) were identified in the final model to be independent factors related to the negative group in multivariate analyses (Table 4).

4. DISCUSSION

We found that 7.1% of patients with AAD had a negative D-dimer result and that high platelet count and low extension score were independent factors related to a negative D-dimer result. Among the patients who had a negative D-dimer result, 44% (4/9) had type A dissection and 33% (3/9) underwent emergency operation. Thus, a negative

D-dimer result alone could not exclude patients with fatal AAD.

D-dimer, a well-established marker of vascular thrombosis, has high sensitivity but low specificity for the diagnosis of AAD [14, 15]. The incidence of the negative D-dimer result in the AAD were 1.1% (1/94) [9] and 8.0% (9/113) [16]. The incidence of the negative D-dimer result in our study was similar to that of previous studies.

4.1 Characteristics of patients with AAD and a negative D-dimer result

In our study, low extension score and high platelet count were independently related to the negative D-dimer result. Previous studies showed that a negative D-dimer result is related to short dissection length, time from symptom onset to admission, young patients, and thrombosed false lumen in patients with AAD [9, 16-17].

Ohlmann et al. [9] reported that D-dimer levels significantly correlate with the extension length of the AAD. Hazui et al. [16] found that a negative D-dimer result may be shown in AAD patients with short dissection length. Our result is consistent with the report of Hazui et al.

Reduced platelet counts have been reported in patients with AAD [15]. Morello et al. [18] reported that white blood cell and platelet counts may be used in patients at low pre-test probability to fine-tune risk assessment of acute aortic syndrome. The reduction of platelet counts may be related to the extensive consumption of platelet due to

hypercoagulable status [19]. Moreover, Sbarouni et al. [20] reported that platelet count is inversely related to D-dimers in AAD. The present study demonstrated that high platelet count was an independent factor related to the negative group. Paradoxically, the results of our study supported that the reduction of platelet counts is caused by the extensive consumption of platelet due to hypercoagulable status.

Eggebrecht et al. reported that plasma D-dimer concentration is negatively correlated with the time from symptom onset to hospital admission [17]. However, other studies did not find such relationship [21, 22]. No difference was found in the time from the onset of AAD to hospital admission between the two groups in our study.

Hazui et al. [16] found that negative results of D-dimer test may be found in young (less than 70 years old) patients. Moreover, D-dimer assay is more likely to give a positive result in patients over 50 years [23], limiting the usefulness of the test. Although specific recommendations to use age-adjusted cutoffs were also published [24, 25], no precise information after this survey was available as to whether suggestions have been assessed. However, young patients (less than 70 years old) and a negative D-dimer result were not relevant in our study.

Recent studies have reported that D-dimer concentrations are higher in patients with AAD and a patent false lumen than in those with a thrombosed false lumen because

coagulative and fibrinolytic systems could be stimulated in patent false lumen [9]. Ohlmann et al. [26] reported that D-dimer levels might well be below the cutoff threshold in patients presenting an acute thoracic aortic syndrome caused by aortic intramural hematoma. In our study, 67% of patients in the negative group had a completely thrombosed false lumen and no patient in this group had patent false lumen.

4.2 Impact of a negative D-dimer in the management of patients suspected AAD

Eggebrecht et al. [17] reported that thoracic aortic dissection patients with higher D-dimer die earlier, more frequently undergo emergency endovascular or surgical procedure, and have more complications. Meanwhile, patients with short segment dissections and thrombosed false lumens may have low D-dimer levels [9, 27]. Several reports have indicated that the status of the false lumen is associated with outcome and patients with a completely thrombosed false lumen have shown good outcomes [26, 28]. Patients with a negative D-dimer result have been reported to have a good prognosis and do not require immediate surgical intervention [15, 29].

By contrast, our study showed that 44% of the patients with a negative D-dimer result had a type A dissection and 33% of the patients underwent emergency operation. The reason for emergency operation was a life-threatening condition due to cardiac tamponade in each patient in the negative group. These findings may be attributed to the

fact that all patients who underwent emergency operation had a partially thrombosed false lumen. Mortality is reported to be increased in patients with a partially thrombosed lumen [30]. These patients less frequently have re-entry tear. Thus, an increase in pressure in the false lumen results in an increase in wall tension and elevates the risk of aneurysm expansion, redissection, and rupture [30, 31]. Furthermore, blood-flow quantification and velocity mapping can demonstrate bidirectional flow within a false lumen that exhibits partially thrombosed lumen. This turbulent or helical flow can induce aortic wall shear stress and may be associated with an elevated risk of aneurysmal dilatation or tear [32]. In our study, several patients in the negative group had short dissection length and partially thrombosed false lumen. Patients who have dissection with high false lumen pressure involving a critical site, e.g., DeBakey type II involving a Valsalva antrum, might have a life-threatening condition, even if the dissection length is short and the D-dimer is negative. To the best of our knowledge, this study is the first to clarify the association between a negative D-dimer result and occurrences of a life-threatening condition in AAD. Taken together, the results obtained in our study suggest that careful attention should be paid to the possibility of fatal conditions in patients with a negative D-dimer result.

4.3 Study limitations

This study has several limitations. First, it was a retrospective analysis of a single center and evaluated a relatively small number of patients. In particular, the number of patients with AAD in the negative group was very small, but our sample size as a single-center study was not negligible. Although this is a single center study, patients were initially evaluated in 31 hospitals of the region. Second, subjects also included both Stanford type A and B patients, as the number was small for an analysis of either type A or B dissection to be performed separately. However, it seems that the mechanisms of production of D-dimer are the same between type A and B dissections. Finally, our study had five kinds of D-dimer kit (Supplement 1). The types of assays used to measure D-dimer were not evaluated.

4.4 Conclusions

High platelet count and low extension score were independent factors related to a negative D-dimer result. Notably, the negative group included patients with fatal conditions although this group had shorter dissection than the positive group. Physicians should recognize that a negative D-dimer result alone cannot exclude patients with fatal AAD.

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Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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Table 1. Baseline characteristics of patients with acute aortic dissection.

	Negative group n = 9	Positive group n = 117	p value
Age (years)	66 ± 10	69 ± 11	0.4
Men, n (%)	6 (67)	65 (56)	0.7
Stanford type A dissection, n (%)	4 (44)	84 (72)	0.1
Past history, n (%)			
Hypertension	7 (78)	82 (70)	1.0
Diabetes mellitus	0	3 (3)	-
Ischemic heart disease	2 (22)	11 (9)	0.2
Cerebrovascular disease	2 (22)	9 (8)	0.1
Thoracic aortic aneurysm	0	5 (4)	-
Prior cardiovascular surgery	0	8 (7)	-
Referred from another hospital	7 (78)	70 (60)	0.4
Time from the onset of symptoms to admission			
Median (min)	110 (75-120)	58 (42-115)	0.2
			0.1
1 h ≦TIME (%)	2 (22)	60 (51)	
1 h <TIME≦2 h (%)	5 (56)	29 (25)	
2 h <TIME<24 h (%)	2 (22)	28 (24)	
Presenting symptoms (%)			
Chest pain	5 (56)	72 (62)	0.7
Back pain	5 (56)	59 (50)	1.0
Disturbance of consciousness	1 (11)	14 (12)	1.0
Physical findings			
Blood pressure (%)			0.9
Hypertensive	5 (56)	54 (46)	
Normotensive	2 (22)	28 (24)	
Hypotensive	2 (22)	35 (30)	
Aortic regurgitation murmur (%)	2 (22)	10 (9)	0.2
Aortic dissection detection risk score			0.7
0, n (%)	0 (0)	1 (1)	
1, n (%)	3 (33)	50 (43)	
2 or 3, n (%)	6 (67)	66 (56)	

TIME: time from the onset of symptoms to admission

Table 2. Laboratory date, chest radiography, electrocardiography, and initial diagnostic imaging results of patients with acute aortic dissection.

	Negative group n = 9	Positive group n = 117	p value
Laboratory data at initial assessment			
WBC count (/μl)	8516 ± 3242	9188 ± 3409	0.5
CRP (mg/dl)	0.07 ± 0.04	0.53 ± 1.22	0.2
Platelet count (10^4/μl)	22.2 ± 3.7	16.6 ± 4.6	0.0005
Creatinine (mg/dl)	0.8 ± 0.3	1.1 ± 0.9	0.3
Chest radiography findings (%)			
Widened mediastinum	6 (67)	73 (62)	
Displacement of aortic wall calcium	0 (0)	7 (6)	
Pleural effusion	1 (11)	9 (8)	
Electrocardiographic findings (%)			
Abnormal Q and/or ST deviation	3 (33)	21 (18)	1.0
T wave abnormality	0 (0)	15 (13)	-
Echocardiographic findings (%)			
Aortic regurgitation	2 (22)	27 (23)	1.0
Pericardial effusion	3 (33)	29 (25)	0.6
CT findings (%)			
False lumen patency			0.01
Patent	0 (0)	49 (42)	0.01
Partial thrombosis	3 (33)	33 (28)	0.7
Complete thrombosis	6 (67)	35 (30)	0.05
Arch vessel involvement	0 (0)	20 (17)	
Coronary artery involvement	0 (0)	8 (7)	
Pericardial effusion	3 (33)	30 (26)	0.6
Periaortic hematoma	1 (11)	5 (4)	0.3
Extension score	3 (2-3)	4 (2-6)	0.008

WBC: white blood cell; CRP: C-reactive protein; CT: computer tomography

Table 3. Treatment of patients with acute aortic dissection.

	Negative group n = 9	Positive group n = 117	p value
Treatment			0.17
Medical	6	48	
Surgical	3	69	
Ascending aorta replacement (including hemiarch repair)	2	21	
Ascending aorta and total arch replacement	0	45	
Bentall's operation	1	3	
Extraanatomical bypass	0	1	
Simultaneous CABG	0	4	
Simultaneous AVR	0	3	
Thoracic endovascular aortic repair	0	2	
Y-graft replacement	0	1	

CABG: coronary artery bypass grafting; AVR: aortic valve replacement

Table 4. Univariate and Multivariate logistic regression models for independent factors related to negative results of D-dimer testing on diagnosis of AAD.

	Univariate			Multivariate		
Clinical characteristic	OR	95% CI	p value	OR	95% CI	p value
Age	0.97	0.92-1.04	0.44			
Age <60	1.23	0.24-6.35	0.80			
Male	1.55	0.36-6.48	0.55			
Stanford type B AAD	3.18	0.80-12.6	0.09			
Hypertension	1.56	0.31-7.86	0.59			
Diabetes mellitus	4.75	0.44-51.0	0.19			
Ischemic heart disease	2.75	0.51-14.9	0.24			
Cerebrovascular disease	1.50	0.16-13.4	0.71			
TIME	0.99	0.99-1.00	0.72			
TIME, <60 min	0.29	0.05-1.46	0.13	0.23	0.03-1.5	0.12
Chest pain	0.50	0.12-1.96	0.32			
ADD risk score	0.44	0.11-1.64	0.22			
Platelet count	1.24	1.08-1.43	0.002	1.31	1.09-1.58	0.003
Aortic regurgitation on echocardiogram	0.90	0.18-4.63	0.91			
Pericardial effusion on CT	1.45	0.34-6.16	0.61			
Complete thrombosis on CT	4.69	1.11-19.8	0.03			
Extension score	0.54	0.32-0.89	0.01	0.56	0.33-0.96	0.03

OR: odds ratio; 95% CI: 95% confidence interval

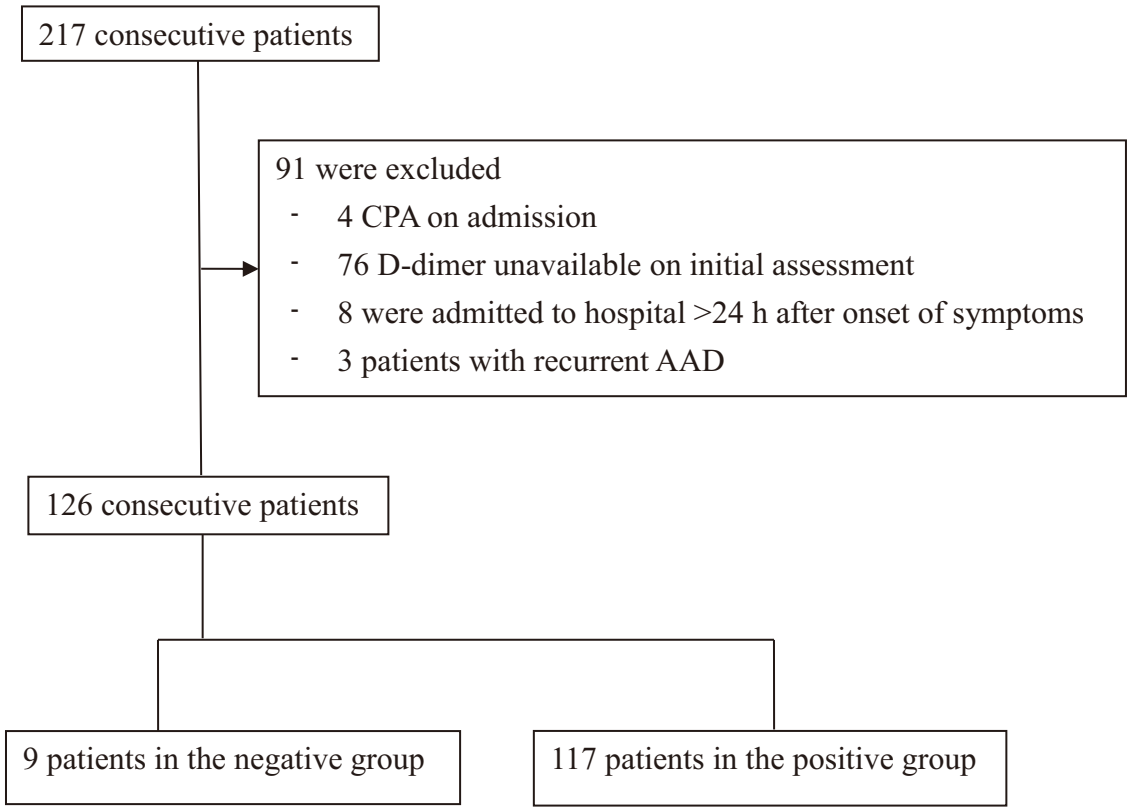
AAD: acute aortic dissection; TIME: time from the onset of symptoms to admission; ADD risk score: aortic dissection detection risk score; CT: computed tomography

Supplement 1. Details of the five D-dimer kits including assay, upper limit of the normal range, and type of units.

D-dimer kit names	Assay type	Upper limit of the normal range	Company	Type of units	No. of patients n = 126
Nanopia D-dimer	Latex turbidimetric immunoassay	1.0 μg/ml	Sekisui Medical, Japan	DDU	58
LIAS AUTO D-DIMER NEO	Latex turbidimetric immunoassay	1.0 μg/ml	Sysmex corporation, Kobe, Japan	DDU	63
LPIA-ACE D-Dimer II	Latex turbidimetric immunoassay	1.0 μg/ml	LSI Medicine Corporation, Japan	DDU	3
Evatest D-Dimer	Fluorescence immunoassay	1.0 μg/ml	Nissui pharmaceutical corporation, Japan	DDU	1
Sta-Liatest-D-Di	Latex turbidimetric immunoassay	0.5 μg/ml	Diagnostica Stago	FEU	1

DDU: D-dimer unit; FEU: fibrinogen equivalent unit

Supplement 2. Study enrollment flowchart.



CPA: cardiopulmonary arrest; AAD: acute aortic dissection