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Use of coagulation-fibrinolysis markers for prognostication of Stanford type A acute aortic dissection

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Abstract

Purpose: Coagulation-fibrinolysis markers are widely used for the diagnosis of Stanford type A acute aortic dissection (SAAAD). However, the role of these markers in estimating prognosis remains unclear.

Methods: A single-center retrospective study was conducted to identify the relationship between preoperative D-dimer and fibrinogen levels on SAAAD postoperative early prognosis.

Results: Of 238 SAAAD patients who underwent surgery between January 2012 and December 2018, 201 (84.5%) and 37 (15.5%) patients constituted the survival and non-survival groups, respectively, 30 days after surgery. D-dimer and fibrinogen levels in the survival and non-survival groups were 45.2 ± 74.3 vs. 91.5 ± 103.6 μg/mL ($p = 0.014$) and 224.3 ± 95.6 vs. 179.9 ± 96.7 μg/mL ($p = 0.012$), respectively. According to logistic predictor analysis of 30-day mortality, significant factors showed patent type (OR 10.89, 95% CI 1.66–20.31) and malperfusion (OR 4.63, 95% CI 1.74–12.32). Increasing D-dimer (per +10 μg/mL) and decreasing fibrinogen (per −10 μg/mL) were significantly associated with patent type and malperfusion. Receiver operating characteristic analysis was performed to distinguish between survival and non-survival. The cutoff value of D-dimer was 60 μg/mL (sensitivity 61.1%; specificity 82.5%; area under curve [AUC] 0.713 ± 0.083); fibrinogen was 150 mg/dL (sensitivity 44.4%; specificity 84.0%; AUC 0.647 ± 0.092). Kaplan-Meier survival curve analysis showed that patients with D-dimer levels > 60 μg/mL and fibrinogen levels < 150 mg/dL had significantly low survival rates at 30 days after surgery (60.0%, $p < 0.001$).

Conclusion: Preoperative coagulation-fibrinolysis markers may be useful for predicting early prognosis in SAAAD.

Keywords

coagulation, fibrinolysis, D-dimer, prognosis, aortic dissection, stanford A type

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Introduction

Acute aortic dissection (AAD), especially Stanford type A with patent false lumen, is a potentially life-threatening cardiovascular disease that requires accurate early diagnosis and rapid surgical intervention.

Typical symptoms of AAD include (i) acute-onset tearing pain in the chest, back, or abdomen; (ii) asymmetric blood pressure; and (iii) widened mediastinum on chest radiography. However, patients often present with non-specific symptoms, which may result in misdiagnosis.

The use of coagulation-fibrinolysis markers has been implicated in the diagnosis of AAD. D-dimer, a fibrin fragment elevated in coagulopathies and AAD, may be used to rule out the disease.[1–5] Recently, fibrinogen and fibrin degradation products have also been employed for the initial assessment of patients with suspected Stanford type A AAD (SAAAD).[6–9] However, despite the utility of coagulation-fibrinolysis markers for SAAAD diagnosis, the role of these markers in predicting prognosis in patients

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with SAAAD remains unclear. Here, we aimed to retrospectively examine the relationship between preoperative coagulation-fibrinolysis markers (D-dimer and fibrinogen) on the postoperative early prognosis of patients with SASAD (postoperative 30-day mortality).

Methods

Patients

A retrospective single-center study was conducted to collect data from a prospectively maintained registry of patients with SAAAD who underwent artificial graft replacement. The study design was approved by the appropriate ethics review board, and all patients gave written informed consent. The first author and corresponding author had full access to the trial data for analysis.

Patient selection

Patients with SAAAD who underwent artificial graft replacement between January 2012 and December 2018 at our hospital were eligible. Patients who underwent the procedure for approximately 24 h from the onset of symptoms were excluded.

Clinical studies

The preoperative (age, sex, coagulation-fibrinolysis markers, other laboratory data, complications, and timing of the operation, computed tomography imaging information), operative (surgical procedures, operation time, bleeding, and transfusion volume), and postoperative (intensive care unit stay, intubation time, postoperative complications, aortic dissection-related event, 30-day mortality, and total mortality) data of patients with SAAAD was analysed. Preoperative complications were defined as cardiac tamponade, cerebral/peripheral malperfusion, shock, aortic valve insufficiency, and rupture. Postoperative complications included stroke, bleeding events requiring re-sternotomy, any infection, and circulation failure with mechanical circulation support. Postoperative aortic dissection-related events were defined as organ dysfunction, rupture, malperfusion, and progressive dilatation of the aorta, which requiring surgical intervention.

All patients underwent preoperative contrast-enhanced computed tomography (CT). Patent subtype SAAAD was defined as having a false lumen that was contrasted on a preoperative contrast-enhanced CT scan. Contrarily, thrombosed subtype SAAAD was defined as having a false lumen that was not contrasted on preoperative contrast-enhanced CT scan. The location of primary entry was divided as follows: aortic root to ascending aorta (zone 0) and aortic arch to descending aorta.

Statistical analysis

Data are presented as mean ± standard deviation. The student's unpaired *t*-test and chi-square test were used to compare the laboratory values and other data between the survival and non-survival groups. Linear regression analysis was performed for D-dimer and fibrinogen values. Receiver operating characteristic (ROC) analysis was performed to distinguish between survival and non-survival. Logistic regression analysis was performed to evaluate 30-day mortality and postoperative aortic dissection-related events. Survival curves were constructed using the Kaplan-Meier method. The data were analyzed using log-rank analysis. The level of statistical significance was set at $p < 0.05$. All statistical analyses were performed using statistical software (StatMateV; ATMS Co., Ltd, Tokyo, Japan).

Results

From the pool of 252 patients with SAAAD, a total of 238 patients were finally selected for this study. The mean age of the patients was 65.7 ± 12.5 years, 45.4% were male, and 70.6% were of the patent type. Clinical data of the patients are presented in Table 1. The most remarkable abnormality in all patients was a D-dimer level of 52.5 ± 81.2 μg/mL. The postoperative 30-day mortality rate was 15.1%, and the occurrence of aortic dissection-related events was 16.8%. According to linear regression analysis of the relationship between D-dimer and fibrinogen, we found a negative correlation between the two ($|r| = 0.3$, $p < 0.001$) (Figure 1). All patients were divided into survival and non-survival groups besed on 30-day mortality. The survival group that were alive at 30 days postoperatively and the non-survival group that died within 30 days after surgery were 201 (84.5%) and 37 (15.5%), retrospectively. Patent-type rate, location of primary entry, malperfusion complication rate, operation time, cardiopulmonary bypass time, and postoperative outcomes were significantly different between the subtypes. There were also significant differences in D-dimer and fibrinogen values when all patients with SAAAD were divided into survival and non-survival groups. The D-dimer levels in the non-survival group (91.5 ± 103.6 μg/mL) were significantly higher than those in the survival group (45.2 ± 74.3 μg/mL) ($p = 0.014$). However, the fibrinogen levels in the survival group (224.3 ± 95.6 mg/dL) were significantly higher than in the non-survival group (179.9 ± 96.7 mg/dL) ($p = 0.012$).

ROC analysis showed that D-dimer and fibrinogen were predictors of the prognosis of SAAAD in comparison with fibrinogen. For predicting survival, the sensitivity and specificity at a cutoff value of D-dimer at 60 μg/mL were 61.1% and 82.5%, respectively (Figure 2). The sensitivity

Table 1. Patients' characteristics: survival and non-survival groups.

Variables	Over all n = 238	Survival n = 201	Non-survival n = 37	p value
Age (years)	65.7 ± 12.5	65.8 ± 12.7	65.3 ± 11.4	0.83
Male; %	45.4%	45.8%	43.2%	0.92
Body weight (kg)	65.2 ± 2.4	64.4 ± 15.4	68.3 ± 6.9	0.33
Duration from onset to operation (hours)	6.3 ± 5.4	6.4 ± 5.5	5.7 ± 4.8	0.44
Pre-operative Ejection Fraction (%)	57.2 ± 8.1	57.7 ± 10.3	56.8 ± 13.1	0.78
Laboratory data				
Fibrinogen (mg/dL)	217.5 ± 96.8	224.3 ± 95.6	179.9 ± 96.7	0.012
D-dimer (μg/mL)	52.5 ± 81.2	45.2 ± 74.3	91.5 ± 103.6	0.014
Platelet counts (10^4 /μL)	17.2 ± 5.5	17.6 ± 5.3	15.4 ± 6.1	0.052
HbA1c (%)	5.8 ± 0.6	5.8 ± 0.56	6.0 ± 0.76	0.18
Creatine (mg/dL)	1.07 ± 1.19	1.03 ± 1.01	1.26 ± 1.9	0.48
Aspartate transaminase (U/L)	66.7 ± 169.4	63.6 ± 155.8	83.5 ± 230.7	0.62
Alanine transaminase (U/L)	45.8 ± 105.3	42.5 ± 86.8	63.6 ± 174.3	0.48
Preoperative CT				
Patent type; %	70.6%	66.7%	91.9%	0.0038
Legion of primary entry, ascending aorta; %	41.2%	55.7%	75.7%	0.037
Legion of primary entry, arch or descending aorta; %	54.6%	44.3%	24.3%	0.037
Preoperative status				
Cardiac tamponade; %	22.7%	21.4%	29.7%	0.37
Malperfusion (cerebral, peripheral); %	12.2%	8.0%	35.1%	< 0.001
Shock; %	7.1%	5.5%	16.2%	0.047
Aortic valve insufficiency; %	11.8%	12.4%	8.1%	0.64
Rupture; %	2.5%	2.5%	2.7%	0.62
Operative information				
Ascending aorta replacement (alone); %	49.6%	47.3%	62.2%	0.14
Hemi or total arch replacement; %	41.2%	42.8%	32.4%	0.32
Aortic root or aortic valve replacement; %	10.9%	11.0%	11.0%	0.79
Coronary artery bypass; %	4.2%	3.0%	10.8%	0.083
Operation time (minutes)	395.5 ± 144.5	380.1 ± 141.5	490.5 ± 127.6	< 0.001
Cardiopulmonary bypass time (minutes)	226.9 ± 93.4	215.9 ± 82.8	290.7 ± 122.7	0.0017
Circulatory arrest time (minutes)	56.3 ± 25.7	54.9 ± 24.8	63.7 ± 29.4	0.13
Bleeding (ml)	2098.3 ± 1349.9	2025.3 ± 1163.6	2426.7 ± 2112.6	0.67
Red cell concentrates (units)	9.3 ± 5.9	8.7 ± 4.9	11.7 ± 9.3	0.49
Fresh frozen plasma (units)	18.5 ± 8.5	17.5 ± 8	23.3 ± 9.8	0.13
Platelet concentrates (units)	40.2 ± 14.2	40.8 ± 10.8	38.1 ± 22	0.75
Postoperative information				
Duration of intubation (day)	2.2 ± 3.1			
ICU stay (day)	7.1 ± 7.9			
Hospital stay (day)	30.7 ± 19.8			
Post-operative ECMO; %	2.5%	0%	16.2%	< 0.001
Post-operative stroke; %	8.4%	9.0%	5.4%	0.69
Post-operative bleeding event; %	4.2%	4.0%	5.4%	0.96
Post-operative infection; %	5.9%	5.0%	10.8%	0.31
Post-operative aortic dissection related event; %	16.8%	2.5%	94.6%	< 0.001
30-day mortality; %	15.1%			
Total mortality; %	18.1%			

CT: computed tomography, ICU: intensive care unit, ECMO: extracorporeal membrane oxygenation.
Red cell concentrates 140ml/unit, Fresh frozen plasma 120ml/unit, Platelet concentrate 10ml/unit in Japan.
Mean ± standard deviation.

and specificity at a cutoff fibrinogen level of 150 mg/dL were 44.4% and 84.0%, respectively (Figure 2).

The correlation between preoperative conditions, operative procedures, and 30-day mortality is presented in Table 2. Logistic regression analysis revealed that an elevation of D-dimer, declination of fibrinogen, patent type, complication of malperfusion, and primary entry at the ascending aorta were associated with 30-day mortality. A similar test was used to predict the occurrence of aortic dissection-related events (Table 3). Logistic regression

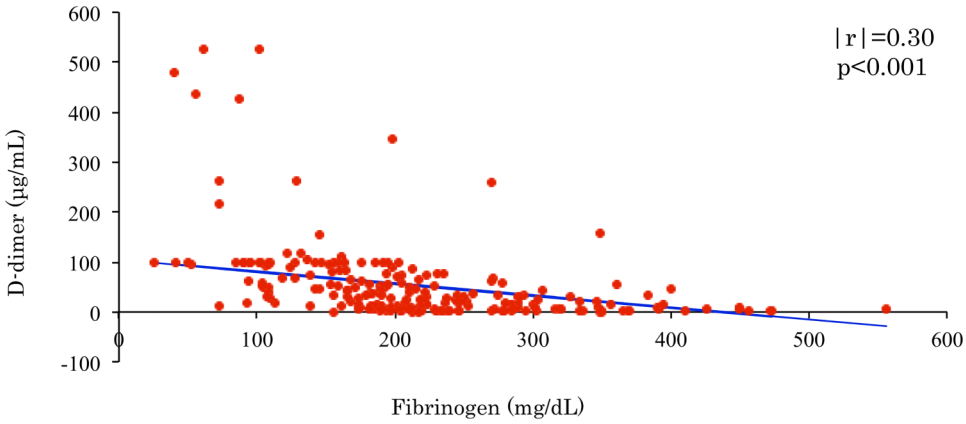

Figure 1. Linear regression analysis. The relationship between D-dimer and fibrinogen values was evaluated using linear regression analysis.

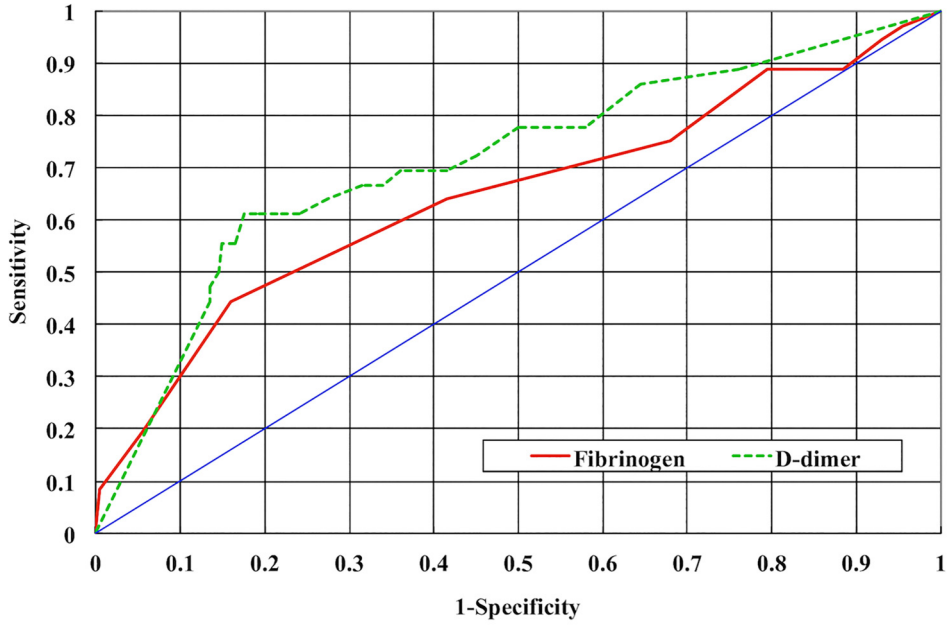

Figure 2. Receiver operating characteristics curves to distinguish survival and non-survival groups. The prediction of 30-day outcomes of acute aortic dissection was analyzed using D-dimer and fibrinogen levels. Cutoff value: D-dimer 60 μg/mL (sensitivity: 61.1%; specificity: 82.5%; area under curve: 0.71 ± 0.083); fibrinogen 150 mg/dL (sensitivity: 44.4%; specificity: 84.0%; area under curve: 0.65 ± 0.092).

analysis revealed that an elevation of D-dimer, declination of fibrinogen, patent type, complication of malperfusion, and ascending aorta replacement were associated with aortic dissection-related events. The factors that affected prognosis were patent type and malperfusion. The results of the logistic regression analysis of the relationship between these factors and coagulation-fibrinolysis markers are shown in Table 4. Particularly, high D-dimer levels were significantly related to the patent type.

Patients were stratified into four groups based on the D-dimer and fibrinogen values. The distribution of these strata was as follows: D-dimer < 60 μg/mL and fibrinogen > 150 mg/dL (group A, 65.9%), D-dimer < 60 μg/mL and fibrinogen < 150 mg/dL (group B, 5.5%), D-dimer > 60 μg/mL and fibrinogen > 150 mg/dL (group C, 12.7%), and D-dimer > 60 μg/mL and fibrinogen < 150 mg/dL (group D, 15.9%). The survival curve was constructed and analyzed using the Kaplan-Meier method and log-rank test, respectively (Figure 3). The 30-day survival rate in group D (60.0%) was significantly lower than that in group A (91.7%), group B (82.5%) and group C (75.0%) ($p < 0.001$).

Table 2. Logistic predictor analysis of 30-day mortality.

	Univariate			Multivariate		
	OR	95%CI	p value	OR	95%CI	p value
Age; per year	0.99	0.97–1.03	0.97			
Sex; male	0.67	0.35–1.3	0.24			
False lumen; patent type	4.66	1.37–15.86	0.014	10.89	1.40–84.47	0.022
Primary entry; ascending aorta	2.87	1.23–6.70	0.015	1.95	0.78–4.87	0.15
Cardiac tamponade	1.65	0.74–3.64	0.22			
Malperfusion	5.81	2.47–13.71	< 0.001	4.63	1.74–12.32	0.0021
Shock	3.21	1.09–9.48	0.035	2.15	0.55–8.37	0.27
AVI	0.59	0.17–2.07	0.41			
D-dimer; per 10 μg/mL	1.047	1.01–1.085	0.011	1.03	0.99–1.072	0.15
Fibrinogen; per -10 mg/dL	1.057	1.008–1.11	0.023	1.038	0.98–1.094	0.17
Ascending aorta replacement	1.84	0.89–3.82	0.1			
Aortic arch replacement	0.56	0.27–1.19	0.13			
Aortic root replacement	0.88	0.28–2.74	0.83			
combined with CABG	3.39	0.91–12.69	0.069			

AVI; aortic valve insufficiency, CABG; coronary artery bypass grafting; OR; odds ratio, 95%CI; 95% confidence interval.

Table 3. Logistic predictor analysis of aortic dissection-related events.

	Univariate			Multivariate		
	OR	95%CI	p value	OR	95%CI	p value
Age; per year	0.99	0.97–1.03	0.87			
Sex; male	0.73	0.39–1.38	0.33			
False lumen; patent type	5.78	1.71–19.5	0.0047	5.81	1.66–20.31	0.0059
Primary entry; ascending aorta	2.12	0.99–4.52	0.053			
Cardiac tamponade	1.34	0.62–2.90	0.46			
Malperfusion	5.24	2.27–12.19	< 0.001	4.89	1.98–12.07	< 0.001
Shock	2.87	0.995–8.29	0.051			
AVI	0.54	0.15–1.87	0.33			
D-dimer; per 10 μg/mL	1.044	1.008–1.08	0.017	1.022	0.98–1.064	0.29
Fibrinogen; per -10 mg/dL	1.059	1.01–1.11	0.015	1.046	0.99–1.1	0.091
Ascending aorta replacement	2.26	1.09–4.67	0.028	2.89	1.34–6.25	0.007
Aortic arch replacement	0.57	0.28–1.18	0.13			
Aortic root replacement	0.59	0.17–2.08	0.41			
combined with CABG	3.26	0.88–12.14	0.078			

AVI; aortic valve insufficiency, CABG; coronary artery bypass grafting; OR; odds ratio, 95%CI; 95% confidence interval.

Discussion

In the present study, we examined the role of coagulation-fibrinolysis markers in predicting the prognosis of SAAAD. Abnormalities in coagulation-fibrinolysis markers were useful as a diagnostic tool, although our study showed that they can also be a poor prognostic factor. It has been reported previously that abnormalities in coagulation-fibrinolysis markers were also associated with severe aortic dissection (patent aortic dissection and malperfusion).[2,6] In other words, abnormalities in coagulation-fibrinolysis markers were pronounced in the presence of the patent type or malperfusion.

Evidently, abnormalities in coagulation-fibrinolysis markers may be associated with patent type. Disseminated intravascular coagulation is a major cause of coagulation-fibrinolysis abnormalities in patients with SAAAD.[10] With the consumption of coagulation factors in the false lumen, the patent subtype of SAAAD influences the severity of disseminated intravascular coagulation. In cases of dissection, a strong correlation between aneurysmal diameter and D-dimer has been previously reported.[11] In the same study, the authors recommended that the coagulation-fibrinolysis markers be measured in patients with SAAAD because fibrinolysis is associated with a large false lumen

Table 4. Logistic analysis of adverse prognostic factors (patent type and malperfusion) by coagulation-fibrinolysis markers.

	Univariate			Multivariate		
	OR	95%CI	p value	OR	95%CI	p value
False lumen; patent type						
D-dimer; per 10 μg/mL	1.51	1.28–1.79	< 0.001	1.42	1.18-1.67	< 0.001
Fibrinogen; per -10 mg/dL	1.089	1.05–1.13	< 0.001	1.027	0.98–1.076	0.25
Malperfusion						
D-dimer; per 10 μg/mL	1.038	1.001–1.076	0.046	1.02	0.98–1.065	0.38
Fibrinogen; per -10 mg/dL	1.06	1.005–1.12	0.031	1.045	0.99–1.11	0.14

OR; odds ratio, 95%CI; 95% confidence interval.

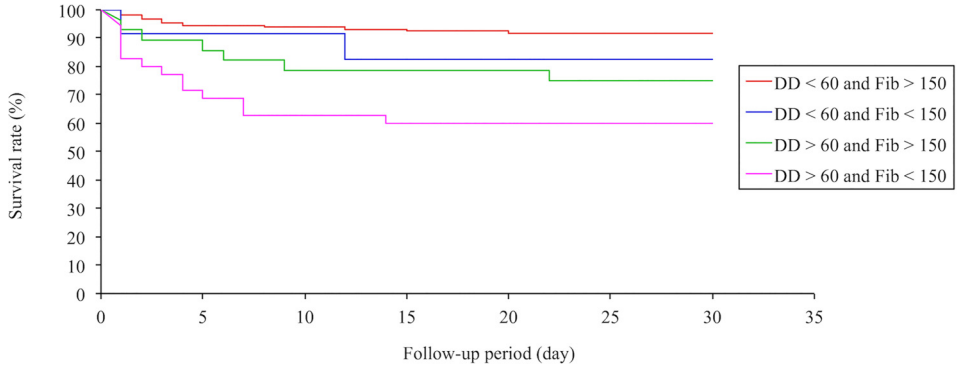

Figure 3. Kaplan-Meier survival curves within 30 days after surgery. The D-dimer and fibrinogen values are divided into the following four groups: D-dimer (DD) < 60 μg/mL and fibrinogen (Fib) >150 mg/dL, DD < 60 μg/mL and Fib < 150 mg/dL, DD > 60 μg/mL and Fib > 150 mg/dL, and DD > 60 μg/mL and Fib < 150 mg/dL.

diameter.[11] The association between malperfusion and abnormalities in coagulation-fibrinolysis markers may also be related to the size of the false lumen. False luminal compression of the true lumen is more likely to occur in a large false lumen than in a small one.

In this study, there was an inverse relationship between D-dimer and fibrinogen levels and short-term prognosis in patients with SAAAD. In addition, preoperative high D-dimer levels or low fibrinogen levels were associated with postoperative aortic dissection-related events. In patent SAAAD subtypes, the false lumen is sometimes larger than the true lumen. A large false lumen was reported to predispose fatal complications, such as organ malperfusion, due to compression of the true lumen.[12–14] Several studies have estimated that approximately 4.8%-34% of patent subtype SAAAD cases are complicated by malperfusion.[15,16] Furthermore, the perioperative mortality of SAAAD complicated by malperfusion was reported to range from 29%-89%.[16] However, early diagnosis and treatment, such as early reperfusion, have improved the surgical outcomes of patients with SAAAD and malperfusion.[17,18] Central repair for ATAAD was more likely to improve malperfusion of the aortic arch branches, compared to malperfusion of the abdominal branches or lower extremities.[19] Branch artery malperfusion patterns in acute aortic dissection was reported as follow: branch artery is compressed by aortic false lumen, branch true lumen is compressed by branch false lumen, and branch artery is impeded by false luminal thrombus.[19] This may be due to the adverse effects of the large size of the false lumen, which extends not only laterally but also longitudinally. Our study has shown that abnormal coagulation-fibrinolysis markers are associated with high short-term mortality rates or postoperative aortic dissection-related event occurrence in patients with patent subtype SAAAD and malperfusion. Nevertheless, early surgical intervention may improve the prognosis.

Recent advancements in imaging technologies (e.g. CT and magnetic resonance imaging) and novel biochemical diagnostic methods (e.g. smooth muscle myosin heavy chain) have improved the diagnosis of SAAAD, thereby allowing early and optimized treatment. However, not all hospitals are equipped with these relatively advanced facilities. Although these imaging and biochemical techniques have been used to diagnose SAAAD, the prognosis of SAAAD is difficult to predict using these methods. In contrast, coagulation-fibrinolysis markers are widely used clinically with relatively fast turnaround time, which is crucial for prompt diagnosis and emergency surgical intervention to improve the outcomes of SAAAD.

There were several limitations to our study. First, we did not include other types of AAD (e.g. Stanford type B) or other representative diseases (e.g. pulmonary embolism and acute myocardial infarction) that can present with abnormal coagulation-fibrinolysis markers. However, several reports have shown proportionally lower D-dimer values for these diseases compared with our findings.[2,20] Second, the timing of blood sampling from onset was not standardized between patients, ranging a few hours to over 20 h. Third, false luminal thickness and length were not analyzed in this study. From this results, we believed size of false lumen and disorder of coagulation-fibrinolysis markers were closely related. Therefore, further studies must be conducted to address these issues.

Conclusion

Preoperative coagulation-fibrinolysis markers may help predict early prognosis with SAAAD. A high D-dimer level and low fibrinogen level indicate a patent subtype of SAAAD, which is associated with a worse short-term prognosis, especially when complicated with malperfusion.

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Declaration of conflicting interests

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