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Research paper

An acute aortic dissection prognostic score for predicting early in-hospital mortality in acute thoracic aortic dissection

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ABSTRACT

Study objective: Acute thoracic aortic dissection (ATAD) has a high mortality rate. Factors that contribute to its onset include the environment, genetic factors, and infectious diseases. Recently, the presence of monocytes/macrophages has been suggested to attract inflammatory and immune cells to lesions. This, together with levels of D-dimer, brain natriuretic peptide (BNP), aspartate aminotransferase (AST), and lactate dehydrogenase (LD), may be useful in predicting a prognosis for ATAD. This study examined the relationship between a combination of such laboratory data and prognosis in ATAD.
Design: A single-center retrospective study. The association between early mortality from ATAD and laboratory data was statistically investigated.
Setting: Treatment strategies were at the discretion of each attending physician.
Participants: A total of 118 patients with ATAD (59 early deaths and 59 survivors).
Main outcome measures: The value of D-dimer, BNP, AST, and LD levels, and the peripheral blood monocyte ratio as scores for the early prediction of a prognosis without requiring advanced testing equipment.
Results: The AST/LD, D-dimer, and BNP levels were significantly elevated in those who died prematurely. In contrast, the monocyte ratio in the peripheral blood leukocyte fraction was significantly decreased. The AST/LD, which was associated with cardiac troponin I, was the most significant variable. An average positive value from each test was defined as an acute aortic dissection prognostic score (AAD-PS). The area under the curve on the receiver operating characteristic was 0.895.
Conclusion: In ATAD patients, the AAD-PS may be a potentially new and useful test item for predicting prognosis.

1. Introduction

Acute thoracic aortic dissection (ATAD) has a high mortality rate [1], highlighting the necessity of a prompt diagnosis. Most acute aortic dissections are Stanford type A, which has a poor prognosis and requires surgery [2,3]. Mortality increases by 1–2 % per hour in untreated early-stage patients, with mortality rates as high as 60–70 % within one week [4].

However, almost no biomarkers exist that are specific for acute aortic dissection, and it is therefore necessary to rely on an imaging diagnosis. The causes for ATAD are varied and include poorly controlled hypertension, atherosclerosis, genetic disorders, and bicuspid aortic valves but its prediction is difficult [5]. Inflammatory cells are thought to be involved in the progression of the dissection; more specifically, it has recently been suggested that macrophages are involved in inflammation and immunity [6,7].

Reports exist that D-dimer and brain natriuretic peptide (BNP) levels are useful for a diagnosis of ATAD. However, the mechanism of ATAD is often unknown, making it difficult to differentiate this from other diseases such as pulmonary embolism and heart failure [8,9].

As has been previously shown in cases of cardiac tamponade, which causes death in acute aortic dissection, many monocytes/macrophages infiltrate into the communicating aortic dissection and vessel wall. Such monocytes/macrophages express monocyte chemoattractant protein-1, a potent migration factor for monocytes [10,11]. In addition, high-sensitivity cardiac troponin I (hs-cTnI) is significantly elevated in cases of cardiac tamponade complications [10].

As has been previously reported, the troponin I level is highly

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Table 1
Characteristics of patients with acute thoracic aortic dissection.

Parameters	Early deaths (≤ 24 h)	Survivors	Total	*P*-value
No. of patients, total (%)	59 (50.0 %)	59 (50.0 %)	118	
Mean age ± SD, years (range)	80.07 ± 11.20 (53–97)	68.39 ± 14.67 (35–93)	74.23 ± 14.25 (35–97)	< 0.001
Age (>70 years)	49 (83.1 %)	28 (47.4 %)	77 (65.3 %)	< 0.001
Gender (female)	37 (62.7 %)	23 (39.0 %)	60 (50.8 %)	0.010
Stanford type A	51(86.4 %)	31(52.5 %)	82 (69.5 %)	< 0.001
History of hypertension	24 (40.7 %)	42 (71.2 %)	66 (55.9 %)	< 0.001
Communicating aortic dissection	42 (71.2 %)	31 (52.5 %)	73 (61.9 %)	0.037
Abdominal dissection	25 (42.4 %)	45 (76.3 %)	70 (59.3 %)	< 0.001
Cardiac tamponade	42 (71.2 %)	9 (15.3 %)	51 (43.2 %)	< 0.001
Aortic rupture	24 (40.7 %)	1 (1.7 %)	25 (21.2 %)	< 0.001
Mean inner diameter of ascending aorta ± SD, mm	41.74 ± 9.11	42.72 ± 8.35	42.23 ± 8.71	0.545

SD: standard deviation. For parameters that could not be evaluated in all cases, the denominator is listed as the number of cases surveyed.

sensitive and useful for following the development of cardiac tamponade, which greatly affects the prognosis [10]. However, since troponin I is also elevated in acute myocardial infarction, its value for predicting a prognosis alone is thought to be limited [12]. Aspartate aminotransferase (AST) has been suggested to be associated with organ dysfunction related to prognosis [13], and, in our previous study, it was found to be significantly elevated in patients with cardiac tamponade.

In this study, we investigated the D-dimer level, which is considered useful for a diagnosis, and the BNP level, which is associated with prognosis, in patients with ATAD. In addition, we focused on levels of lactate dehydrogenase (LD), AST, and troponin I, and the monocyte to leukocyte count ratio in peripheral blood from the perspective of monocyte/macrophage involvement. As an alternative to specific prognostic or diagnostic indicators, the usefulness of an "acute aortic dissection prognostic score" (AAD-PS), which combines these common test items, for predicting prognosis was evaluated. Such indicators can be easily tested not only in medical institutions with advanced equipment but also in general emergency hospitals before differentiating between Stanford types A and B aortic dissections. In anticipation, we focused on the use of these clinical data to support the treatment of ATAD in the face of limited medical resources and time. Specifically, we assessed the use of AAD-PS as a prognostic indicator in ATAD.

2. Materials and methods

2.1. Patients' backgrounds

The blood samples of 118 patients with ATAD, collected at the time of admission between 2012 and 2023, were retrieved from Kitakyushu City Yahata Hospital, a medium-sized emergency and critical care hospital in Kitakyushu, Japan. The patients consisted of 77 women and 41 men, with an age range from 35 to 97 years (mean ± standard deviation [SD]: 74.23 ± 14.25). Of these patients, 82 (69.5 %) had Stanford type A ATAD and 66 (55.9 %) had known hypertension (Table 1). Patients with known connective tissue disease causing aortic dissection, acute infectious conditions, non-compensated liver disease, or traumatic aortic dissection, and those who were receiving dialysis, or had incurable cancer were excluded from this study.

The diagnostic criteria of ATAD were confirmed by echocardiography, computed tomography (CT) or a CT angiogram examination of the aorta. Treatment strategies for cases were determined based on each physician's clinical judgment and what was considered most appropriate under the circumstances.

These retrospective, research-related examinations were conducted according to the guidelines of the Declaration of Helsinki and were approved by the Research Ethics Committee of the Kitakyushu City Hospital Organization.

2.2. Measurement of laboratory variables

Lactate dehydrogenase, AST, white blood cell count (WBC), and peripheral monocyte, D-dimer, and hs-cTnI levels were measured by blood collection immediately after each patient's visit.

Levels of LD, AST, and C-reactive protein (CRP) were measured using BioMajesty JCA-BM6070 (JEOL, Tokyo, Japan) and JCA-BM6010 (JEOL) biochemistry analyzers. The WBC was measured using a XN-2000 hematology analyzer (Sysmex, Kobe, Japan). D-dimer was measured using Coapresta CP3000 (Sekisui Medical, Tokyo, Japan) and CS-2000i (Sysmex, Kobe, Japan) blood coagulation analyzers. Levels of BNP and hs-cTnI in plasma were measured using a PATHFAST (LSI Medience Corporation, Tokyo, Japan) chemiluminescent immunoassay analyzer, and measurement ranges of 4–2000 pg/mL and 0.02–50 ng/mL, respectively. A correlation test of two instruments (Coapresta CP3000 and CS-2000i) for D-dimer measurement at our institution showed that Y(CP3000) = The correlation test at our hospital, which showed that Y(CP3000) = 0.6369×(CS-2000i) + 0.493, $r = 0.9838$, and X was converted to Y (measurement range: 0.5–60 μg/mL). For hs-cTnI below the lower limit of quantification, half of the lower limit of quantification was used, and for D-dimer above the upper limit of quantification, the upper limit of quantification was used. Laboratory personnel were unable to distinguish between cases and controls.

2.3. Sample size

In our original (unpublished) study that used small sample sizes, the response within each subject group was normally distributed with a standard deviation of 0.41. If the true difference between experimental and control means is 0.25, we established that we would need to study 59 experimental subjects and 59 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with a probability power of 0.9. The Type I error probability associated with this test of the null hypothesis is 0.05 [14].

2.4. Statistical analysis

A Chi-square-test, Welch's *t*-test, and (permuted) Brunner–Munzel test were used as appropriate to test for statistical differences between groups, respectively. Odds ratios and corresponding 95 % confidence intervals were calculated from multiple imputation methods to address missing data (data set: m = 20; analysis software: mice ver. 3.13.0) using univariable and multivariable logistic regression models. These statistical analyses were based on two-sided tests and all *p*-values <0.05 were considered statistically significant. All statistical analyses were performed using R commander user interface (The R Foundation for Statistical Computing, Vienna, Austria, version 3.6.1) designed to add statistical functions frequently used in biostatistics. Receiver operating characteristic (ROC) curve analysis was used to assess diagnostic accuracy and define the optimum cut-off value [15]. Samples pertaining to matched cases and controls were always analyzed together in the same batch and laboratory personnel were unable to distinguish cases from controls.

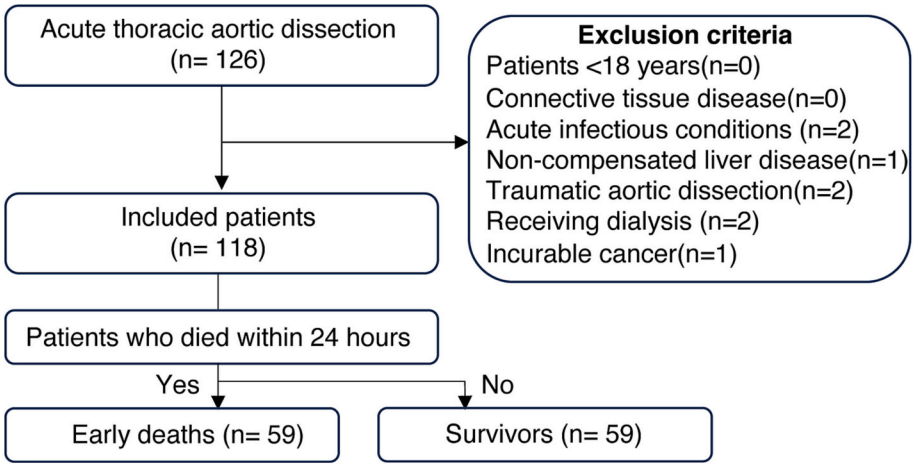

Fig. 1. Flowchart for the study.

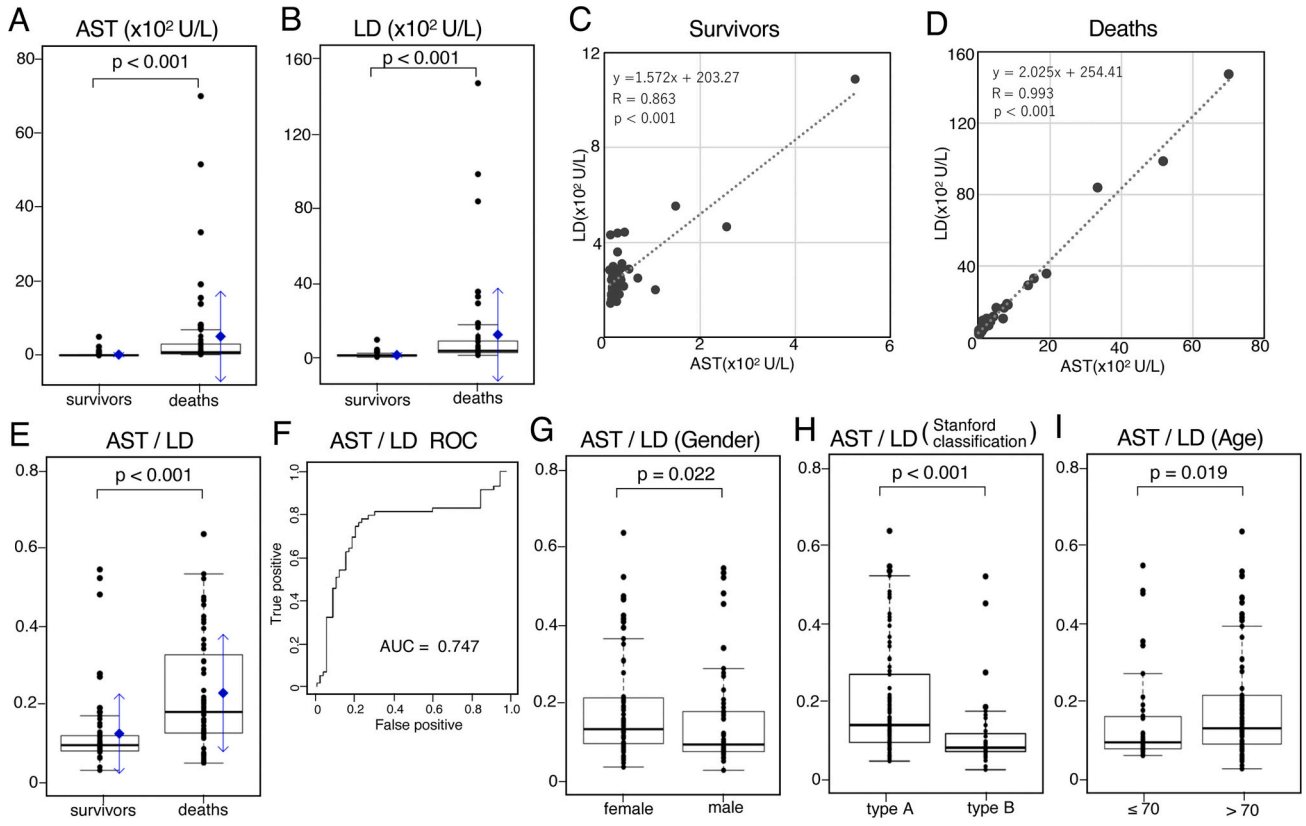

Fig. 2. Relationship between various parameters and AST and LD in ATAD

Levels of aspartate aminotransferase (AST) and lactate dehydrogenase (LD) in survivors of acute thoracic aortic dissection (ATAD) and those who died early were compared (A and B). The correlation between AST and LD levels was examined for the two patient cohorts (C and D). Panel E shows a comparison of AST/LD between survivors and those who died prematurely. Panel F shows a receiver operating characteristic (ROC) curve. Panels G, H, and I show comparisons of AST/LD by patient gender, Stanford classification of ATAD, and patient age above or below 70 years, respectively.

Horizontal bars represent 10th to 90th percentile ranges and boxes indicate 25th to 75th percentile ranges. The horizontal line in each box corresponds to the median. The mean is represented by a blue diamond and standard deviation by blue arrows. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3. Results

3.1. Characteristics of ATAD cases who died early

The study ultimately included 118 patients with ATAD in the analysis (Fig. 1). Patients who died within 24 h of admission showed a significantly older mean age and a higher proportion were women compared to survivors of ATAD ($p < 0.001$ and $p = 0.010$, respectively). Furthermore, as reported in Japanese cardiovascular disease guidelines, age over 70, Stanford type A ATAD, and a communicating aortic dissection were factors for a poor prognosis ($p < 0.001$, $p < 0.001$, and $p = 0.037$, respectively). Cardiac tamponade and aortic rupture were thought to be the causes of death in ATAD ($p < 0.001$ and $p < 0.001$, respectively; Table 1) [15]. However, a significant difference was not

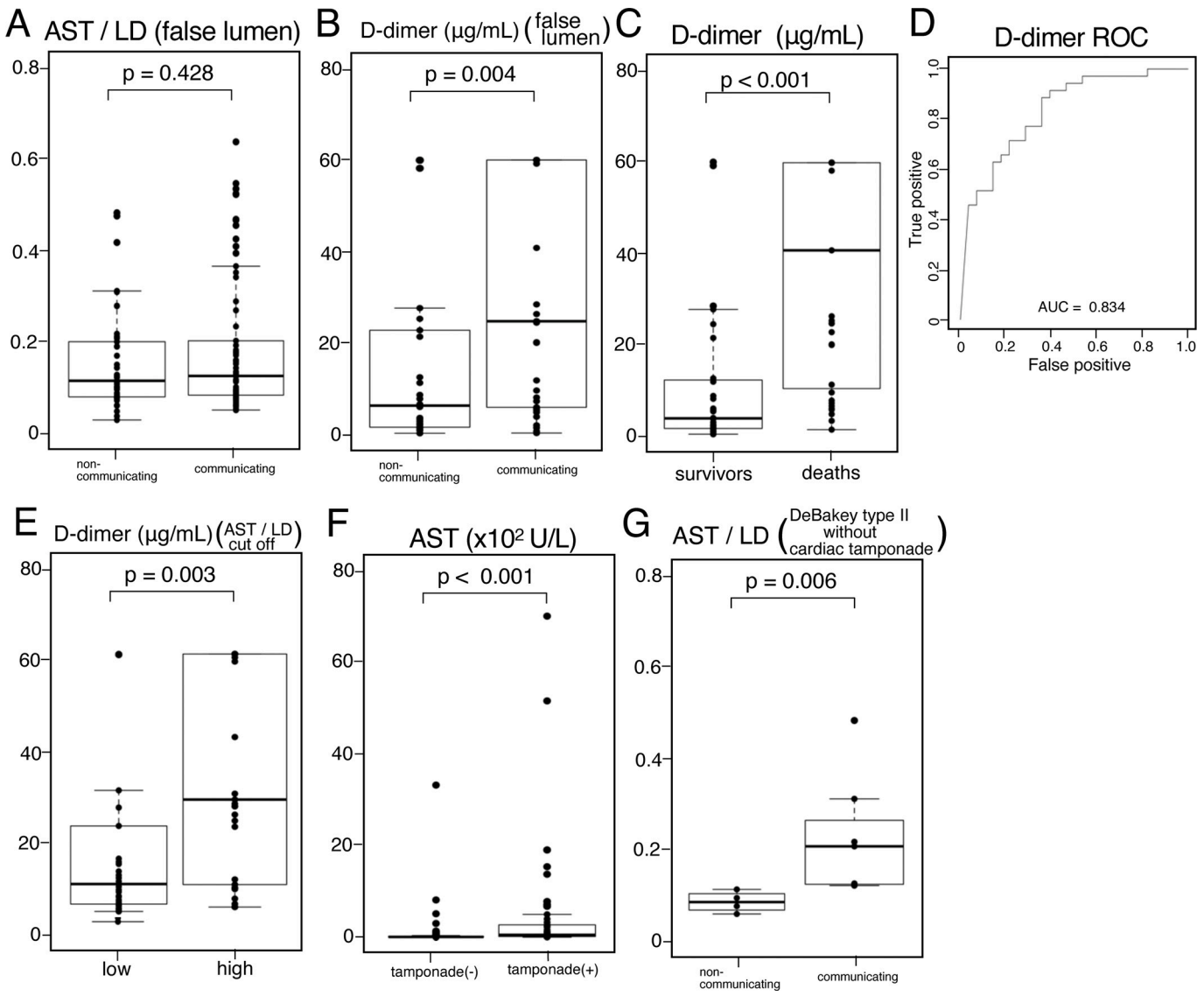

Fig. 3. Comparison of communicating aortic dissection properties in ATAD

Panels A and B compare the aspartate aminotransferase (AST) to lactate dehydrogenase (LD) ratio and D-dimer level in acute thoracic aortic dissection (ATAD) patients with communicating or non-communicating aortic dissections. Panels C and D show a comparison of D-dimer levels in survivors and cases who died early, and a receiver operating characteristic curve (ROC) analysis. Panel E shows a comparison of D-dimer levels at a cutoff value of AST/LD (0.1278).

Panel F shows a comparison of AST between patients with and without cardiac tamponade. Panel G shows a comparison of AST/LD in patients with communicating and non-communicating aortic dissections among DeBakey type II patients without cardiac tamponade.

For D-dimer in Panel E, only quantification range values were used to evaluate the correlation to LD. Horizontal bars represent 10th to 90th percentile ranges and boxes indicate 25th to 75th percentile ranges. The horizontal line in each box corresponds to the median.

found in the diameter of the ascending aorta ($p = 0.545$). A history of hypertension and the presence of abdominal aortic dissection were favorable prognostic factors ($p < 0.001$ and $p < 0.001$, respectively; Table 1).

3.2. Comparison of laboratory data on blood samples from ATAD survivors and those who died early

Levels of AST and LD in patients with ATAD who died prematurely were significantly elevated (Fig. 2A and B; $p < 0.001$ for both) compared to ATAD survivors. However, the data were highly variable with many outliers.

We also investigated the correlation between LD and AST values in the patient cohorts. We found a high correlation in both survivor and non-survivor groups (Fig. 2C, $r = 0.863$, $p < 0.001$; Fig. 2D, $r = 0.993$, $p < 0.001$). We also compared the AST/LD of deceased and surviving cases. We found the AST/LD of deceased cases was significantly higher, and the dispersion of the data was quite small (Fig. 2E). The cutoff value calculated from the ROC curve was 0.1278 and the area under the curve (AUC) was 0.747 (Fig. 2F).

Figs. 2G, H, and I are comparisons of AST/LD by gender, Stanford classification, and age. Significantly higher AST/LD values were observed in females, ATAD cases of Stanford type A, and people older than 70 years ($p = 0.022$, $p < 0.001$, and $p = 0.019$, respectively).

3.3. Contribution of communicating aortic dissection status to laboratory data

Fig. 3A shows a comparison of the AST/LD in non-communicating and communicating aortic dissections; no significant difference was observed ($p = 0.428$). In comparison, a significantly higher D-dimer level was present in patients with a communicating aortic dissection

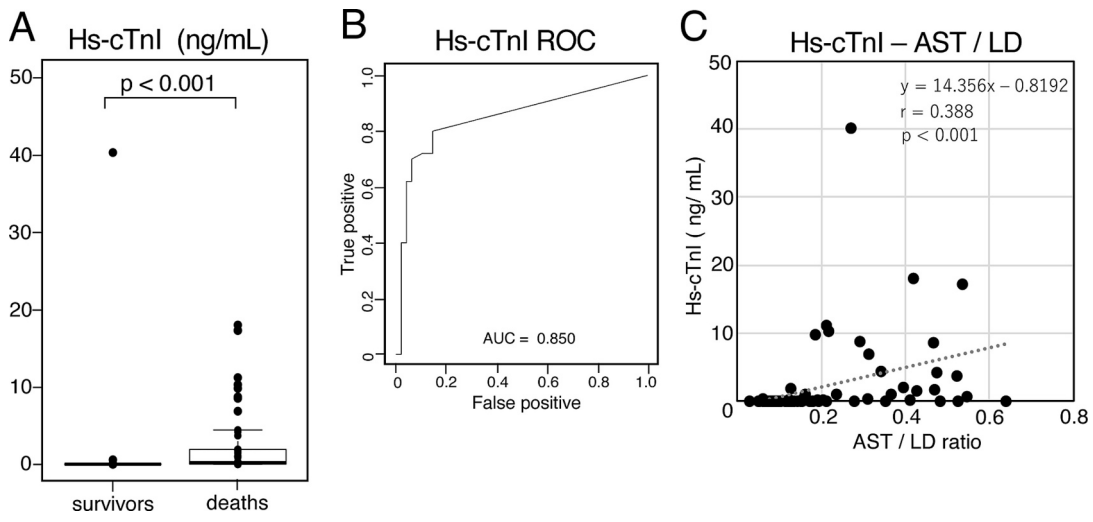

Fig. 4. Usefulness for prognosis of hs-cTnI and correlation with AST/LD ratio

Panel A shows a comparison of the high-sensitivity troponin I (hs-cTnI) level between survivors and those who died of an acute thoracic aortic dissection (ATAD). Panel B show a comparison and receiver operating characteristic (ROC) curve of the hs-cTnI level between survivors and those who died prematurely. Panel C shows the relationship between the aspartate aminotransferase (AST) to lactate dehydrogenase (LD) ratio and hs-cTnI level.

Horizontal bars represent 10th to 90th percentile ranges and boxes indicate 25th to 75th percentile ranges. The horizontal line in each box corresponds to the median.

(false lumen) and in those who died early (Figs. 3B and C; $p < 0.004$ and $p = 0.001$, respectively). The optimal cutoff value for a premature death was determined from the ROC curve and was 6.231 μg/mL, with an AUC of 0.834 (Fig. 3D). In addition, for cases where the AST/LD was above the cutoff value, the D-dimer level was significantly higher (Fig. 3E; $p = 0.003$).

The AST level was significantly higher in cases with cardiac tamponade (Fig. 3F, $p < 0.001$). In cases limited to DeBakey type II with a dissection of only the ascending aorta without cardiac tamponade, a comparison of the AST/LD showed this to be significantly higher in cases with a communicating aortic dissection (Fig. 3G, $p = 0.006$).

3.4. Relationship between hs-cTnI and AST/LD

Fig. 4 shows an evaluation of hs-cTnI levels in ATAD cases. Levels of hs-cTnI were significantly elevated in patients who died prematurely compared to those who survived (Fig. 4A). The optimal cutoff value for % monocytes, determined from the ROC curve, was found to be 0.021 ng/mL, with an AUC of 0.850 (Fig. 4B). The hs-cTnI level correlated with the AST/LD ratio (Fig. 4C; $r = 0.388$, $p < 0.001$).

3.5. Relationship between prognosis and BNP or monocytes

Fig. 5A shows a comparison of BNP levels between survivors and patients who died early from ATAD; this was significantly increased in the latter cohort ($p = 0.020$). The optimal cutoff value, determined from the ROC curve, was found to be 101 pg/mL, with an AUC of 0.720 (Fig. 5B). For Stanford type A ATAD patients only, the difference was more significant (Fig. 5C; $p = 0.013$). The AST/LD was significantly increased in cases with ≤101 pg/mL BNP (Fig. 5D; $p = 0.044$).

Fig. 5E shows a comparison of the ratio of peripheral blood monocyte to leukocyte counts (% monocytes) between survivors and patients who died prematurely; the ratio was significantly lower for the latter ($p < 0.001$). The optimal cutoff value for % monocytes, determined from the ROC curve, was found to be 5.1 %, with an AUC of 0.684 (Fig. 5F). In addition, the % monocyte value was significantly lower in patients with a communicating aortic dissection ($p = 0.040$; Fig. 5G). The AST/LD was significantly increased in cases where the % monocyte value was lower than 5.1 % (Fig. 5H; $p = 0.047$).

3.6. Investigating the effect of AST/LD, and monocyte, BNP, and D-dimer levels on prognosis

The relationships between prognosis and AST/LD, % monocytes, and D-dimer and BNP levels were investigated using univariate and multivariate analyses and by multiple imputation methods. For hs-cTnI, only univariate analyses are presented (Table 2). All items were significantly related in univariate analysis (AST/LD, $p < 0.001$; % monocytes, $p < 0.001$; BNP; $p = 0.002$, D-dimer; $p < 0.001$, and hs-cTnI; $p < 0.001$). All items were also significantly related in multivariate analysis ($p = 0.001$, $p = 0.029$, $p = 0.017$, and $p = 0.004$, respectively).

Therefore, we created a new indicator by dividing the number satisfying ≤0.1278 AST/ALT, >5.1 % monocytes, 101 pg/mL BNP, and ≤ 6.231 μg/mL D-dimer by the number of tests performed. This new index, named the AAD-PS, had a range from 0 to 1 (e.g., if three blood tests were evaluable and two were positive, the result was defined as AAD-PS: 2/3). Table 3 and Fig. 6 show AAD-PS values and significant factors from Table 1. Other than gender and communicating aortic dissection, the AAD-PS had a statistically significant cutoff value. The mean AAD-PS value significantly increased in patients with age (> 70 years), Stanford type A, and complications of cardiac tamponade and aortic rupture, and significantly decreased in patients with a history of hypertension treatment (Fig. 6).

Fig. 7A shows the AAD-PS for survivors and those who died early; the latter had a significantly higher AAD-PS ($p < 0.001$). The appropriate cutoff value for the AAD-PS from the ROC curve was calculated as 0.66. The sensitivity was 0.831, specificity was 0.831 (Table 4), and AUC was 0.895, making this a useful index (Fig. 7B). The AUC of the AAD-PS was greater than the AUC of each test alone. An AAD-PS of >0.66 was considered to be quite valuable for a poor prognostic diagnosis in patients with ATAD. In addition, even when Stanford types A and B were investigated separately, the AAD-PS was significantly higher in cases of early death (Fig. 7C and D).

4. Discussion

Acute aortic dissection occurs in response to various factors, with major causes of an early death being cardiac tamponade and aortic rupture [16,17]. However, the onset of such complications has been very difficult to predict. Recently, for the diagnosis of acute aortic syndrome, an aortic dissection detection risk score (ADD-RS) has often

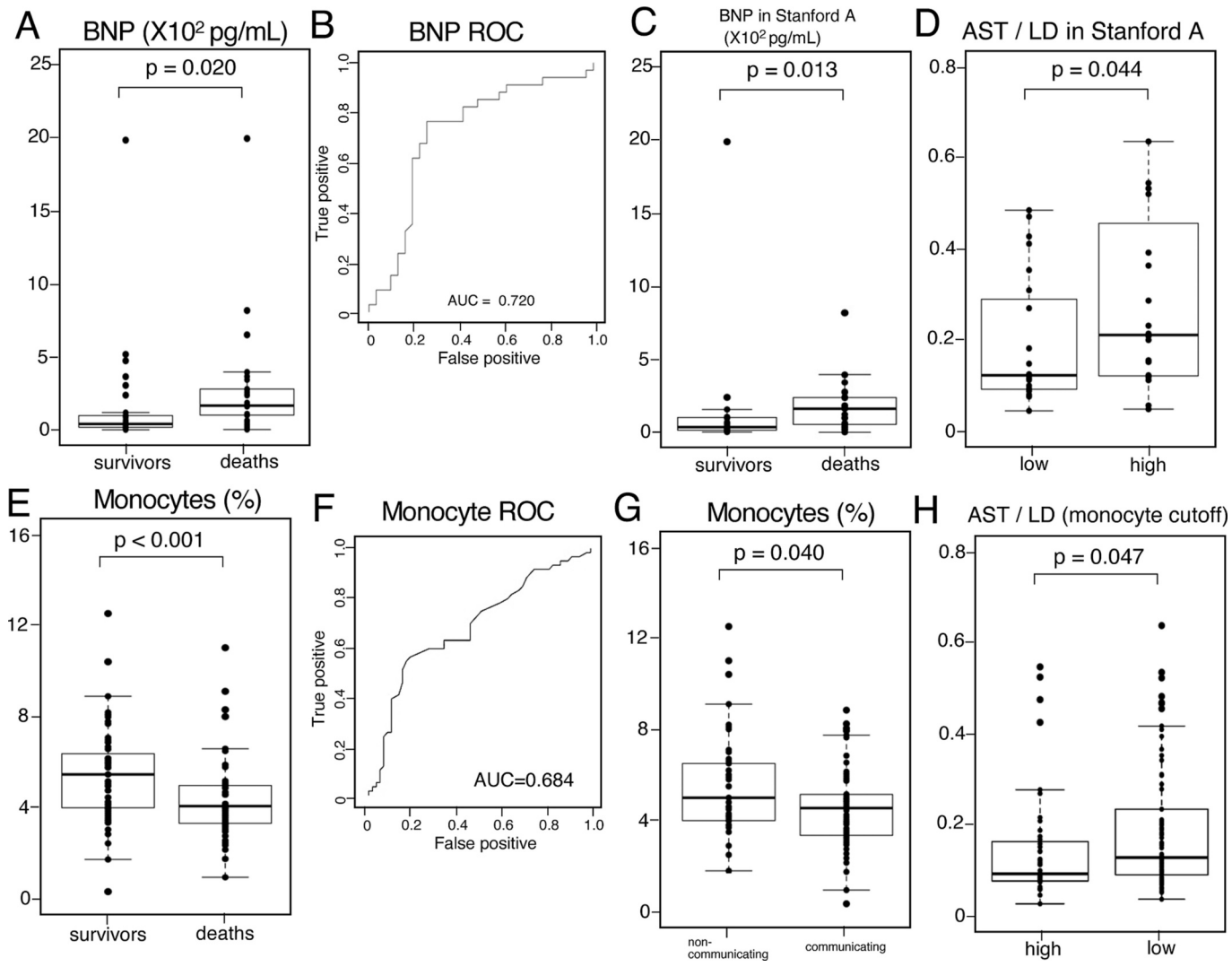

Fig. 5. Expression of BNP and monocyte involvement in ATAD patients with aortic dissection

Panels A and B show a comparison and receiver operating characteristic (ROC) curve of brain natriuretic peptide (BNP) levels between survivors of acute thoracic aortic dissection (ATAD) and those patients who had died early. Figs. C and D are comparisons limited to Stanford type A patients, and are a comparison of BNP and aspartate aminotransferase (AST)/lactate dehydrogenase (LD) at a BNP cutoff value (101 pg/mL), respectively.

Panels E and F show a comparison and ROC curve of the monocyte to white blood cell ratio between survivors and those who died prematurely.

Panel G shows a comparison of the monocyte to white blood cell ratio between ATAD patients with communicating and non-communicating false aortic dissections.

Fig. H shows a comparison of AST/LD at a cutoff value for monocytes (5.1 %).

Horizontal bars represent 10th to 90th percentile ranges and boxes indicate 25th to 75th percentile ranges. The horizontal line in each box corresponds to the median.

Table 2

Univariate and multivariate analyses used to identify independent predictors for early death in patients with acute thoracic aortic dissection.

Parameters		Early deaths		Univariate				Multivariate			
				OR	95 % CI		*P*-value	OR	95 % CI		*P*-value
		(+)	(−)		lower	higher			lower	higher	
AST/LD	≥ 0.1278	43	12	10.526	4.435	24.982	<0.001	13.008	2.924	57.878	0.001
	< 0.1278	16	47								
Monocytes (%)	≥ 5.1	11	33	0.181	0.078	0.419	<0.001	0.184	0.040	0.839	0.029
	< 5.1	48	26								
BNP (pg/mL)	≥ 101	26	8	8.847	2.392	32.728	0.002	18.567	2.661	129.558	0.017
	< 101	8	23								
D-dimer (μg/mL)	≥ 6.231	31	10	14.125	4.061	49.135	<0.001	16.432	1.707	158.198	0.004
	< 6.231	4	18								
Hs-cTnI (ng/mL)	≥ 0.021	41	7	24.903	2.135	4.295	<0.001				
	< 0.021	10	43								

AST: aspartate aminotransferase, BNP: brain natriuretic peptide, CI: confidence interval, Hs-cTnI: high sensitivity troponin I, LD: lactate dehydrogenase, OR: odds ratio.

Table 3
Patients' backgrounds and complications for the AAD-PS.

Parameters	AAD-PS (+)	AAD-PS (−)	*P*-value
No. of patients, total (%)	59 (50.0 %)	59 (50.0 %)	
Early deaths	49 (83.1 %)	10 (16.9 %)	< 0.001
Age (>70 years)	45 (58.4 %)	32 (41.6 %)	0.020
Gender (female)	32 (53.3 %)	28 (46.7 %)	0.461
Stanford type A	47(57.3 %)	35(42.7 %)	0.016
History of hypertension	25 (37.9 %)	41 (62.1 %)	0.003
Communicating aortic dissection	41 (56.2 %)	32 (43.8 %)	0.081
Abdominal dissection	28 (40.0 %)	42 (60.0 %)	0.009
Cardiac tamponade	35 (68.6 %)	16 (31.4 %)	0.006
Aortic rupture	21 (84.0 %)	4 (16.0 %)	< 0.001

AAD-PS: acute aortic dissection prognostic score.

been used [18]. However, the only test data available is the D-dimer level, which has a low specificity [19,20]. Computed tomography is ultimately required for a definitive diagnosis of an aortic dissection in an ADD-RS. However, it must be noted that adverse reactions occur in 0.6 % of patients, of which 0.04 % are severe, when using contrast media in CT [21]. Therefore, it was considered helpful to investigate the use of advanced tests, other than those for D-dimer, for a diagnosis and to predict prognosis in acute aortic dissection. In addition, investigating and evaluating test items that were related to risk factors for cardiac tamponade and communication with the dissection cavity was thought to lead to an early diagnosis and surgical intervention.

A previous investigation into the characteristics of cardiac tamponade cases in Stanford type A ATAD showed that death was caused by restrictive shock, and that AST, LD, and hs-cTnI levels were elevated [10]. In addition, it was found that hs-cTnI correlated with AST/LD. In cases of cardiac tamponade, macrophage infiltration into the medial smooth muscle [22], and large numbers of monocytes in the communicating aortic dissection, were observed [10]. In this study, a correlation was also observed between hs-cTnI and AST (data not shown); AST/LD was a good indicator of aortic dissections, especially in DeBakey type II, which is often complicated by cardiac tamponade and has a high mortality rate. The above factors combined were thought to be the cause of the significant increase in the hs-cTnI level in cases of early death. Furthermore, the AST/LD also correlated with the hs-cTnI level in all cases, suggesting that it may be used as an alternative to the AST/LD. Currently, some hospitals measure troponin T instead of troponin I and the cutoff values vary; therefore, AST/LD is considered to be very important in ensuring the versatility of the test item. We investigated whether AST/LD, monocyte counts, and BNP and D-dimer levels, which are related, influence early mortality in all cases of ATAD, including Stanford type B.

Aspartate aminotransferase and LD reflect an early prognosis. The AST/LD was well maintained between survivors and those who died prematurely, with AST/LD significantly higher for the latter cohort. In this study, it was more useful to evaluate AST/LD, rather than AST and LD alone, for an early prognosis. In addition, a significant increase was observed in other factors known to increase mortality, except for a communicating aortic dissection.

D-dimer is a fibrin degradation product, the elevation of which is induced by the coagulation cascade, and is associated with fibrinolysis [23]. D-dimer decreases when a communicating aortic dissection is occluded by thrombosis [24]; our study also showed a significant decrease. In addition, D-dimer significantly increased in patients who died prematurely. Elevated D-dimer appears to be associated with LD. In comparison, AST was associated with hs-cTnI. When limiting this investigation of communicating aortic dissections to DeBakey type II patients with a focal dissection of the ascending aorta and no cardiac tamponade, AST/LD was found to be significantly increased in such patients. The complication of cardiac tamponade and the extent of aortic dissection may be associated with AST/LD, which was considered to be affected by these variables.

Although the BNP level can represent the degree of heart failure, the evaluation of this as a variable requires caution as it is affected by varied factors such as age and renal function [25]. However, the present study showed that BNP, like N-terminal–pro BNP [26], was associated with an early prognosis. Furthermore, in patients with a Stanford type A aortic dissection, AST/LD was significantly lower in those with low BNP values and was significantly increased in patients with high BNP values. One

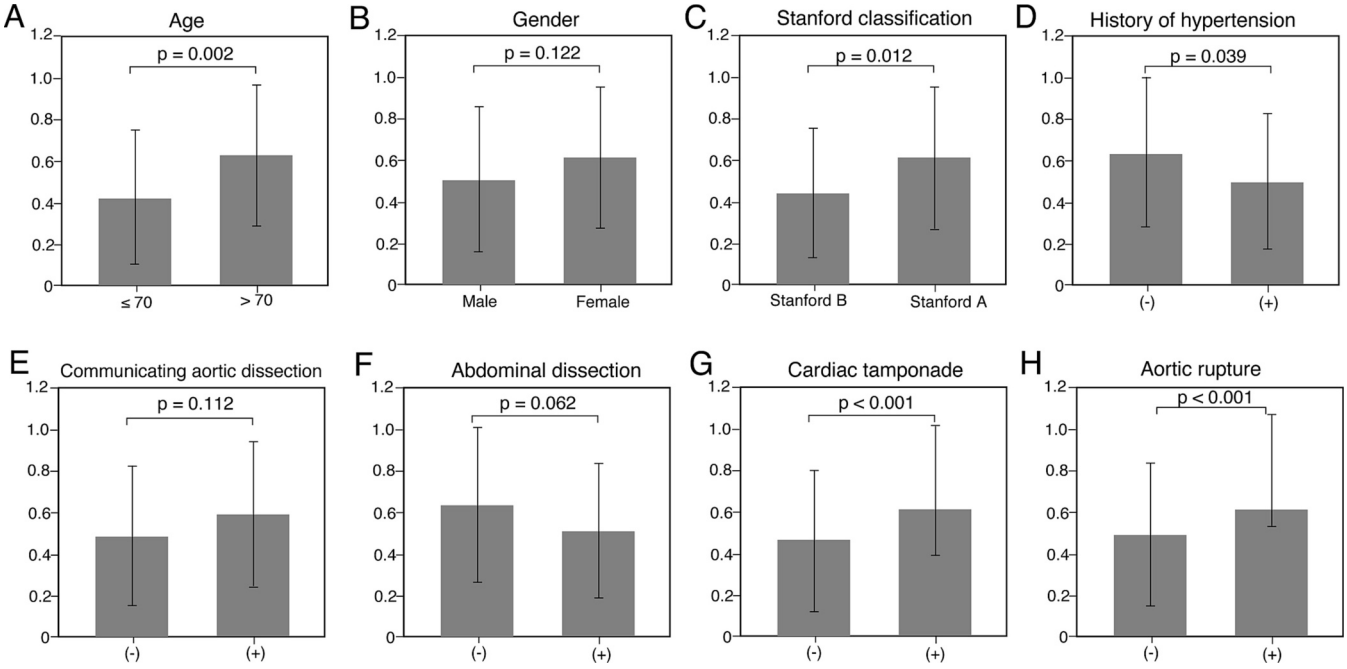

Fig. 6. Comparison of patients' backgrounds and complications for the "acute aortic dissection prognostic score"
Panels A–H show a comparison of background and complications (age, gender, Stanford classification, history of hypertension, communicating aortic dissection, abdominal dissection, cardiac tamponade, and aortic rupture) that are considered to be significantly associated with early death in Table 1 and acute aortic scores. The values are presented as the mean ± standard deviation.

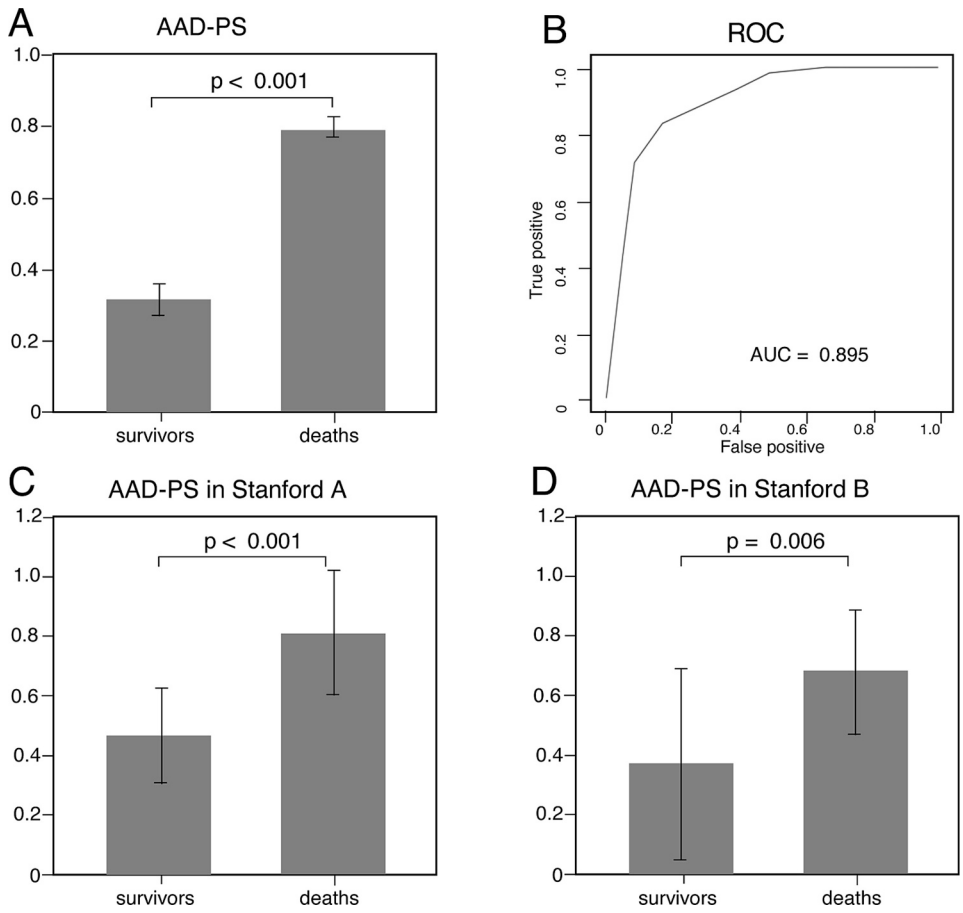

Fig. 7. Evaluation of diagnostic effectiveness of "acute aortic dissection prognostic score"
Panel A shows a comparison of acute aortic dissection scores between survivors and patients who died early among those with an acute aortic dissection. Panel B shows a receiver operating characteristic (ROC) curve for prognosis. Panels C and D show a comparison of acute aortic dissection scores (AAD-PS) between survivors and patients who died early among those with an acute aortic dissection in Stanford A and B, respectively. The values are presented as the mean ± standard deviation.

Table 4
Comparison of sensitivity and specificity of each test for early death.

Parameters	Sensitivity	Specificity
AST/LD (≥ 0.1278)	0.729	0.797
Monocytes (< 5.1 %)	0.814	0.559
BNP (≥ 101 pg/mL)	0.765	0.742
D-dimer (≥ 6.231 μg/mL)	0.886	0.643
AAD-PS (> 6.6)	0.831	0.831

AAD-PS: acute aortic dissection prognostic score, AST: aspartate aminotransferase, BNP: brain natriuretic peptide, LD: lactate dehydrogenase.

reason for this was thought to be that BNP and AST/LD were each affected by Stanford type A cardiac tamponade [10]. The utility of BNP, LD, and cardiac troponins as biomarkers in ATAD is also supported by large multicenter studies [27].

Recent findings suggest that monocytes and macrophages are involved in acute aortic dissection, a condition that differs from acute myocardial infarction, in which CRP and WBC are elevated. Furthermore, our previous studies have not identified a significant increase in CRP or WBC in patients with Stanford type A dissection complicated by cardiac tamponade [10,28], nor has the present study demonstrated a significant association with early prognosis (Supplemental Fig. 1). However, the mechanism of monocyte recruitment remains unclear [29]. Monocytes/macrophages are not only derived from resident cells within the aorta, but also migrate from the bone marrow [30]. Generally, the turnover of monocytes from the bone marrow takes more than a month. It was therefore thought that if a large number of monocytes migrated from the bone marrow to the aorta, the proportion of monocytes in peripheral blood would decrease [31]. Recruitment of a large number of monocytes/macrophages to aortic dissection lesions was shown to increase the immune response and lead to a poor prognosis [6]. Therefore, when the ratio of monocytes to white blood cells was compared between survivors and deceased patients, a significant decrease in peripheral blood monocytes was observed in the latter group.

The population of immune cells in patients with aortic dissection differs from that in healthy people [32]. Since monocytes/macrophages are histologically abundant in and around the communicating aortic dissection [10], this may be considered a monocyte/macrophage supply route. Patients with a communicating aortic dissection were found to have a significantly lower monocyte ratio than patients with an occlusion. Furthermore, since monocyte infiltration is accompanied by tissue damage, a relationship was seen with AST/LD. Additionally, to date, a large-scale multicenter study has highlighted a correlation between total bilirubin and the prognosis of Stanford A, although the factors involved have not been elucidated [27]. In the present study, serum total bilirubin levels were also significantly lower in patients with a poor prognosis (Supplemental Fig. 2). However, the number of cases was small and the results differ from those of a previous large-scale multicenter study. It is

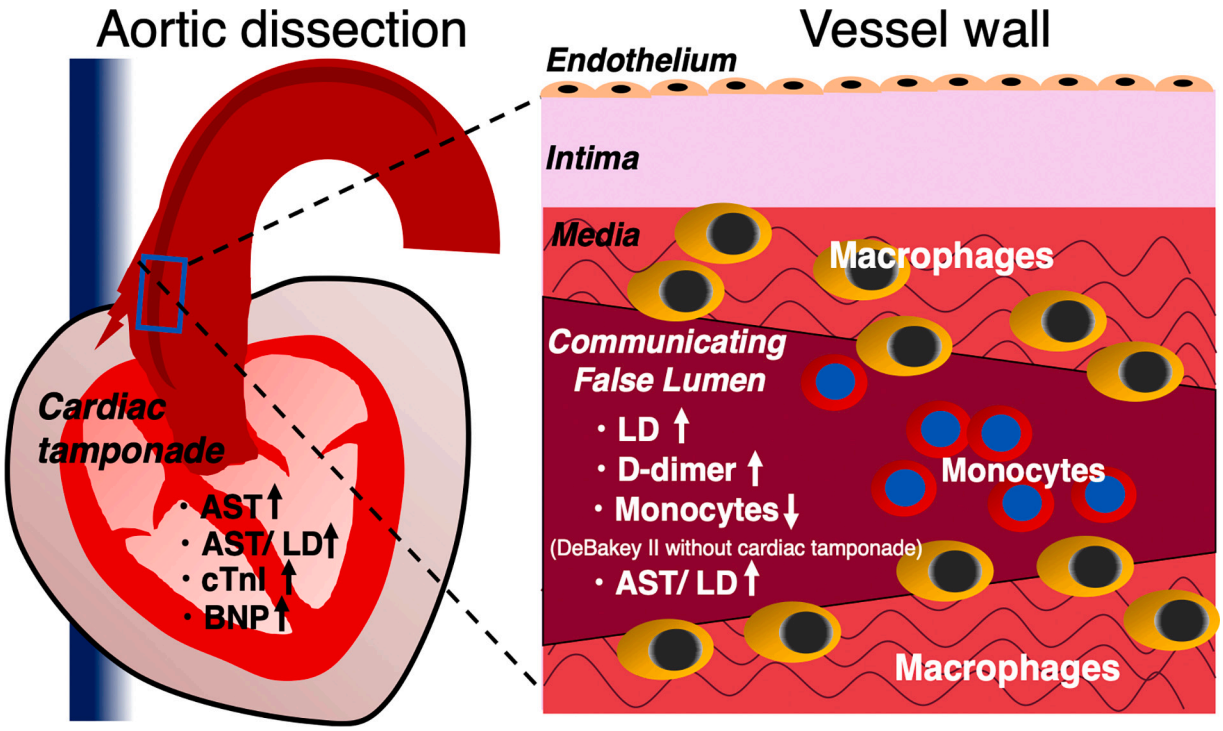

Fig. 8. Schematic diagram
AST, aspartate aminotransferase; BNP, brain natriuretic peptide; cTnI, troponin I; LD, lactate dehydrogenase.

therefore necessary to investigate direct and indirect bilirubin levels independently in future and to carefully elucidate background factors, such as whether the severity of dissection or the presence of other organ damage affects serum total bilirubin levels.

The above results are summarized in Fig. 8. Based on our research, we devised a new index for ATAD termed the AAD-PS. Although D-dimer as a biomarker shows high sensitivity in disease, its specificity is low, making it difficult to distinguish between diseases such as pulmonary infarction and lower limb venous thrombosis. Previous research has evaluated the usefulness of a single blood test for the prognosis of ATAD, with few indicators identified from combining multiple blood tests. A significant association was found with being elderly, Stanford classification, and complications of cardiac tamponade and aortic rupture, which are considered prognostic factors in the guidelines for ATAD [16]. Background factors, other than the patency of the dissecting cavity and a history of hypertension treatment, may be affected by the small number of cases used in this study and missing values. The AAD-PS as a new indicator for ATAD prognosis is simple as it can be completed with just a blood test. It is also highly specific and is extremely useful.

It is hoped that this study will be expanded to more cases in future. In addition, by examining many cases from multiple institutions, including patients' backgrounds, it will be possible to evaluate not only prognostic predictions but also the usefulness of this method for early diagnosis.

This study has several limitations. First, the sample size was small and the study was conducted at a single center. Furthermore, because this study was retrospective in nature, some values were lacking. However, few studies have examined the prognosis of aortic dissection using only blood samples, which is considered important. Therefore, in future, accumulating such data will be beneficial for early diagnosis and determining therapeutic interventions.

5. Conclusions

In this study, we investigated the causes of an early death in patients with ATAD from various perspectives and were able to identify a useful blood test for this disease. Furthermore, by combining blood test variables, we were able to create a new index, termed the "AAD-PS", for predicting a prognosis in ATAD.

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CRediT authorship contribution statement

Satoshi Kimura: Writing – original draft, Software, Methodology. **Hiroaki Sato:** Writing – review & editing, Investigation. **Shohei Shimajiri:** Writing – review & editing, Methodology. **Toshiyuki Nakayama:** Writing – review & editing.

Ethics statement

This study was conducted in accordance with the Declaration of Helsinki and the Ethics Guidelines for Clinical Research issued by the Japanese Ministry of Health, Labor and Welfare. The protocol of this study was approved by the Research Ethics Committee of the Kitakyushu City Hospital Organization with the approval number: 202112001. This retrospective study was conducted in accordance with the ethical guidelines established by the Japanese government, using only information used for medical treatment in clinical practice. Informed consent of patients was obtained through an opt-out methodology or written consent. Information on the research was made public on the Kitakyushu City Hospital Organization website, and the opportunity for the research subjects to refuse participation was guaranteed.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

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