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S100A1 as a potential biomarker for the diagnosis of patients with acute aortic dissection

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Abstract

Objective: Acute aortic dissection (AAD) is a common life-threatening cardiovascular disease. This retrospective study was conducted to analyze the plasma concentration of S100A1 and its diagnostic value for AAD through receiver operating characteristic (ROC) curve and logistic regression analyses.

Methods: Seventy-eight patients with AAD and 77 healthy controls were included, and the relevant clinical data for each group were collected. According to the Stanford classification, the AAD patients were divided into types A and B. The plasma levels of S100A1, D-dimer, hypersensitive C-reactive protein, and cardiac troponin T were detected by enzyme-linked immunosorbent assays.

Results: The S100A1 concentrations in the healthy control, Stanford A, and Stanford B groups were 0.7 ± 0.6, 4.9 ± 2.6, and 3.5 ± 2.2 ng/mL, respectively. The concentration of S100A1 was increased in patients with AAD complicated with aortic regurgitation, pericardial effusion, or in-hospital death. ROC curve analysis showed that the area under the curve was 0.89. Logistic regression analysis revealed that the S100A1 level was an important risk factor for the development of AAD.

Conclusion: Plasma S100A1 is significantly elevated in patients with AAD, and its concentration has potential clinical value for diagnosing AAD.

Keywords

Aortic disease, S100 protein, diagnosis, biological marker, cardiovascular disease, calcium-binding protein

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Background

Acute aortic dissection (AAD) is a common life-threatening disease with a sudden onset, rapid progression, and high mortality.[1] According to the Stanford classification, AAD can be divided into types A and B. The former involves the ascending aorta, whereas the latter does not.[2] The clinical manifestations of AAD vary with the degree of lesion involvement. If patients with type A are not administered treatment promptly, the mortality rate can reach up to 24% within 24 hours and 50% within 48 hours.[3] Thus, the early diagnosis and timely treatment of AAD are critically important for these patients.

The diagnosis and treatment of AAD remain challenging.[4] Additionally, the diagnosis of AAD mainly depends on various imaging techniques, which are relatively time-consuming or unavailable in some hospitals.[5–7] Therefore, biomarkers may be more suitable for the diagnosis of AAD.[8] Previous studies have shown that serum biochemical markers, such as D-dimer and matrix metalloproteinase-9, can be used as non-invasive indicators for the early and rapid clinical diagnosis of AAD.[9–11]

Calcium-binding protein S100 is an acidic protein with a low relative molecular mass. It is widely present in different tissues and belongs to the calcium-binding protein family. Through the regulation of intracellular calcium ions, S100 has various biological functions in the body and participates in cell proliferation, cellular differentiation, protein phosphorylase modulation, and transcription factor regulation.[12] Calcium-binding protein S100A1, a member of the S100 protein family, is one of the most important regulators of myocardial systolic and diastolic functions.[13] S100A1 can serve as an early diagnostic marker of ischemic coronary artery disease in patients with acute myocardial infarction.[14] However, few studies have evaluated S100A1 as a biomarker in patients with AAD. Therefore, in this study, an elevated S100A1 level was used as a marker of AAD to explore its diagnostic value in patients with AAD.

Methods

Case selection

Based on spiral computed tomography aortic reconstruction and echocardiography, patients were diagnosed with primary AAD in the cardiac center and cardiac surgery department of our hospital from January 2015 to December 2019. The exclusion criteria were patients with the following: 1) severe infection; 2) myocarditis or cardiomyopathy; 3) severe liver dysfunction or renal insufficiency; 4) iatrogenic vascular injury; 5) abnormal coagulation; 6) malignant tumors; and 7) other conditions identified by the investigator as inappropriate for enrollment (e.g., pregnancy or patients with a mental disorder). During the same period, healthy subjects were included as a control group. The healthy control participants were from outpatient physical examinations.

The inclusion and exclusion of patients were evaluated by two experienced thoracic and cardiovascular surgeons. The investigation was reviewed and approved by the ethics committee of the hospital, and all enrolled patients provided written informed consent for the study (No. 2015-2967).

Biochemical detection

Venous blood (5 mL) was collected from patients with AAD (type A and type B) at admission and before the operation; the same volume of venous blood was collected from the normal control group after overnight fasting. All samples for determining biomarker concentrations were drawn in ethylenediaminetetraacetic acid-containing

vacuum containers and stored at −80°C until assayed. After standing at room temperature for 20 minutes, the blood was centrifuged at 1000 × g. The supernatant was collected and stored at −20°C, thawed at room temperature before the experiments, and mixed evenly before analysis. Blood was drawn from both groups of patients to measure total cholesterol, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, triglycerides, hypersensitive C-reactive protein (hs-CRP) (Thermo Fisher Scientific, Waltham, MA, USA), cardiac troponin T (cTnT) (Roche Diagnostics, Penzberg, Germany), D-dimer (Thermo Fisher Scientific), and fasting blood glucose. The patients' heart rate, systolic blood pressure, and diastolic blood pressure were also measured.

S100A1 analysis

A human S100A1 enzyme-linked immunosorbent assay kit was obtained from LifeSpan BioScience (Seattle, WA, USA). Skilled technicians strictly followed the protocol to measure S100A1 levels. The assay range was 0.156 to 10 ng/mL. Measurements were made in duplicate and averaged.

Statistical methods

IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA) was used for analysis. Measurement data were expressed as the mean ± standard deviation. One-way ANOVA with the Newman–Keuls post hoc test and Student's t-test or the Wilcoxon matched-pairs signed-rank test were used to determine the differences between groups for Gaussian-distributed data and non-Gaussian-distributed data, respectively. The χ^2 test or Fisher's exact test was used to compare dichotomous data. Linear regression was used for correlation analysis. Logistic regression analysis was used to examine the influence of various clinical variables by estimating the probability of S100A1 levels. Receiver operating characteristic (ROC) curves were used to examine the value of plasma S100A1 in diagnosing AAD. $P < 0.05$ was considered to indicate statistical significance.

Results

Baseline patient data

Between January 2015 and December 2019, we screened 92 consecutive AAD patients who were admitted to our institution. Patients with severe infection (n = 2), myocarditis or cardiomyopathy (n = 3), severe liver dysfunction or renal insufficiency (n = 3), iatrogenic vascular injury (n = 1), abnormal coagulation (n = 1), malignant tumors (n = 2), and other conditions (n = 3) were ineligible for the study. During the same period, 76 healthy subjects were included as a control group. The baseline data of all patients are shown in Table 1. According to the internationally acknowledged AAD clinical Stanford classification, the patients were divided into two groups: 1) Stanford A group: 16 patients, 12 men and 4 women, with a mean age of 62.1 ± 9.4 years and 2) Stanford B group: 61 patients, 41 men and 20 women, with a mean age of 58.6 ± 9.8 years. There were no significant differences in sex, age, body mass index, smoking history, hypertension, diabetes, or history of coronary artery disease between the two groups. Similarly, there were no significant differences in glucolipid metabolism profiles between the two AAD groups. The differences in D-dimer, hs-CRP, and cTNT between the two AAD groups were also not statistically significant.

There was a significant difference in S100A1 levels between the Stanford A group and Stanford B group (Table 1, $p < 0.05$), whereas there were no significant differences in the other variables.

Table 1. Baseline characteristics of patients in the different groups.

Variables	Healthy Control group (n = 76)	AAD groups		p value
		Stanford A group (n = 16)	Stanford B group (n = 61)	
Age (years, mean ± SD)	57.3 ± 9.1	62.1 ± 9.4	58.6 ± 9.8	0.20
Gender (Male/female)	48/28	12/4	41/20	0.19
Body mass index (kg/m^2, mean ± SD)	24.1 ± 2.5	24.4 ± 2.9	24.4 ± 2.4	0.99
Smoking history (n, %)	0	8 (50.0)	38 (62.3)	0.38
Hypertension (n, %)	0	14 (87.5)	52 (85.2)	0.61
Diabetes mellitus (n, %)	0	13 (81.3)	38 (62.3)	0.15
CAD history (n, %)	0	8 (50.0)	34 (55.7)	0.87
FBG (mmol/L, mean ± SD)	5.6 ± 0.4	6.2 ± 1.2	5.8 ± 0.8	0.11
HbA1C (%, mean ± SD)	6.1 ± 0.2	6.5 ± 0.7	6.3 ± 0.6	0.25
TG (mmol/L, mean ± SD)	1.9 ± 1.0	2.3 ± 0.9	1.9 ± 1.1	0.18
LDL-C (mmol/L, mean ± SD)	3.1 ± 0.9	3.1 ± 1.2	3.0 ± 0.9	0.71
hs-CRP (mg/dL, mean ± SD)	2.0 ± 3.0	6.6 ± 3.4	6.4 ± 2.9	0.81
D-dimer (mg/dL, mean ± SD)	0.3 ± 0.2	18.4 ± 16.9	18.5 ± 22.7	0.98
Fibrinogen cleavage products (mg/L, mean ± SD)	10.2 ± 2.5	42.1 ± 11.2	46.8 ± 15.3	0.25
cTNT (ng/mL, mean ± SD)	0.2 ± 0.1	2.5 ± 2.1	1.8 ± 1.5	0.13
S100A1 (ng/mL, mean ± SD)	0.7 ± 0.6	4.9 ± 2.6	3.5 ± 2.2	0.03
Heart rate (bpm, mean ± SD)	73.7 ± 9.7	76.6 ± 13.8	77.6 ± 12.4	0.77
Systolic blood pressure (mmHg, mean ± SD)	130.3 ± 17.4	162.5 ± 46.7	158.8 ± 37.6	0.74
Diastolic blood pressure (mmHg, mean ± SD)	74.4 ± 10.7	71.8 ± 12.8	75.9 ± 10.4	0.18

All data were presented as the mean ± SD.

AAD: acute aortic dissection; CAD: coronary artery disease; FBG: fasting blood glucose; HbA1C: hemoglobin A1c; TG: triglyceride; LDL-C: low-density lipoprotein-cholesterol; hs-CRP: hypersensitive C-reactive protein; cTNT: cardiac troponin T.

S100A1 concentration

The concentrations of S100A1 in the healthy control group, Stanford A group, and Stanford B group were 0.7 ± 0.6, 4.9 ± 2.6, and 3.5 ± 2.2 ng/mL, respectively. The concentrations of S100A1 in patients with and without aortic regurgitation were 4.8 ± 2.4 and 3.4 ± 2.2 ng/mL, respectively, with a significant difference observed between the two groups (Table 2, $p < 0.05$). The concentrations of S100A1 in patients with and without pericardial effusion were 4.7 ± 2.2 and 3.4 ± 2.3 ng/mL, respectively, revealing a significant difference between the two groups (Table 2, $p < 0.05$). The concentration of S100A1 in patients with in-hospital death was 5.8 ± 2.6 ng/mL, and a significant difference was noted between this group and patients without in-hospital death (Table 2, $p < 0.05$).

We also analyzed the levels of S100A1 in patients of different sub-groups. The plasma S100A1 levels in male and female patients were 3.9 ± 2.3 and 3.4 ± 2.2 ng/mL, respectively. The S100A1 concentrations in patients with or without hypertension were 3.5 ± 2.3 and 4.1 ± 2.3 ng/mL, respectively. Similarly, there were no substantial differences between patients with hyperlipidemia, coronary artery disease

history, and smoking history. However, the S100A1 levels in AAD patients with or without diabetes were 4.3 ± 2.4 and 2.7 ± 1.9 ng/mL, respectively, and the difference was significant (Figure 1 $p = 0.002$).

Table 2. S100A1 levels in different sub-groups.

Variables	S100A1 level (ng/mL)	p value
Stanford type		
A (n = 16)	4.9±2.6	0.031
B (n = 61)	3.5±2.2	
Aortic valve regurgitation		
Yes (n = 18)	4.8±2.4	0.032
No (n = 59)	3.4±2.2	
Pericardial effusion		
Yes (n = 22)	4.7±2.2	0.028
No (n = 55)	3.4±2.3	
In-hospital death		
Yes (n = 12)	5.8±2.6	0.001
No (n = 65)	3.4±2.3	

All data were presented as the mean ± SD.

ROC curve analyses of plasma S100A1, D-dimer, hs-CRP, and cTnT

ROC curve analyses were performed to evaluate plasma S100A1, D-dimer, hs-CRP, and cTnT levels in all patients with AAD. The results showed that the area under the ROC curves for S100A1, D-dimer, hs-CRP, and cTnT were 0.89, 0.99, 0.88, and 0.85, respectively. When the concentration of S100A1 was 1.10 ng/mL, the sensitivity of plasma S100A1 in AAD diagnosis was 84.4%, and the specificity was 85.5% (Figure 2).

Logistic regression analysis

Analyses were performed to test whether any of the following factors influence the S100A1 concentrations (Table 3).

According to the results of logistic regression analysis, 18 significant variables

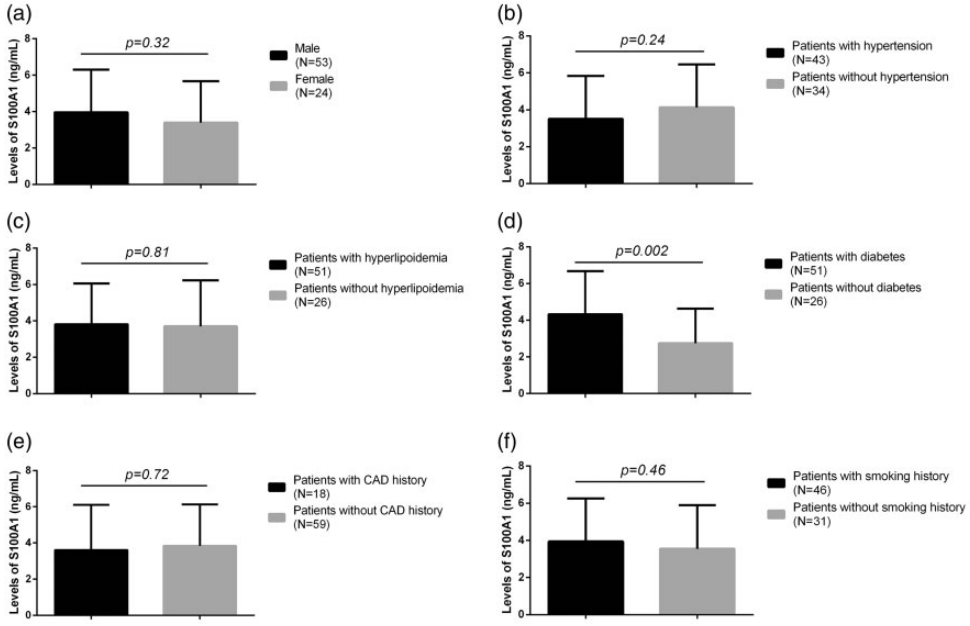

Figure 1. The levels of S100A1 in patients with different sub-groups. The plasma levels of S100A1 were detected by enzyme-linked immunosorbent assays. Measurements were made in duplicate and averaged, and the data were expressed as the mean ± standard deviation.
CAD: coronary artery disease.

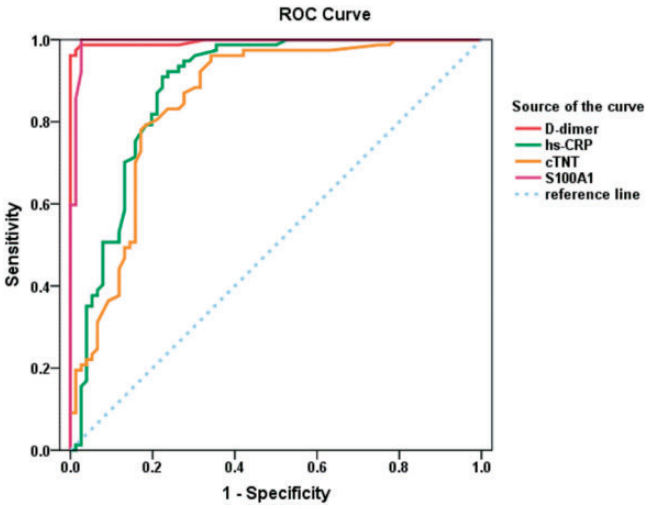

Figure 2. ROC curves using S100A1, D-dimer, hs-CRP, and cTNT levels for the prediction of AAD. The plasma levels of S100A1, D-dimer, hs-CRP, and cTNT in AAD patients were detected by enzyme-linked immunosorbent assays. The AUCs of the ROC curves of S100A1, D-dimer, hs-CRP, and cTnT were 0.89, 0.99, 0.88, and 0.85, respectively.
AAD: acute aortic dissection; hs-CRP: hypersensitive C-reactive protein; cTNT: cardiac troponin T; AUC: area under the curve; ROC: receiving operating characteristic.

Table 3. Logistic regression analysis.

Variables	β value	SE	Wald	p value	OR	95% CI
Age (years)	−0.04	0.09	0.17	0.68	0.97	0.82–1.14
Gender	−0.43	1.11	0.15	0.70	0.65	0.08–5.71
Body mass index (kg/m^2)	0.03	0.16	0.04	0.85	1.03	0.75–1.41
Smoking history	−0.12	1.22	0.01	0.92	0.89	0.08–9.58
Hypertension	−1.49	1.48	1.02	0.31	0.23	0.01–4.08
Diabetes mellitus	0.47	1.44	0.11	0.74	1.61	0.10–26.71
CAD history	1.88	1.55	1.45	0.22	6.55	0.31–138.51
FBG (mmol/L)	0.06	0.55	0.01	0.91	1.06	0.36–3.13
HbA1C (%)	0.10	0.86	0.01	0.90	1.11	0.21–5.97
TG (mmol/L)	−1.39	0.77	3.21	0.07	0.25	0.06–1.14
LDL-C (mmol/L)	−0.66	0.64	1.09	0.29	0.51	0.15–1.79
hs-CRP (mg/dL)	0.44	0.32	1.93	0.16	1.55	0.84–2.89
D-dimer (mg/dL)	−0.07	0.04	2.72	0.09	0.93	0.86–1.01
cTNT (ng/mL)	0.48	0.45	1.12	0.29	1.61	0.66–3.91
S100A1 (ng/mL)	−1.31	0.62	4.43	0.03	0.27	0.08–0.91
Heart rate (bpm)	−0.04	0.05	0.49	0.48	0.96	0.87–1.06
Systolic blood pressure (mmHg)	0.02	0.01	1.25	0.26	1.02	0.98–1.05
Diastolic blood pressure (mmHg)	−0.14	0.09	2.44	0.12	0.87	0.73–1.04

SE: standard error; OR: odd ratio; CI: confidence interval; CAD: coronary artery disease; FBG: fasting blood glucose; HbA1C: hemoglobin A1c; TG: triglyceride; LDL-C: low-density lipoprotein-cholesterol; hs-CRP: hypersensitive C-reactive protein; cTNT: cardiac troponin T.

were analyzed by multivariate nonconditional logistic regression. The results showed that the S100A1 level was a significant risk factor for AAD ($p = 0.03$, 95% confidence interval: 0.08–0.91). The detailed results are shown in Table 3.

Discussion

Based on previous work,[14] we retrospectively reviewed patients with AAD to examine the value of S100A1 in diagnosing AAD. The results suggested that the plasma concentration of S100A1 was significantly increased in patients with AAD and showed potential diagnostic value for AAD. Thus, S100A1 may be an effective biomarker for the clinical diagnosis of AAD.

In recent years, with continuous improvements in living standards and aging of the population, the incidence of various common diseases that may contribute to AAD, such as hypertension, coronary atherosclerosis, and arteriosclerosis, has increased each year, leading to greater increases in the prevalence of AAD. Thus, AAD has become an important disease seriously endangering human life and health.[15] Because of the lack of typical symptoms, AAD is often misdiagnosed as acute myocardial infarction or other cardiovascular diseases, resulting in the delay of treatment.[16] The primary methods for diagnosing AAD are magnetic resonance imaging, computed tomography angiography, and ultrasound, which are regarded as diagnostic challenges for physicians in emergency cases.[17] Thus, a set of markers with high sensitivity and specificity are needed for the early diagnosis of AAD in the clinic.

To date, researchers have identified over 20 S100 proteins with similar structure and function, which exist in different subcellular locations and regulate intracellular and extracellular $Ca2^{+}$. These include S100A1 to S100A13, S100B, S100C, calgranulin C, calcium-binding protein 3, alarmins, and calgizzarin.[18] Moore et al. first isolated and identified calcium-binding protein S100 in 1965, and 21 isoforms have been isolated and identified to date. The human *S100A1* gene is located at 1q21 and is approximately 1.6 Mbp.[19] The S100A1 protein forms a D-dimer structure composed of two homologous subunits, with a relative molecular mass of approximately 10 kDa; its hydrophobic C-terminus is an important functional group.[20] The expression of S100A1 is highly tissue- and cell-specific. S100A1 is expressed at very low levels in skeletal muscle but is abundant in healthy myocardial cells and vascular smooth muscle, mainly in the left ventricle and to a lesser extent in the right ventricle and atrium.[21,22] S100A1 is upregulated during right ventricular hypertrophy and downregulated in the terminal stage of heart failure, suggesting that the expression of S100A1 is related to myocardial contractility. S100A1 mediates the release, uptake, and transport of $Ca2^{+}$ in myocardial cells by regulating the calcium ATP enzyme and ryanodine receptor in the sarcoplasmic reticulum, making it the most important regulator of myocardial systolic and diastolic functions.[23] It has been revealed that plasma S100A1 is elevated during acute myocardial ischemia, suggesting that S100A1 can serve as an early marker of this condition.[14,24] Here, we found a significant difference in the S100A1 levels between the Stanford A group and Stanford B group. We speculated that AAD might involve the ascending aorta or aortic root and influence coronary perfusion. This may explain why the concentration of S100A1 in Stanford A type AAD was significantly higher compared with Stanford B AAD. In addition, we observed that the level of S100A1 was higher in AAD patients with severe complications, such as aortic valve regurgitation, pericardial effusion, and in-hospital death. This suggests that S100A1 may be related to the severity

of the disease and can potentially be used as a prognostic marker in the future.

Previous studies showed that D-dimer levels are notably elevated in patients with AAD, and low D-dimer levels can act as an exclusion index for AAD.[25] This may be because when AAD occurs, the body stimulates systemic inflammation in response to stress, leading to the release of inflammatory cytokines and triggering pseudo-intraluminal thrombus formation, thereby further activating the endogenous coagulation cascade. Activation of the endogenous coagulation cascade is accompanied by activation of the fibrinolysis system and results in the rapidly increased expression of D-dimer in the plasma.[26] As such, D-dimer plays a role in the diagnosis of AAD. Similarly, some researchers found that the elevated cardiac troponin and N-terminal pro-B-type natriuretic peptide levels in patients with AAD might be associated with an increased risk of in-hospital mortality.[27,28] In the present study, S100A1 was compared with D-dimer, hs-CRP, and cTnT; the area under the curve of S100A1 was 0.88, indicating that the detection of plasma S100A1 levels has some value in the diagnosis of AAD and may be a useful biomarker for the clinical diagnosis of this disease.

There were some limitations to this study. The underlying diseases, scope and location of dissection, and course of the disease can influence prognostic factors in patients with AAD. In addition, there is still a lack of point-of-care testing for S100A1 at present. Thus, the relationship between plasma S100A1 levels and patients with AAD or acute coronary syndrome requires further analysis in a large sample size.

Conclusions

Elevated plasma S100A1 levels may have potential diagnostic value in AAD. However, additional further studies are required to discriminate between AAD and acute myocardial infarction.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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