Assessing Serum Levels of ADAMTS1 and ADAMTS4 as New Biomarkers for Patients with Type A Acute Aortic Dissection

Authors' Contribution:
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Background: Type A AAD, a serious cardiovascular emergency requiring urgent surgery, is the most common and serious AAD. The aim of this study was to investigate the diagnostic value of ADAMTS1 and ADAMTS4 in patients with type A acute aortic dissection (AAD).

Material/Methods: Immunohistochemistry and qRT-PCR were used to evaluate the protein and mRNA expression levels of ADAMTS1 and ADAMTS4 in 14 type A acute aortic dissection (AAD) tissues and 10 control aortic tissues. Serum ADAMTS1 and ADAMTS4 expression levels in 74 patients with type A AAD, 36 patients with hypertension (HPT), and 34 healthy donors were examined by ELISA. The diagnostic value of serum ADAMTS1 and ADAMTS4 were determined by receiver operator characteristic curve (ROC). Furthermore, the dynamic change of serum ADAMTS1, ADAMTS4, D-dimer, and CRP were detected before and after surgery at different time-points in 14 patients with type A AAD.

Results: ADAMTS1 and ADAMTS4 protein and mRNA expression levels were found to be significantly higher in 14 type A AAD tissues ($p<0.0001$) compared with 10 control tissues. Serum ADAMTS1 and ADAMTS4 levels were significant higher in patients with type A AAD than those in the HPT and HD group ($p<0.0001$ for both). The AUC value, sensitivity, and specificity of ADAMTS1 were 0.9710 (95% CI: 0.9429 to 0.9991), 87.84%, and 97.06%, respectively, and those of ADAMTS4 were 0.9893 (95% CI: 0.9765 to 1.002), 94.59%, and 97.06%, respectively. In addition, serum ADAMTS4 level was gradually decreased with the time extension after surgery, similar to D-dimer change.

Conclusions: These data suggest that measurement of serum ADAMTS1 and ADAMTS4 levels could be potential diagnostic biomarkers for type A AAD, and ADAMTS4 might be a risk factor associated with type A AAD.

MeSH Keywords: ADAM Proteins • Biological Markers • Vertebral Artery Dissection

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Background

Type A acute aortic dissection (AAD), a cardiovascular emergency, is characterized by serious complication which present initially or develop subsequently, causing acute myocardial ischemia [1–4]. Type A AAD possess a very high mortality rate with 1-2% per hour during the first 48 hours, which means about 50% die within 48 hours when left untreated, thus making early diagnosis and treatment critical for survival [5,6].

Currently, imaging methods such as enhanced computed tomography (CT), transesophageal echocardiography (TEE), and magnetic resonance imaging (MRI) are widely used for the diagnosis of AAD, but these imaging modalities are limited by being expensive, time-consuming, incompatibility with implanted metal devices, and unavailable in some hospitals [7]. Furthermore, despite improved diagnostic and therapeutic techniques, overall in-hospital mortality for AAD still reaches about 25–30% [8]. To identify rapid, accurate, economical, and accessible diagnostic biomarkers for screening suspected AAD, the International Registry of Acute Aortic Dissection Substudy on Biomarkers (IRAD-Bio study) has confirmed that D-dimer could be used as a diagnostic marker of AAD, but the specificity is only 67% [9,10]. In addition, serum levels of smMHC, sE-LAF, PC1, and Lumican are potential biomarkers for early diagnosis of AAD, but their sensitivities are only 68.57%, 82.86%, 85.71%, and 73.33%, respectively [11–14]. In addition, the diagnosis method for Lumican using isobaric tags for relative and absolute quantitation (iTRAQ) approach is too complicated [12-14]. A recent study further showed that MMP-2 may be a specific marker of type A AAD, but the diagnostic potential was not evaluated [15]. Thus, further investigation of accurate biomarkers in early diagnosis for surgical treatment of type AAD is important to reduce the risk of in-hospital death.

As members of the secreted matrix metalloproteinase family, a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) genes were first described in 1997 [16]. Now, 19 different mammalian ADAMTS proteinases have been identified [17] which play key roles in adhesion, cell fusion, signaling, proteolysis, and extracellular matrix (ECM) degradation [18]. In recent years, some members of the ADAMTS family, such as ADAMTS1 and ADAMTS4, are particularly well-studied and have been found to play pivotal roles in the development and progression of cardiovascular diseases [19–22]. As secreted molecules of macrophages, neutrophils, aortic endothelial cells, and vascular smooth muscle cells (VSMCs) [23–25], ADAMTS1 and ADAMTS4 functioned in ECM remodeling by digesting modular proteoglycans, such as versican, aggrecan, brevican, and α2-macroglobulin [26,27]. Studies have shown that higher expression of ADAMTS1 is associated with acute vascular events such as atherosclerotic plaque rupture [19,28]. More importantly, ADAMTS1 and ASAMTS4 are increased in pathological

tissue of patients with AAD [24,25]. However, little is known about the diagnostic value of ADAMTS1/ADAMTS4 expression in type A AAD. In the present study, we detected the expression of ADAMTS1 and ADAMTS4 in tissues and serum of patients with type A AAD and assessed their value as diagnostic and monitoring markers in type A AAD.

Material and Methods

Affected aortic samples and human blood

Aortic tissue samples of 14 patients with type A AAD were collected from the Department of Cardiac Surgery, Renmin Hospital of Wuhan University, between January 2014 and December 2016. Control specimens of acute aortic dissection (n=10) were obtained from age-matched organ donors. The demographic and detailed clinical characteristics of the 14 type A AAD patients are shown in Table 1. All of the type A AAD patients were free from connective tissue disorders such as Marfan syndrome, Ehlers-Danlos syndrome, and aortitis diagnosed according to clinical history and physical examination. Type A AAD patients who arrived at the hospital 10 h after the onset of clinical symptoms were excluded from the study. The diagnosis of type A AAD was confirmed by computed tomography and electrocardiogram. Affected aortic specimens were obtained at surgery from 14 type A AAD patients who underwent surgery for ascending aorta and total arch replacement with descending aorta elephant trunk. In addition, blood samples from these 14 type A AAD patients were also collected upon arriving at the hospital (day 0), and also on the first (day 1), third (day 3), and fifth (day 5) day after surgery. Serum levels of white blood cells (WBC), platelets (PLT), D-dimer, hs-CRP, total cholesterol (TCH), high-density lipoprotein cholesterol (HDL-Ch), and low-density lipoprotein cholesterol (LDL-Ch) were measured in the Department of Laboratory Medicine, Renmin Hospital of Wuhan University. The blood samples from patients with type A AAD (74 cases) or HPT (36 cases) were collected within 1 h after arrival in the hospital's Emergency Department. The clinical baseline characteristics in type A AAD, HPT, and HD are shown in Table 2. The study was approved by the Ethics Committee of Renmin Hospital of Wuhan University (Hubei, China), and written informed consent was obtained from all of the subjects.

Immunohistochemistry

Hematoxylin and eosin-stained slides of each type A AAD patients and controls were examined as previously described [29] (Figure 1A); then, representative aortic areas were marked and their corresponding tissue blocks were selected. Immunohistochemical assays were performed on 4-μm-thick paraffin-embedded aortic tissue sections. Briefly, the

Table 1. Demographic and baseline characteristics of the populations.

Patient ID	SEX	Age	Weight (Kg)	Past medical history			
				Hypertension	Diabetes	Hyperlipemia	Others
1	Female	50	60	Yes	No	Yes	No
2	Male	37	50	Yes	No	No	CRF, Uremia, Smoking
3	Male	55	80	Yes	No	No	Smoking, drinking
4	Male	53	70	Yes	No	No	Drinking
5	Male	35	65	Unknown	No	No	Smoking
6	Female	69	64	Yes	No	No	No
7	Male	63	85	Yes	No	No	Cataract (lens exchange surgery, 2015)
8	Male	48	68	Yes	No	No	No
9	Male	58	75	Yes	No	No	No
10	Female	59	50	Yes	No	No	No
11	Male	47	80	Yes	No	No	No
12	Male	60	84	Yes	No	No	Renalcalculus, smoking, drinking
13	Female	53	76	Yes	No	No	No
14	Male	62	75	Yes	No	No	No

Patient ID	Clinical parameters									
	WBC (×10^9/L)	PLT (×10^9/L)	hs-CRP (mg/L)	D-Dimer (mg/L)	TCH (mmol/L)	HDL-Ch (mmol/L)	LDL-Ch (mmol/L)	SBP (mmHg)	DBP (mmHg)	HR (times/min)
1	11.8	90	6.3	4.71	4.81	0.89	3.34	155	68	60
2	9.74	180	98.99	3.6	3.07	0.98	1.45	149	91	108
3	10.91	121	3.36	11.76	4.74	1.08	2.89	122	59	59
4	12.31	97	8.73	6.92	5.13	0.98	4.11	125	95	104
5	11.21	106	6.53	5.98	4.81	1.12	3.41	158	74	88
6	10.86	135	8.76	4.33	4.63	1.02	3.01	182	90	100
7	9.3	74	0.846	15.43	3.24	0.77	1.22	139	89	81
8	9.12	102	36.74	6.07	2.93	1.03	2.01	132	93	73
9	10.31	112	7.53	2.31	3.98	1.25	3.03	160	90	82
10	9.21	89	10.32	3.21	2.98	1.01	2.31	133	94	106
11	10.02	110	8.39	3.02	5.61	1.32	3.45	106	72	116
12	8.27	135	9.37	8.61	5.32	1.68	3.51	110	70	60
13	13.44	206	7.26	7.25	4.87	0.89	2.7	174	105	68
14	14.31	197	0.37	2.72	4.48	0.77	2.87	141	74	65

Table 1 continued. Demographic and baseline characteristics of the populations.

Patient ID	Drug treatments				Complications	Prognosis
	β blockers	CCB	SNP	Lyticcocktail		
1	Yes	Yes	Yes	Yes	Massive cerebral infarction	Dead
2	Yes	Yes	No	Yes	Cardiac tamponade, metabolic acidosis, septicemia, hypoproteinemia	Dead
3	No	No	No	Yes	No	Cured
4	Yes	No	No	No	Crrhythmia, fungal infection	Cured
5	Yes	Yes	No	Yes	Pneumonia	Cured
6	Yes	Yes	Yes	Yes	Pneumonia, fungal infection	Cured
7	Yes	Yes	No	Yes	Septicemia, LCOS, cerebral infarction	Dead
8	No	Yes	No	Yes	No	Cured
9	Yes	Yes	No	Yes	Fungal infection	Cured
10	Yes	Yes	No	Yes	No	Cured
11	Yes	Yes	No	Yes	No	Cured
12	No	Yes	No	Yes	Renal insufficiency, hyperkalemia	Cured
13	Yes	Yes	No	Yes	No	Cured
14	Yes	Yes	No	Yes	No	Cured

Table 2. Clinical baseline characteristics in AAD, HPT and healthy groups.

| Clinic variables	HD	HPT	AAD
Number	34	36	74
Age (year)	50±7	53±13	51±10
gender (Male/Female)	27/7	30/6	58/16
Smoking, n (%)	18 (53%)	20 (56%)	45 (61%)
Hypertention, n (%)	–	36 (100%)	68 (92%)
SBP (mm Hg)	128±17	159±25	162±23
DBP (mm Hg)	80±13	94±20	93±13
Period of hospitalization (day)	–	–	17±4.62
WBC (×10^9/L)	6.59±1.67	7.14±2.30	11.83±1.79
PLT (×10^9/L)	218±41	205±23	125±21
hs-CRP (mg/L)	1.12±0.41	1.65±0.53	13.71±2.65
D-Dimer (mg/L)	0.24±0.09	0.55±0.18	6.29±1.15
TCH (mmol/L)	5.13±1.12	4.97±0.71	5.20±1.25
HDL-Ch (mmol/L)	1.19±0.23	1.33±0.29	1.17±0.06
LDL-Ch (mmol/L)	2.53±0.59	2.19±0.48	2.81±0.71
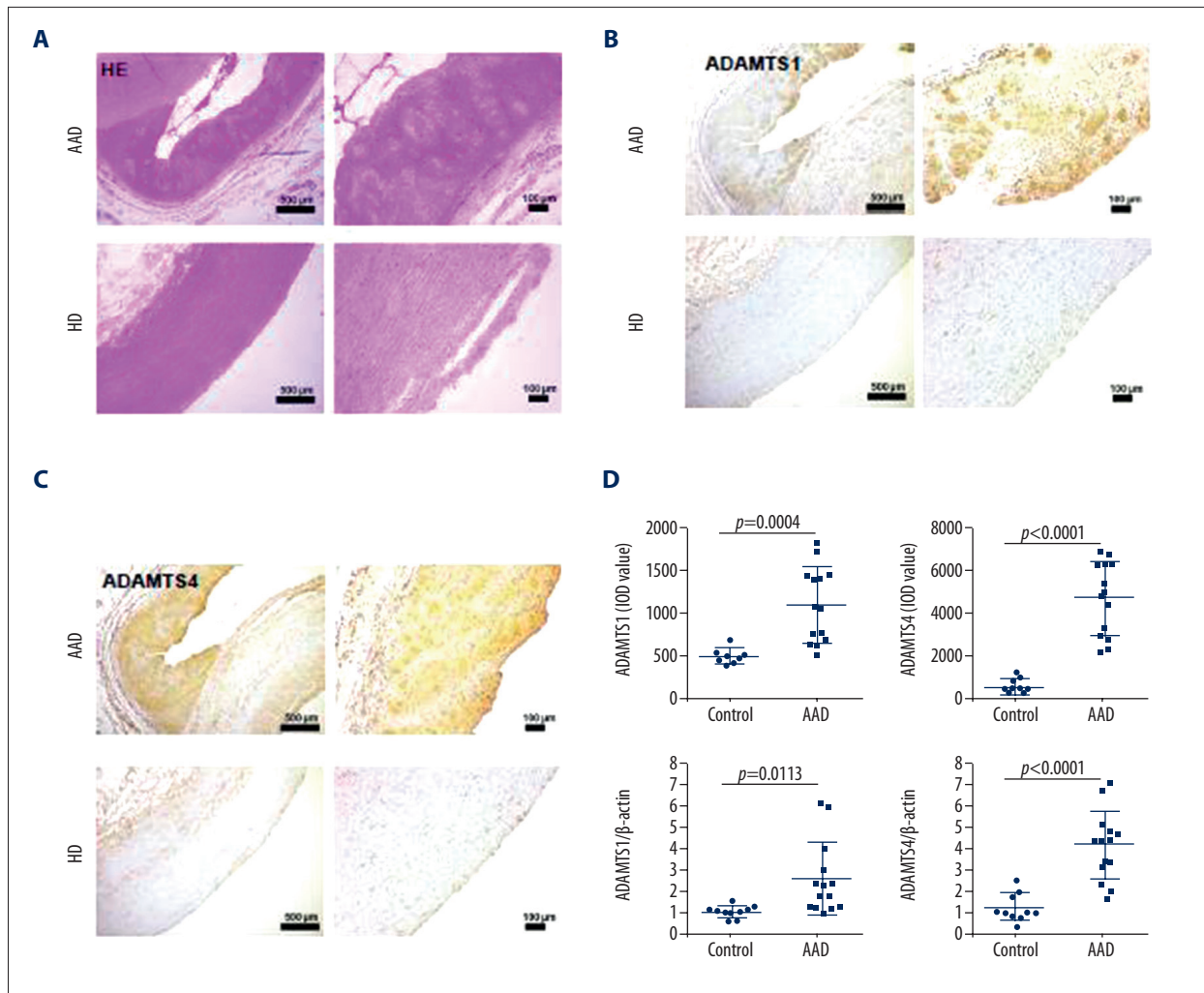
Figure 1. Representative H&E-stained sections and immunohistochemical staining and expression levels of ADAMTS1 and ADAMTS4 protein and mRNA in type A AAD aortic tissues and control aortic tissues. (**A**) Typical H&E-stained sections and immunostaining for ADAMTS1 (**B**) and ADAMTS4 (**C**) were arranged each for type A AAD aortic tissues and control aortic tissues. (**D**) Protein and (**E**) mRNA expression of ADAMTS1 and ADAMTS4 in type A AAD aortic tissues and control aortic tissues. The *t* test showed a significant difference between type A AAD aortic tissues (14 cases) and control aortic tissues (10 cases).

formalin-fixed paraffin-embedded tissue slides were dewaxed in xylene and rehydrated gradually through 3 alcohol changes (100%, 95%, and 85% for 5 min each). Microwave irradiation for 3 min in pH 6.0 citric buffer and cooling at room temperature for 60 min were used to unmask the antigens. Incubation of the slides in 3% H_2O_2/phosphate-buffered saline was used to block endogenous peroxidase activity. Non-specific binding sites were blocked with goat serum. Rabbit polyclonal to ADAMTS1 and ADAMTS4 (Abcam, Cambridge, MA, USA) were used as primary antibody. Tissue antigens were visualized with an EnVision Detection kit (GK500705: Gene Tech, Shanghai, China). Counterstaining of tissue sections was performed with hematoxylin for 5 min. Omission of primary antibodies was used to create negative control slides for all assays.

IOD value was measured to determine the positive-staining density as previously described [30]. A Leica CCD camera DFC420 connected to a Leica DM IRE2 microscope (Leica Microsystems Imaging Solutions, LTD., Cambridge, UK) was used as an imaging system. The IODs in each image were measured and counted using Image-Pro Plus v6.0 software (Media Cybernetics, Inc., Bethesda, MD, USA).

Quantitative real-time polymerase chain reaction (qRT-PCR)

Total RNA was extracted from the aortic specimens using a standard Trizol reagent (Invitrogen, Carlsbad, CA). Reverse transcription was conducted with Prime Script TM Master
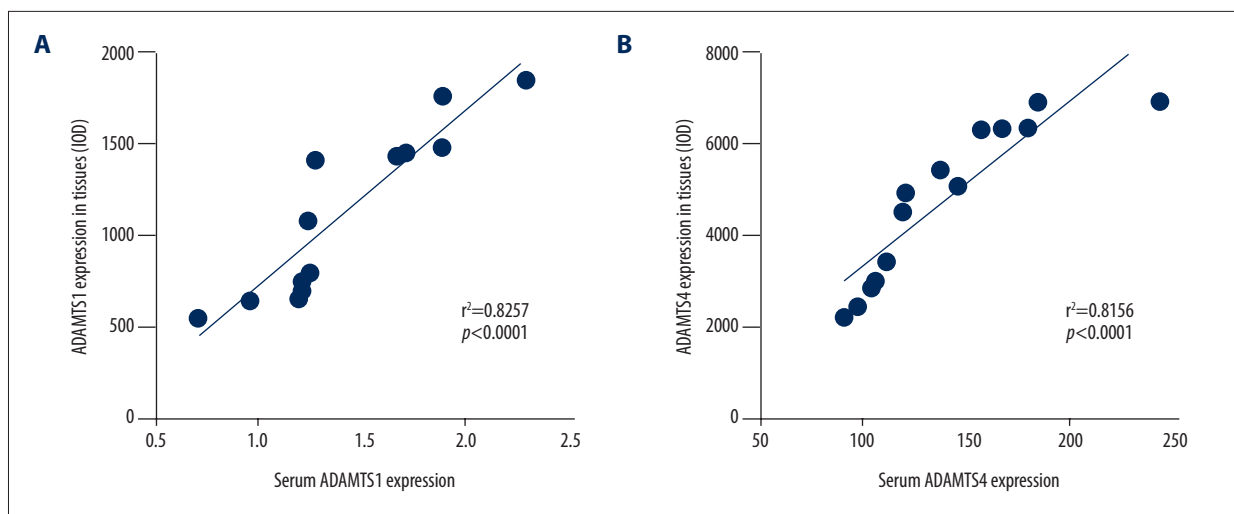
Figure 2. Correlation of ADAMTS1 and ADAMTS4 expression in tissues and serum. (**A**) ADAMTS1 expression in tissues had positive correlation with serum ADAMTS1, $p<0.0001$. (**B**) ADAMTS4 expression in tissues had positive correlation with serum ADAMTS4, $p<0.0001$.

Mix (Takara, Tokyo, Japan) according to the manufacturer's instructions. Then, qRT-PCR was performed with SYBR Premix EX Taq TM II (Takara) according to its product manual on the Bio-Rad IQ5 real-time PCR detection system (Bio-Rad, California, USA). β-actin was used as the internal reference, and ADAMTS1 and ADAMTS4 mRNA expression level were calculated by $2^{-\Delta\Delta Ct}$ method. The following primers were used: ADAMTS1 (forward, 5'-TTTGGCCAGCAGCTACATCT-3'; reverse, 5'-CACACCTTCACAGAGGC TGA-3'), ADAMTS4 (forward, 5'-CGCTGAGTAGATTCGTGGAGAC-3'; reverse, 5'-AGTTGACAG GGTTTCGGATGC-3'), β-actin (forward, 5'-ATCTGGCACCACACCTTC-3'; reverse, 5'-AGCCAGG TCCA GACGCA-3').

Enzyme-linked immunosorbent assay (ELISA)

Serum ADAMTS1 and ADAMTS4 levels were determined by a human enzyme-linked immunoassay (ELISA) kit (MyBioSoure, San Diego, CA, USA) strictly following the manufacturer's instructions. Serum samples, standard samples, and appropriate controls were added into the wells of reaction and incubated for 2 h at 37°C. After washing away any unbound substances, 100 μl of detection antibody was added into each well for 1 h at 37°C, followed by the addition of streptavidin-horseradish peroxidase for 30 min at 37°C. Then, we added 100 μl of substrate liquid to each well for 20 min at 37°C in the dark. The color biological reaction was duly terminated with stop solution and the optical density was measured by microplate reader immediately at 450 nm. Standard curves were made according to the concentration of the standard sample and corresponding value of optical density of each well.

Statistical analysis

Data are presented as the mean ±SD and analyzed using GraphPad Prism V.6.00 software (GraphPad Software, San Diego CA, USA). Differences among different groups were tested by one-way ANOVA followed by Neuman-Keuls post hoc test. A non-parametric rank correlation analysis was used to analyze the correlation of ADAMTS1 and ADAMTS4 in matched 14 tissues and serum specimens. The diagnostic value of serum ADAMTS1 and ADAMTS4 was evaluated using receiver operating characteristic (ROC) curves. Two-sided p values under 0.05 were considered statistically significant.

Results

Type A AAD aortic tissues showed increased protein and mRNA expression of ADAMTS1 and ADAMTS4 compared with normal aortic tissues

Immunohistochemistry analysis was used to analyze the protein expression levels of ADAMTS1 and ADAMTS4 in 14 type A AAD aortic tissues and 10 control aortic tissues from surgically resected samples. The protein expression of ADAMTS1 and ADAMTS4 were higher in the type A AAD aortic tissues than in control aortic tissues (Figure 1B, 1C). As shown in Figure 1D, the protein expression level (based on IOD) of ADAMTS1 ($p=0.0004$, left panel) and ADAMTS4 ($p<0.0001$, right panel) in the type A AAD aortic tissues were significantly higher than in control normal aortic tissues.

Furthermore, the mRNA relative expression level of ADAMTS1 and ADAMTS4 in 14 type A AAD aortic tissues and 10 control
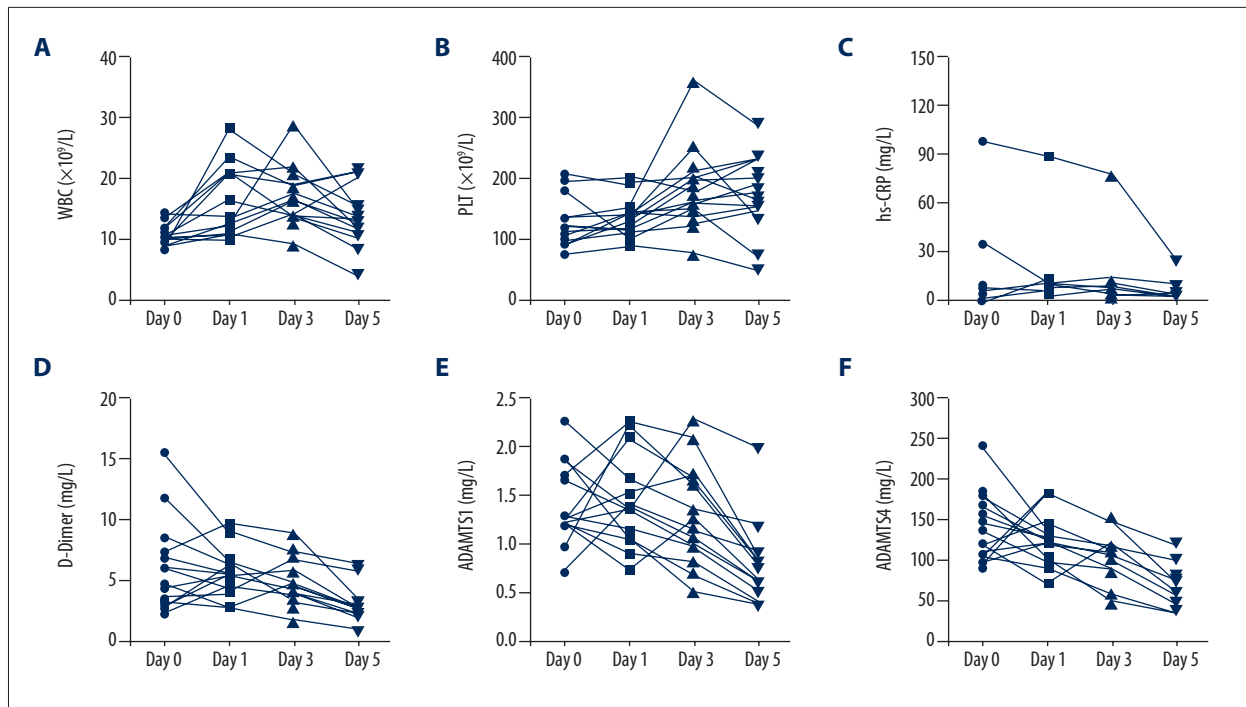
Figure 3. Serum level of WBC (**A**), PLT (**B**), hs-CRP (**C**), D-Dimer (**D**), ADAMTS1. (**E**) and ADAMTS4 (**F**) in the 14 type A AAD patients at different days after arrival in the hospital's Emergency Department were detected by ELISA.
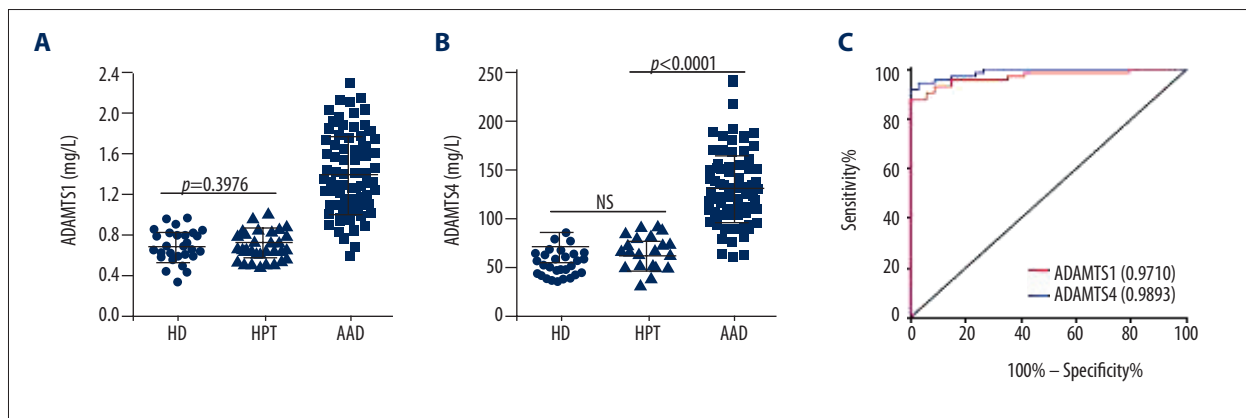

Figure 4. ADAMTS1 and ADAMTS4 protein expression are elevated in blood from type A AAD patients compared with HPT patients and HD. The concentration of ADAMTS1 (**A**) and ADAMTS4 (**B**) were assayed using an enzyme-linked immunosorbent assay in human peripheral blood samples from healthy donors (n=34), HPT patients (n=36), and type A AAD patients (n=74). (**C**) The ROC curve analysis: the diagnosis of serum ADAMTS1 and ADAMTS4 for type A AAD versus HPT and HD. The AUC for ADAMTS1 and ADAMTS4 were 0.9710 and 0.9893, respectively. AUC indicates area under the receiver operating curve.

aortic tissues were detected by qRT-PCR. As shown in Figure 1E, the mRNA relative expression level of ADAMTS1 (p=0.0113, left panel) and ADAMTS4 (p<0.0001, right panel) in the type A AAD aortic tissues were significantly higher than in control normal aortic tissues.

Expression of ADAMTS1 and ADAMTS4 in tissues and serum specimens displayed a similar trend

To verify whether the ADAMTS1 and ADAMTS4 expression in type A AAD tissues is consistent with serum of patients, we performed a non-parametric rank correlation analysis for the expression of ADAMTS1 and ADAMTS4 in matched 14 tissues and serum specimens at day 0. Serum detection values of ADAMTS1 and ADAMTS4 corresponded to tissues detection.

As shown in Figure 2A and 2B, results showed that expression of ADAMTS1 (r^2=0.8257, p<0.001) and ADAMTS4 (r^2=0.8156, p<0.001) in tissues and serum showed a positive correlation.

Serum ADAMTS1 and ADAMTS4 levels were gradually decreased after surgery

High plasma D-dimer and CRP levels are important independent risk factors for increased in-hospital mortality in patients with type A AAD, and these patients may benefit more from surgical intervention [31,32]. In our hospital, the change of WBC, PLT, hs-CRP, and D-dimer was routinely monitored every other day after surgery. Then, we further simultaneously detected serum ADAMTS1 and ADAMTS4 levels in the 14 patients with type A AAD before and after surgical intervention. As shown in Figure 3, serum ADAMTS4 was markedly decreased at day 1 after surgery, and displayed a similar declining trend with serum D-dimer in the following days. However, the declining trend of ADAMTS1 and hs-CRP was not as obvious as that of ADAMTS4 and D-dimer. Thus, these results suggest that the serum level of ADAMTS4 might be a risk factor associated with type A AAD.

Type A AAD patients presented higher level of serum ADAMTS1 and ADAMTS4 than HPT patients and HD

We then further evaluated the diagnostic potential of serum ADAMTS1 and ADAMTS4 levels in AAD. Serum ADAMTS1 level was significantly increased in the type A AAD group compared with hypertensive patients (HPT) and healthy donors (HD) (p<0.0001 for both, Figure 4A). There was no significant difference in ADAMTS1 levels between HPT and HD groups. Similarly, the ADAMTS4 level in type A AAD group was significantly higher than in the HPT and HD groups (p<0.0001 for both, Figure 4B). The areas under the ROC curve (AUC) were calculated to compare the accuracies achieved when using ADAMTS1 or ADAMTS4 for diagnosis of type A AAD (Figure 4C). The AUC value, sensitivity, and specificity of ADAMTS1 for type A AAD versus HD was 0.9710 (95% CI: 0.9429 to 0.9991), 87.84%, and 97.06%, respectively. For ADAMTS4, the AUC value, sensitivity, and specificity were 0.9893 (95% CI: 0.9765 to 1.002), 94.59%, and 97.06%, respectively. These results suggest that the serum levels of ADAMTS1 and ADAMTS4 have potential to be used as diagnostic biomarkers for type A AAD.

Discussion

There is growing evidence that ADAMTS enzymes may be associated with vascular pathologies. As well-studied members of the ADAMTS family, ADAMTS1 has been recently identified as having the potential to be a therapeutic target in individuals with heritable thoracic aortic aneurysms and dissections

(TAAD) [23], and ADAMTS4 is mainly produced by macrophages and its levels increase during atherosclerotic lesion development [20]. In the present study, we found that the protein levels of ADAMTS1 and ADAMTS4 were both significantly increased in pathological tissues and serum of type A AAD patients, compared with normal or HPT controls.

A series of serum biomarkers for discriminating AAD and risk factors associated with AAD in-hospital death have been reported, such as D-dimer, CRP, and platelet counts [10,32–35]. In our study, ADAMTS1 and ADAMTS4 showed powerful discriminating ability: their sensitivity/specificity were 87.84%/97.06% and 94.59%/97.06%, respectively, similar to the 88% sensitivity of MRI and higher than the 75% sensitivity of CT, as well as smMHC, sELAF, PC1, and Lumican in AAD diagnosis [36,37], which highlights their potential efficiency as biomarkers for AAD diagnosis. The AUC values of ADAMTS1 and ADAMTS4 were 0.9710 and 0.9893, respectively, which further indicates the high accuracy of ADAMTS1 and ADAMTS4 in the diagnosis of type A AAD. D-dimer is an effective biomarker for the diagnosis of AAD patients, and the specificities of serum ADAMTS1 and ADAMTS4 were both higher than that of serum D-dimer (69.1%) in the diagnosis of AAD, and their sensitivities were almost the same [10].

We also found that serum ADAMTS4 displayed a similar decreasing trend with serum D-dimer before and after surgery, but the change in ADAMTS1 level was not as obvious as those in ADAMTS4 and D-dimer. D-dimer is an important risk factor and independent predictor of in-hospital mortality of patients with type A AAD [32,38,39]. Thus, serum ADAMTS4 may be a potential risk factor for type A AAD, but its association with in-hospital death needs to be confirmed in a large-scale study, as we had only 3 death events in 14 type A AAD patients. CRP and platelet counts were confirmed to be important risk factors associated with AAD in-hospital death [32,35]. However, serum CRP and platelet counts were unchanged before and after surgery in our study, which may be due to our small sample size.

Beside ADAMTS1/4, dysregulation of several other members of have recently been reported to play important roles in the development of cardiovascular diseases, including ADAMTS5, ADAMTS7, ADAMTS13, and ADAMTS16 [40–42]. ADAMTS7 promotes atherosclerosis by modulating the phenotype of vascular smooth muscle cells, and targeting its function could be a novel therapeutic strategy for atherosclerosis and coronary atherosclerotic diseases in humans [42]. However, ADAMTS13 alleviated atherosclerotic lesion progression via a von Willebrand factor (VWF)-dependent inflammatory mechanism [43]. Thus, these findings further underline the important pathophysiological roles of the ADAMTS family in cardiovascular diseases, and this needs to be comprehensively investigated in future.

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[Chemical Abstracts/CAS] [Index Copernicus]

Conclusions

In conclusion, our data suggest that the protein and mRNA expression level of ADAMTS1 and ADAMTS4 were both up-regulated in type A AAD tissues, and serum ADAMTS1 and ADAMTS4 levels were significantly increased in type A AAD patients. Serum ADAMTS1 and ADAMTS4 could serve as potential biomarkers for discerning type A AAD patients from HPT patients and the healthy population.

Conflicts of interest

None.

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