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# Association between plasma ADAMTS-7 levels and severity of disease in patients with stable obstructive coronary artery disease

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**Abstract**

The metalloproteinase family of a disintegrin and metalloproteinase with thrombospondin motifs-7 (ADAMTS-7) was reported to be a novel locus associated with human coronary artery disease. This study aimed to investigate plasma ADAMTS-7 levels in stable obstructive CAD patients and elucidate the relationship between plasma ADAMTS-7 levels and the severity of CAD assessed by the Syntax score.

This was a single center cross-sectional study performed in 182 CAD patients. ELISA was used to measure plasma ADAMTS-7 levels. All patients were divided into subgroup according to the ADAMTS-7 median in this cohort: high group with ADAMTS-7 ≥0.99 ng/mL and low group with ADAMTS-7 <0.99 ng/mL. Furthermore, all patients were divided into tertiles according to their Syntax scores (low group: Syntax score ≤10.0; moderate group: 10.0 <Syntax score ≤18.0; high group: Syntax score >18.0). We followed up the participants continuously until the first major adverse cardiovascular event (MACE) for a mean time of 22.0 months.

Plasma ADAMTS-7 levels in the high Syntax score group were significantly higher compared with the low Syntax score group (3.29 [0.08–26.3] ng/mL vs 1.24 [0.15–8.78] ng/mL, $P=0.010$). Plasma ADAMTS-7 levels were significantly positively correlated with the Syntax score tertiles ($r=0.157$, $P=0.035$). Logistic regression analysis indicated that the plasma ADAMTS-7 level was one of the independent predictors for the Syntax score tertiles ($B=1.118$, 95% CI: 1.194–7.830, $P=0.020$), together with HbA1c ($B=0.946$, 95% CI: 1.248–5.312, $P=0.010$), uric acid ($B=-0.019$, 95% CI: 0.974–0.988, $P<0.001$), and coronary artery calcium score ($B=-0.001$, 95% CI: 0.998–0.999, $P<0.001$). Compared with the low ADAMTS-7 group, the high ADAMTS-7 group had significantly higher Syntax score (17.10±8.42 vs 14.96±8.11, $P=0.047$). Kaplan–Meier analysis showed patients in the high plasma ADAMTS-7 group tend to have a lower event-free survival rate than patients in the low plasma ADAMTS-7 group, unfortunately, no difference was detected (86.8% vs 88.0%, log rank=0.314, $P=0.575$).

The plasma ADAMTS-7 level was positively correlated with the Syntax score significantly. The elevated plasma ADAMTS-7 level may be involved in the severity of disease in patients with stable coronary artery disease.

**Abbreviations:** ADAMTS = a disintegrin and metalloproteinase with thrombospondin motifs, ALT = glutamic-pyruvic transaminase, AMI = acute myocardial infarction, BMI = body mass index, CABG = coronary artery bypass graft, CAC = coronary artery calcium, CAD = coronary artery disease, CAG = coronary angiography, CIs = confidence intervals, DES = drug-eluting stent, ECMs = extracellular matrix, EDTA = ethylenediamine tetraacetie acid, FBG = fasting blood glucose, GWAS = genomewide association studies, HbA1c = glycosylated hemoglobin, HDL-C = high-density lipoprotein cholesterol, Hs-CRP = high sensitivity C-reactive protein, HU = hounsfield units, LDL-C = low-density lipoprotein cholesterol, LVEF = left ventricular ejection fraction, MACE = major adverse cardiovascular event, MMPs = matrix metalloproteinases, MSCT = multi-slice computer tomography, NLR = neutrophil to lymphocyte ratio, NT-pro BNP = N-terminal pro-brain natriuretic peptide, Scr = serum creatinine, SD = standard deviation, TC = total cholesterol, TG = triglyceride, UA = uric acid.

**Keywords:** ADAMTS-7, coronary artery disease, MACE, syntax score

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## 1. Introduction

Matrix metalloproteinases (MMPs) are members of a zinc-dependant enzyme family which degrades extracellular matrix (ECM).[1] The disturbance of the physiologic balance between ECM production and degradation could result in coronary atherosclerosis and coronary artery disease (CAD).[2] Recent study identified metalloproteinase family of a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) also degrade ECM, which showed close association with CAD. Importantly, ADAMTS-7 was reported to be a novel locus associated with human CAD but not acute myocardial infarction (AMI) in 3 recent genomewide association studies (GWAS).[3,4,5] MMPs and ADAMTSs act not only in the plaque rupture stage but also in the initial stages of atherosclerosis.[6,7] Thus, it is also important to investigate ADAMTS in the early stage of CAD (such as stable CAD patients), and its relationship with severity of CAD as atherosclerosis progresses. However, to our best knowledge, no study has examined plasma ADAMTS-7 levels in stable CAD patients or its relationship with severity of CAD.

The Syntax score is a comprehensive angiographic scoring system that is derived entirely from the coronary anatomy and coronary lesion characteristics.[8] The Syntax score was initially designed to quantify lesion complexity. However, its value to predict major adverse cardiovascular event (MACE) was validated in stable CAD patients.[9] Therefore, the Syntax score is important in the management of CAD. However, the association between MMPs and ADAMTS and the Syntax score has not been reported.

The aim of the study was to investigate plasma ADAMTS-7 levels in stable CAD patients and elucidate the relationship between plasma ADAMTS-7 levels and the severity of CAD assessed by the Syntax score. Furthermore, we explored the predictive value of plasma ADAMTS-7 levels on MACEs.

## 2. Methods

### 2.1. Subjects

This is a single center retrospective cross-sectional study. The study recruited stable coronary heart disease (CAD) patients with at least 50% diameter stenosis as determined by coronary angiography (CAG) in at least one of the main coronary arteries. From December 1st 2007 to September 31st 2012, 182 patients who were admitted to Peking University Third Hospital (PUTH) for a coronary angiography were enrolled in our study. Patients with acute coronary syndrome (The diagnosis of ACS was made according to American and European guidelines), [10–12] valvular heart disease, cardiomyopathy, severe congenital heart disease, congestive heart failure, chronic or current infections, autoimmune disease, chronic kidney disease, chronic hepatic disease, rheumatoid arthritis, severe osteoarthritis, and bone injury within 3 months were excluded. Patients after surgical revascularization were excluded because the Syntax score was not validated in those subjects. Each participant was assigned a randomized research number, and the authors had no access to personal information that could identify individual participants during or after data collection. The protocol was approved by institutional guidelines of the Ethics Committee of Peking University Third hospital. All subjects were aware of the investigational nature of the study and gave their written consents.

### 2.2. Laboratory analysis

Each patient was assigned a unique Patient Number, so that personal information of the patients was kept secret; we only use Patient Number in our research. Blood samples were taken after at least 12-hour fast in the morning and collected into vacuum tubes containing ethylenediamine tetraacetie acid (EDTA) for the measurement of plasma lipid profile, fasting blood glucose, liver and renal function, and high sensitivity C-reactive protein (hs-CRP), all of which were analyzed by colorimetric enzymatic assays with use of an Auto-Analyzer (HITACHI-7170). Fasting plasma glucose and hemoglobin A1c levels were determined at the central chemistry lab of Peking University Third Hospital. All classification and management of patients were independent of these results.

### 2.3. Measurement of ADAMTS-7

The plasma ADAMTS-7 level was measured in duplicates using ELISA kits (Cloud-Clone Corp, Houston, TX, product No. SEB974Hu) according to manufacturer's specifications at the core laboratories in Institute of Vascular Medicine, Peking University Third Hospital. The minimal detection limits for ADAMTS-7 was 0.057 ng/mL. The coefficient of variation for intra- and inter-assay variation was less than 10% and 12%, respectively. These assays were performed by an investigator blinded to the sources of the samples.

### 2.4. Syntax score and angiographic analysis

CAG was performed by the standard Judkins' technique. CAGs were analyzed by 2 cardiologists who were blinded to the clinical data. Minimal luminal diameter, reference diameter, and percent diameter stenosis were assessed by quantitative coronary angiography. From the baseline diagnostic angiogram, each coronary lesion producing $\geq$50% diameter stenosis in vessels $\geq$1.5 mm was scored separately and added together to provide the overall Syntax score, according to the Syntax score algorithm.[8] The number of diseased vessels in the 4 major coronary arteries (left main, left anterior descending, left circumflex, and right coronary artery), as well as the number of total drug-eluting stents (DES) were recorded. The patients were divided into tertiles according to their Syntax score (low Syntax score group: Syntax score $\leq$10.0; moderate Syntax score group: 10.0 $<$Syntax score $\leq$18.0; high Syntax score group: Syntax score $>$18.0).

### 2.5. MSCT and CAC score

All multi-slice computer tomography (MSCT) examinations were performed using a 64-row scanner (General Electric, South San Francisco, CA) with a protocol for prospective triggering (SnapShot Pulse, GE Healthcare). Scanning parameters for the unenhanced calcium scoring scan were: 100 kV tube voltage; tube current was adjusted according to the body mass index (BMI), 0.28 s rotation time, and 2.5 mm slice thickness. Coronary artery calcium (CAC) score measurements were performed by 2 experienced readers separately blinded to the patient information with the CaScoring software and then used the average as score. CAC was defined as a plaque of at least 3 contiguous pixels (area of 1.02 $mm^2$) with a density of $>$ 130 Hounsfield units (HU). The lesion score was calculated by multiplying the lesion area by a density factor derived from the maximal Hounsfield unit within this area, as described before.[13–15] Total CAC score was

determined by summing individual lesion scores from each of the 4 main coronary arteries (left main, left anterior descending, left circumflex, and right coronary artery).

### 2.6. Follow-up and patients' outcome

All patients were continuously followed up until the first major adverse cardiovascular event (MACE), for a mean time of 22.0 months (1–75 months, interquartile range: 28.0 months). MACE was defined as (1) all-cause death, (2) nonfatal myocardial infarction, (3) unplanned coronary revascularization. The event-free survival time was the time before the first MACE. Follow-up data were obtained by the same physician through outpatient interviews and/or telephone calls.

### 2.7. Statistical analysis

Descriptive data are presented as the mean ± standard deviation (SD) for continuous variables, as medians (minimal, maximal) for discontinuous variables, and as frequencies for categorical variables. The clinical and laboratory data were analyzed with an independent *t* test or 1-way analysis of variance for continuous variables and nonparametric test (Mann–Whitney test or Kruskal–Wallis test) for discontinuous variables, chi-square tests for categorical data. Correlations between the Syntax score and other variables, such as plasma ADAMTS-7, were evaluated by Spearman analysis. Multiple linear regression was used separately to identify the predictive impacts of plasma ADAMTS-7 and the syntax score. The ADAMTS-7 was defined by the median value of plasma ADAMTS-7 (0.99 ng/mL). The association between plasma ADAMTS-7, syntax group, and MACE was separately explored by multinominal Logistic regression analysis in which different confounders were controlled in a stepwise manner. The odds ratio and the corresponding 95% confidence intervals (CIs) were calculated. Kaplan–Meier analysis was used to estimate the no-event survival rate between ADAMTS-7 subgroups. Significance was assumed at a 2-sided $P$ value $< 0.05$. Statistical analysis was performed using SPSS 19.0 (SPSS Inc., Chicago, IL).

## 3. Results

### 3.1. Patient characteristics

The clinical characteristics of the study participants across the Syntax score tertiles (low Syntax score group: Syntax score $\leq$10.0; moderate Syntax score group: 10.0 <Syntax score $\leq$18.0; high Syntax score group: Syntax score >18.0) are summarized

**Table 1**

**Clinical characteristics and plasma ADAMTS-7 levels among all patients across the Syntax score tertiles.**

| Variables | Low (n = 85) | Moderate (n = 37) | High (n = 60) | *P* |
|---|---|---|---|---|
| Age, y | 62.64 ± 9.72 | 65.84 ± 9.45 | 65.18 ± 9.81 | 0.144 |
| Male, % | 60.0 | 68.0 | 70.0 | 0.413 |
| Smoking, % | 26.0 | 39.0 | 40.0 | 0.139 |
| Hypertension, % | 70.0 | 79.0 | 73.0 | 0.620 |
| Diabetes, % | 25.0 | 32.0 | 52.0 | <0.001*,‡ |
| Hyperlipidemia, % | 49.0 | 53.0 | 55.0 | 0.801 |
| TC, mmol/L | 4.31 ± 0.95 | 4.22 ± 1.00 | 4.40 ± 1.01 | 0.685 |
| TG, mmol/L | 1.44 (0.49–5.71) | 1.47 (0.73–4.38) | 1.64 (0.40–10.40) | 0.418 |
| HDL-C, mmol/L | 0.99 (0.69–2.75) | 1.00 (0.55–1.90) | 0.91 (0.59–1.61) | 0.061 |
| LDL-C, mmol/L | 2.46 ± 0.72 | 2.45 ± 0.82 | 2.66 ± 0.83 | 0.250 |
| UA, μmol/L | 317 ± 62 | 347 ± 79 | 396 ± 82 | ≤0.001*,† |
| FBG, mmol/L | 5.10 (4.20–10.10) | 5.30 (2.50–10.40) | 5.50 (3.80–14.00) | 0.090 |
| HbA1c, % | 5.80 (5.00–10.20) | 5.80 (5.10–8.80) | 5.80 (4.60–9.60) | 0.972 |
| ALT, U/L | 21.2 ± 11.8 | 18.7 ± 10.0 | 20.0 ± 12.2 | 0.541 |
| Scr, μmol/L | 83.5 ± 16.7 | 85.3 ± 22.1 | 88.1 ± 17.3 | 0.182 |
| Hs-CRP, mg/L | 2.14 (0.24–8.21) | 3.24 (0.05–37.57) | 3.41 (0.22–23.78) | 0.132 |
| NLR | 1.95 (0.72–7.98) | 2.12 (1.22–7.67) | 2.19 (0.67–4.71) | 0.367 |
| NT-proBNP, pg/mL | 235.4 (14.5–1611.0) | 250.6 (33.1–1229.0) | 442.7 (9.3–3887.0) | 0.384 |
| Number of diseased vessels, % | | | ≤0.001*,† | |
| 1 | 51.8 | 0 | 0 | |
| 2 | 34.1 | 23.7 | 20 | |
| 3 | 14.1 | 76.3 | 80 | |
| Number of DES, % | | | 0.742 | |
| 0 | 1.1 | 5.3 | 3.3 | |
| 1 | 94.1 | 84.2 | 78.4 | |
| 2 | 4.8 | 10.5 | 15 | |
| CABG | 0 | 0 | 3.3 | 0.891 |
| ADAMTS-7 | 1.24 (0.15–8.78) | 2.71 (0.06–34.7) | 3.29 (0.08–26.3) | 0.017* |
| CAC score | 193.12 (0–1829.00) | 129.01 (0–2612.00) | 652.70 (0–4027.00) | <0.001*,‡ |

Data are presented as mean ± SD or n (%) or median (range).

ADAMTS = a disintegrin and metalloproteinase with thrombospondin motifs, ALT = glutamic-pyruvic transaminase, CABG = coronary artery bypass graft, CAC = coronary artery calcium, DES = drug-eluting stent, FBG = fasting blood glucose, HbA1c = glycosylated hemoglobin, HDL-C = high-density lipoprotein cholesterol, High = syntax score>18, Hs-CRP = high sensitivity C-reactive protein, LDL-C = low-density lipoprotein cholesterol, Low = syntax score≤10, Moderate = 10<syntax score≤18, NLR = Neutrophil to lymphocyte ratio, NT-pro BNP = N-terminal pro-brain natriuretic peptide, Scr = serum Creatinine, TC = total cholesterol, TG = triglyceride, UA = uric acid.

* High vs. Low.

† Moderate vs. Low.

‡ High vs. Moderate.

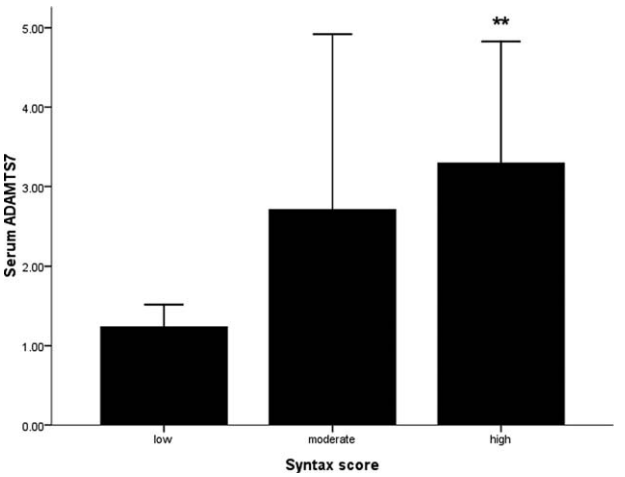


**Figure 1.** Plasma ADAMTS-7 levels in different Syntax score tertiles: Plasma ADAMTS-7 level was measured by ELISA, and compared among different Syntax score tertiles (low Syntax score group: Syntax score ≤10.0; moderate Syntax score group: 10.0 <Syntax score ≤18.0; high Syntax score group: Syntax score >18.0). $^{**}P<0.001$. ADAMTS = a disintegrin and metalloproteinase with thrombospondin motifs.

in Table 1. Compared with the moderate and the low Syntax groups, patients in the high Syntax score group were more likely to have a history of diabetes mellitus (52.0% vs 32.0% and 25.0%, $P=0.003$), higher plasma uric acid (UA) levels (396 μmol/L vs 347 μmol/L and 317 μmol/L, $P<0.001$), and higher frequency of multivessel disease as reported previously ($P<0.001$).[16] We also found significant difference in coronary artery calcium (CAC) scores among the 3 Syntax tertiles (652.70 vs 129.01 and 193.12, $P<0.001$); further analysis confirmed that CAC score was significantly higher in the high Syntax score group comparing with moderate ($P=0.004$) and low ($P<0.001$) Syntax score groups. This study found no difference in the number of drug-eluting stent (DES) in PCI and CABG among the 3 Syntax score tertiles.

### 3.2. Association between plasma ADAMTS-7 levels and the syntax score

There were significant difference in plasma ADAMTS-7 levels among high, moderate, and low Syntax score groups ($P=0.023$). Further analysis found that the plasma ADAMTS-7 level in the high Syntax score group was significantly higher than that in the low Syntax score group (3.29 (0.08–26.3) ng/mL vs 1.24 (0.15–8.78) ng/mL, $P=0.010$), whereas no significant difference in plasma ADAMTS-7 levels between moderate and low Syntax score groups (2.71 (0.06–34.7) ng/mL vs 1.24 (0.15–8.78) ng/mL, $P=0.190$), high and moderate Syntax score groups (3.29 (0.08–26.3) ng/mL vs 2.71 (0.06–34.7) ng/mL, $P=0.660$) (Fig. 1).

As shown in Table 2, the plasma ADAMTS-7 level was significantly positively correlated with the Syntax score tertiles ($r=0.157$, $P=0.035$), and significantly negatively correlated with hyperlipidemia history ($r=-0.147$, $P=0.048$) and smoking ($r=-0.157$, $P=0.034$).

### 3.3. Association between plasma ADAMTS-7 levels and clinical characteristics

To clarify the association between plasma ADAMTS-7 levels and clinical characteristics, all patients were divided into 2 subgroups on the basis of plasma ADAMTS-7 levels. The cutoff value of plasma ADAMTS-7 was defined by the median value (0.99 ng/mL) in the cohort. Patients were separated into low group (plasma ADAMTS-7 <0.99 ng/mL, n = 90) and high group (plasma ADAMTS-7 ≥0.99 ng/mL, n = 92). As shown in Table 3, compared with the low group, the high group had significantly higher Syntax score (17.10 ± 8.42 vs 14.96 ± 8.11, $P=0.047$). Other clinical characteristics had no significant differences between the 2 subgroups.

**Table 2**

**Correlation between serum ADAMTS-7 levels and clinical characteristics.**

| | Spearman correlation | P |
|---|---|---|
| Age | 0.016 | 0.83 |
| Male | –0.087 | 0.24 |
| Smoking | –0.157 | 0.034* |
| Hypertension | 0.014 | 0.849 |
| Diabetes | 0.087 | 0.243 |
| Hyperlipidemia | –0.147 | 0.048* |
| TC | –0.002 | 0.975 |
| TG | –0.127 | 0.086 |
| HDL-C | 0.044 | 0.553 |
| LDL-C | 0.001 | 0.991 |
| UA | 0.044 | 0.556 |
| FBG | –0.007 | 0.929 |
| HbA1c | –0.053 | 0.480 |
| ALT | –0.085 | 0.255 |
| Scr | 0.011 | 0.882 |
| Hs-CRP | 0.146 | 0.050 |
| NLR | 0.087 | 0.241 |
| NT-proBNP | 0.021 | 0.790 |
| Syntax score tertiles | 0.157 | 0.035* |
| Number of diseased vessels | 0.088 | 0.240 |
| Number of DES | 0.143 | 0.054 |
| CAC score | -0.022 | 0.774 |

ADAMTS = a disintegrin and metalloproteinase with thrombospondin motifs, ALT = glutamic-pyruvic transaminase, CAC = coronary artery calcium, DES = drug-eluting stent, FBG = fasting blood glucose, HbA1c = glycosylated hemoglobin, HDL-C = high-density lipoprotein cholesterol, Hs-CRP = high sensitivity C-reactive protein, LDL-C = low-density lipoprotein cholesterol, NLR = neutrophil to lymphocyte ratio, NT-pro BNP = N-terminal pro-brain natriuretic peptide, Scr = serum creatinine, TC = total cholesterol, TG = triglyceride, UA = uric acid.
* $P<0.05$.

After a mean follow-up of 22.0 months (1–75 months, interquartile range: 28.0 months), a total of 12 patients (13.2%) in the high group suffered combined MACEs with 2 recurrent nonfatal MIs, and 10 re-PCIs. Meanwhile, 11 patients (12.0%) in the low group suffered combine MACEs with 1 recurrent nonfatal MIs and 10 re-PCIs. No dearth occurred in both groups. Kaplan–Meier analysis showed patients in the high plasma ADAMTS-7 group tend to have a lower event-free survival rate than patients in the low plasma ADAMTS-7 group; unfortunately, no difference was detected (86.8% vs 88.0%, log rank = 0.314, $P=0.575$) (Fig. 2). All patients were taking dual antiplatelet treatment.

### 3.4. Association between the Syntax score and clinical characteristics

As shown in Table 4, the Syntax score were significantly positively correlated with smoking ($r=0.214$, $P=0.004$), diabetes history ($r=0.196$, $P=0.008$), plasma UA levels ($r=0.421$, $P<0.001$), fasting blood glucose (FBG) ($r=0.168$, $P=0.024$), CAC score ($r=0.305$, $P<0.001$), number of diseased vessels ($r=0.667$, $P<0.001$), and MACE ($r=0.238$, $P=0.001$).

**Table 3**

**Clinical characteristics of all patients according to ADAMTS-7.**

| Variables | Low (n = 90) | High (n = 92) | *P* |
|---|---|---|---|
| Age, years old | 63.96 ± 9.82 | 64.12 ± 9.60 | 0.949 |
| Male, % | 69.0 | 62.0 | 0.327 |
| Smoking, % | 39.0 | 28.0 | 0.130 |
| Hypertension, % | 73.0 | 74.0 | 0.796 |
| Diabetes, % | 31.0 | 40.0 | 0.236 |
| Hyperlipidemia, % | 59.0 | 46.0 | 0.075 |
| TC, mmol/L | 4.31 ± 0.98 | 4.33 ± 0.98 | 0.694 |
| TG, mmol/L | 1.61 (0.40–10.40) | 1.46 (0.51–5.71) | 0.270 |
| HDL-C, mmol/L | 0.98 (0.55–1.83) | 0.97 (0.68–2.75) | 0.694 |
| LDL-C, mmol/L | 2.51 ± 0.76 | 2.56 ± 0.80 | 0.633 |
| UA, μmol/L | 349 ± 80 | 350 ± 80 | 0.946 |
| FBG, mmol/L | 5.25 (2.50–14.00) | 5.30 (3.50–10.60) | 0.869 |
| HbA1c, % | 5.80 (5.10–9.90) | 5.80 (4.60–10.20) | 0.908 |
| ALT, U/L | 21.2 ± 12.2 | 19.5 ± 10.8 | 0.316 |
| Scr, μmol/L | 84.7 ± 19.5 | 85.3 ± 24.3 | 0.843 |
| Hs-CRP, mg/L | 1.40 (0.05–20.98) | 2.00 (0.22–37.57) | 0.113 |
| NLR | 2.00 (0.72–7.98) | 2.15 (0.67–7.67) | 0.217 |
| NT-proBNP, pg/mL | 124.1 (9.3–1611.0) | 140.4 (14.6–3887.0) | 0.779 |
| Syntax score | 14.96 ± 8.11 | 17.10 ± 8.42 | 0.047* |
| Number of diseased vessels, % | | 0.670 | |
| 1 | 25.6 | 22.8 | |
| 2 | 27.8 | 27.2 | |
| 3 | 46.6 | 50 | |
| Number of stents, % | | 0.661 | |
| 0 | 2.2 | 2.2 | |
| 1 | 92.2 | 83.7 | |
| 2 | 5.6 | 13.0 | |
| CABG | 0 | 1.1 | 0.530 |
| CAC score | 235.0 (0–3138.0) | 191.0 (0–4027.0) | 0.454 |

ALT = glutamic-pyruvic transaminase, CABG = coronary artery bypass graft, CAC = coronary artery calcium, DES = drug-eluting stent, FBG = fasting blood glucose, HbA1c = glycosylated hemoglobin, HDL-C = high-density lipoprotein cholesterol, High = serum ADAMTS-7 ≥0.99 ng/mL, Hs-CRP = high-sensitivity C-reactive protein, LDL-C = low-density lipoprotein cholesterol, Low = serum ADAMTS-7 <0.99 ng/mL, NLR = neutrophil to lymphocyte ratio, NT-pro BNP = N-terminal pro-brain natriuretic peptide, Scr = serum creatinine, TC = total cholesterol, TG = triglyceride, UA = uric acid.

* $P < 0.05$.

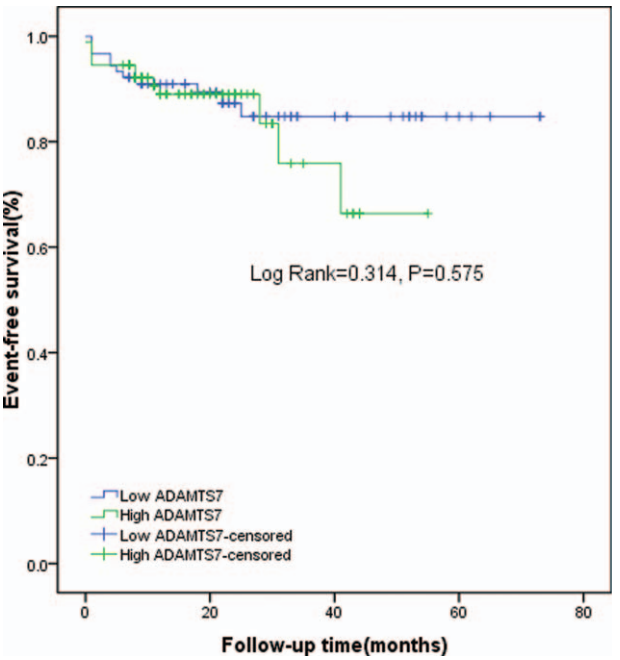


**Figure 2.** Kaplan–Meier analysis for cumulative event-free survival rates between the low and high ADAMTS-7 groups: Patients were separated into low and high ADAMTS-7 groups, cumulative time (months) until first MACE was recorded. Kaplan–Meier analysis was employed to compare to the survival curve between low and high ADAMTS-7 groups. ADAMTS = a disintegrin and metalloproteinase with thrombospondin motifs, MACE = major adverse cardiovascular event.

Logistic regression analysis (Table 5) indicated that ADAMTS-7 was one of the independent predictor for the Syntax tertiles ($B = 1.118$, 95% CI: 1.194–7.830, $P = 0.020$), together with HbA1c ($B = 0.946$, 95% CI: 1.248–5.312, $P = 0.010$), UA ($B = -0.019$, 95% CI: 0.974–0.988, $P < 0.001$), CAC score ($B = -0.001$, 95% CI: 0.998–0.999, $P < 0.001$), smoking ($B = 1.121$, 95% CI: 1.176–8.008, $P = 0.022$), and diabetes history ($B = 1.819$, 95% CI: 2.130–17.835, $P = 0.001$), when adjusted other confounders including age, gender, and so on.

## 4. Discussion

Our present study demonstrated that the patients in the high Syntax score group had higher plasma ADAMTS-7 levels than the patients in the low Syntax score group. The plasma ADAMTS-7 level was significantly positively correlated with the Syntax score tertiles. Moreover, it was one of the independent predictors of the Syntax group. When we separated all patients into the low and high ADAMTS-7 groups, we found the high ADAMTS-7 group had a significantly higher Syntax score. However, there was no difference in the event-free survival rate between low and high ADAMTS-7 groups.

**Table 4**

**Correlation between the Syntax score and clinical characteristics.**

| | Spearman correlation | *P* |
|---|---|---|
| Age | 0.096 | 0.199 |
| Male | 0.106 | 0.155 |
| Smoking | 0.214 | 0.004† |
| Hypertension | 0.051 | 0.500 |
| Diabetes | 0.196 | 0.008† |
| Hyperlipidemia | 0.063 | 0.397 |
| TC | 0.020 | 0.786 |
| TG | 0.070 | 0.344 |
| HDL-C | −0.133 | 0.074 |
| LDL-C | 0.085 | 0.254 |
| UA | 0.421 | ≤0.001† |
| FBG | 0.168 | 0.024* |
| HbA1c | −0.072 | 0.334 |
| ALT | −0.096 | 0.199 |
| Scr | 0.192 | 0.110 |
| Hs-CRP | 0.037 | 0.622 |
| NLR | 0.100 | 0.181 |
| NT-proBNP | 0.134 | 0.086 |
| MACE | 0.238 | 0.001† |
| Number of diseased vessels | 0.667 | ≤0.001† |
| Number of DES | 0.118 | 0.088 |
| CAC score | 0.305 | ≤0.001† |

ALT = glutamic-pyruvic transaminase, CAC = coronary artery calcium, DES = drug-eluting stent, FBG = fasting blood glucose, HbA1c = glycosylated hemoglobin, HDL-C = high-density lipoprotein cholesterol, Hs-CRP = high sensitivity C-reactive protein, LDL-C = low-density lipoprotein cholesterol, NLR = neutrophil to lymphocyte ratio, NT-pro BNP = N-terminal pro-brain natriuretic peptide, Scr = serum creatinine, TC = total cholesterol, TG = triglyceride, UA = uric acid.

* $P < 0.05$.

† $P < 0.01$.

**Table 5**

**Logistic regression analysis for association between Syntax score tertiles and variables.**

| Variables | *B* | Std. Error | Wald | *P* | Exp (B) | 95% CI of Exp (B) |
|---|---|---|---|---|---|---|
| ADAMTS-7 group | 1.118 | 0.480 | 5.431 | 0.020 | 3.058 | 1.194–7.830 |
| CAC score | –0.001 | 0.0004 | 14.144 | <0.001 | 0.999 | 0.998–0.999 |
| UA | –0.019 | 0.004 | 28.405 | <0.001 | 0.981 | 0.974–0.988 |
| HbA1c | 0.946 | 0.370 | 6.549 | 0.010 | 2.575 | 1.248–5.312 |
| Diabetes | 1.819 | 0.542 | 11.256 | 0.001 | 6.164 | 2.130–17.835 |
| Smoking | 1.121 | 0.489 | 5.251 | 0.022 | 3.069 | 1.176–8.008 |
| Constant | 1.422 | 2.467 | 0.332 | 0.564 | | |

ADAMTS-7 group: Low = serum ADAMTS-7 <0.99 ng/mL, CAC = coronary artery calcium, CI = confidence interval, HbA1c = glycosylated hemoglobin, High = serum ADAMTS-7≥0.99 ng/mL, UA = uric acid.

In the 3 recent GWAS studies, variants rs4380028, rs1994016, and rs3825807 in the ADAMTS-7 gene were associated with human CAD but not acute myocardial infarction (AMI).[3,4,5] Moreover, rs3825807 G/G genotype in the ADAMTS-7 locus was associated with lower atherosclerosis prevalence and severity.[17] However, the direct report of circulation ADAMTS-7 levels in stable CHD patients is still lacking. To the best of our knowledge, the present study is the first study to investigate the associations between plasma ADAMTS-7 and severity of CAD in human. Here, we found significantly higher plasma ADAMTS-7 levels in the high Syntax score group, and a significant correlation of plasma ADAMTS-7 levels with the Syntax score tertiles. Importantly, the plasma ADAMTS-7 level was an independent predictor for the Syntax group.

Wu et al reported that plasma ADAMTS-7 levels were higher in patients with left ventricular ejection fraction (LVEF) ≤35% compared with those with LVEF >35% after AMI.[18] Logistic regression analysis indicated that the association between ADAMTS-7 and heart failure after AMI was independent from traditional cardiovascular risk factors and other biomarkers.[18] Pioneering research has also shown ADAMTS-7 accelerated vascular smooth muscle cell migration[19] and inhibited endothelial cell proliferation and migration,[20] which exacerbated atherosclerosis and neointima formation as a result. Meanwhile, ADAMTS-7 knockout mice showed reduced native atherosclerosis and neointimal formation, suggesting ADAMTS-7 as a promising new therapeutic target in CAD.[6] Our results for the first time establish a positive correlation between the plasma ADAMTS-7 level and the severity of coronary stenosis in stable CAD patients. Possible mechanisms include: elevated circulation ADAMTS-7 may impair endothelial function by inhibiting endothelial cell proliferation and migration,[20] meanwhile promote plaque progression by accelerating vascular smooth muscle cell migration,[19] which results in accelerating the severity of coronary stenosis.

In this study, we explored the correlation between plasma ADAMTS-7 levels and clinical characteristics. We found that the plasma ADAMTS-7 level was significantly negatively correlated with hyperlipidemia history and smoking, which have been identified as a major source of endothelial injury. No previous report on the correlation between plasma ADAMTS-7 and hyperlipidemia history or smoking. However, it has been shown that another number of ADAMTS family called ADAMTS-13, whose activity was significantly lower in smokers compared to nonsmokers in healthy subjects.[21] Hyperlipidemia caused by high-fat diet in mice tend to have lower ADAMTS-13 activity.[22] To our surprise, we did not detect significant correlation between plasma lipid levels and ADAMTS-7, although hyperlipidemia history was significantly correlated with ADAMTS-7. On the one hand, it seems hyperlipidemia interact with ADAMTS-7 in a chronic rather than the acute process. On the other hand, different enrolled subjects and limited sample size may also contribute to our negative findings.

The Syntax score was reported to be associated with the CAC score in stable CAD patients[23] and NLR in non-ST segment elevation myocardial infarction patients.[24] We found in the present cohort CAC score but not NLR was significantly positively correlated with Syntax score, and the CAC score was an independent predictor for the Syntax tertiles. It was found that the ADAMTS-7 expression was upregulated in calcified arteries of rats with chronic renal failure, and in radial arteries of uraemic patients, which shed lights on the role of ADAMTS-7 in vascular calcification.[25] However, no association between plasma ADAMTS-7 levels and CAC score was found, indicating possible different roles of circulating and vascular ADAMTS-7 in vascular calcification.

As far as we know, there was no related research about the ADAMTS-7 and prognosis in cardiovascular disease patients. In the present study, we divided all patients into low and high ADAMTS-7 groups, due to small sample size, we did not detect significant difference in hyperlipidemia history or smoking between the 2 groups. All patients were continuously followed up for a mean time of 22.0 months until the first MACE defined as all-cause death; nonfatal myocardial infarction; unplanned coronary revascularization. Also, a significant difference was not detected in the survival analysis between the 2 groups, although the high plasma ADAMTS-7 group tends to have a lower cumulative event-free survival rate than patients in the low plasma ADAMTS-7 group. And, therefore, further clinical research about the role ADAMTS-7 played in CAD need to be performed in a deep-going way.

### *4.1. Study limitations*

The present study is a single-center, retrospective study with its inherent limitations. First, a relative small number of patients were enrolled. Second, it was a cross-sectional study. It is very difficult for us to set completely healthy population as control group, so it could not deduce a casual connection. Moreover, there is no established reference of plasma ADAMTS-7 level available from large-scale clinical trials among the same patient population so the cutoff value in the present study is purely suggestive. Finally, large sample size and better design studies including detailed information such as imaging intravascular ultrasound data are required to further evaluate the potential mechanisms involving the role of ADAMTS-7.

## 5. Conclusion

The plasma ADAMTS-7 level was positively correlated with the Syntax score significantly. The elevated plasma ADAMTS-7 level

may be involved in the severity of disease in patients with stable coronary artery disease.

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