

Plasma α 1-antitrypsin: A Neglected Predictor of Angiographic Severity in Patients with Stable Angina Pectoris

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Abstract

Background: As an acute phase protein, α 1-antitrypsin (AAT) has been extensively studied in acute coronary syndrome, but it is unclear whether a relationship exists between AAT and stable angina pectoris (SAP). The purpose of the present study was to investigate the association between AAT plasma levels and SAP.

Methods: Overall, 103 SAP patients diagnosed by coronary angiography and clinical manifestations and 118 control subjects matched for age and gender were enrolled in this case-control study. Plasma levels of AAT, high-sensitivity C-reactive protein (hsCRP), lipid profiles and other clinical parameters were assayed for all participants. The severity of coronary lesions was evaluated based on the Gensini score (GS) assessed by coronary angiography.

Results: Positively correlated with the GS ($r = 0.564$, $P < 0.001$), the plasma AAT level in the SAP group was significantly higher than that in the control group (142.08 ± 19.61 mg/dl vs. 125.50 ± 19.67 mg/dl, $P < 0.001$). The plasma AAT level was an independent predictor for both SAP (odds ratio [OR] = 1.037, 95% confidence interval [CI]: 1.020–1.054, $P < 0.001$) and a high GS (OR = 1.087, 95% CI: 1.051–1.124, $P < 0.001$) in a multivariate logistic regression model. In the receiver operating characteristic curve analysis, plasma AAT level was found to have a larger area under the curve (AUC) for predicting a high GS (AUC = 0.858, 95% CI: 0.788–0.929, $P < 0.001$) than that of hsCRP (AUC = 0.665, 95% CI: 0.557–0.773, $P = 0.006$; $Z = 2.9363$, $P < 0.001$), with an optimal cut-off value of 137.85 mg/dl (sensitivity: 94.3%, specificity: 68.2%).

Conclusions: Plasma AAT levels correlate with both the presence and severity of coronary stenosis in patients with SAP, suggesting that it could be a potential predictive marker of severe stenosis in SAP patients.

Key words: α 1-antitrypsin; Angiography; Coronary Artery Disease; Gensini Score; Inflammation; Stable Angina Pectoris

INTRODUCTION

Stable angina pectoris (SAP) is one of the most common subtypes of coronary artery disease (CAD), affecting approximately 54 million patients worldwide. An individual's prognosis can vary considerably from chronic recurrent angina pectoris to acute myocardial infarction (AMI). Early and accurate identification of SAP patients with high risk is of great clinical value.^[1] An increasing number of inflammatory markers and acute phase proteins have been tested in CAD, and their plasma levels have been confirmed to be correlated with different clinical characteristics and the prognosis of these patients.^[2-4] However, there is a lack of clinically useful, highly specific biomarkers for SAP to guide treatment decisions for SAP patients.

α 1-antitrypsin (AAT) is an acute phase protein that is mainly produced in the liver. An elevated plasma AAT level has been widely confirmed in the setting of AMI and acute coronary syndrome (ACS);^[4-6] however, data regarding this marker in SAP patients are limited. Recently, a study using proteomic techniques found that AAT was differentially expressed in atherosclerotic plaques,^[7] indicating its role in the long-term progression of atherosclerosis. However, previous studies on the relationship between plasma AAT concentrations and the severity of CAD are insufficient. A higher plasma AAT level was observed in patients with higher Gensini scores (GSs) who did not have AMI,^[8] which implies an association between plasma AAT levels and coronary stenosis. However, few receiver operating characteristic (ROC) curve analyses of plasma AAT concentration for predicting CAD severity have been performed. Moreover, plasma

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AAT concentration is likely to be different in patients with SAP and unstable angina pectoris (UAP) because of their differing pathological features. Thus, it is unclear whether plasma AAT is an independent predictor for the severity of coronary atherosclerosis in SAP patients.

Accordingly, we proposed that elevated plasma AAT levels in SAP patients could be a valuable predictor for the risk and severity of the disease. To test this hypothesis, plasma AAT levels were first compared between SAP patients and controls. We also investigated the diagnostic value of this marker in the identification of SAP patients with severe coronary lesions.

METHODS

Study population

We consecutively recruited 103 CAD patients with SAP at Fuwai Hospital from July to October 2012 for this study. SAP was defined as chest pain typical of cardiac ischemia on exertion or emotional stress that is relieved by rest or nitrates. The pattern of chest pain did not change within at least 1 month. All patients had undergone coronary angiography and had angiographically documented narrowing of at least 50% of the luminal diameter of a major coronary artery. Subjects with AMI, heart failure (left ventricular ejection fraction <30%), cardiomyopathies, and valvular disease were excluded. Also from July to October 2012, a total of 118 age- and gender-matched controls without CAD were enrolled. They were determined to be free of CAD by a history lacking angina and other heart diseases, a normal electrocardiogram (ECG) and normal results of exercise ECG stress testing. The exclusion criteria for both groups were as follows: Acute or chronic infection, definite inflammatory and immune-associated diseases, bleeding, surgery or trauma within 12 weeks prior to admission, liver or renal dysfunction and neoplasms. Patients were also excluded if they had been taking statin drugs or any anti-inflammatory medications. The study protocol complied with the *Declaration of Helsinki* and was approved by the ethics committee of Fuwai Hospital. All of the participants provided written informed consent.

All participants received a standard medical history, physical examination and laboratory assessment. The participants were diagnosed with hypertension if their systolic blood pressure was ≥ 140 mmHg and/or their diastolic blood pressure was ≥ 90 mmHg; hypertension was also diagnosed by self-report of a physician diagnosis, and if any anti-hypertensive treatment was taken at admission. Diabetes mellitus (DM) was diagnosed according to the standards of the American Diabetes Association, which include a fasting plasma glucose level ≥ 7.0 mmol/L, a 2-h postload glucose level ≥ 11.1 mmol/L, self-report of a physician diagnosis, and if any hypoglycemic medication taken at admission. Smokers were defined as those who regularly smoked five cigarettes or more a day, and if patients had stopped smoking for more than 10 years preceding disease onset, they were classified as nonsmokers. In addition, body mass index (BMI) was calculated as weight (kg)/height² (m²).

Coronary angiography

Selective coronary angiography was performed using a standard Judkins technique. CAD was defined as the presence of obstructive stenosis in any of the main coronary arteries, including the left main coronary artery (LM), left anterior descending artery (LAD), left circumflex coronary artery (LCX) and right coronary artery, and any of the main branches of the vascular system of more than 50% of the lumen diameter. The severity of coronary lesions was assessed by the GS,^[9] which was calculated according to the severity of stenosis as follows: 1 point for <25% stenosis, 2 points for 26%–50% stenosis, 4 points for 51%–75% stenosis, 8 points for 76%–90% stenosis and 32 points for complete occlusion. The score was then multiplied by a coefficient representing the importance of the lesion's position in the coronary artery system. For example, coefficients of 5 for the LM, 2.5 for the proximal region of the LAD and LCX, 1.5 for the middle region, and 1 for the distal region of the LAD and mid-distal region of the LCX. All results were analyzed by at least two experienced interventional physicians from the cardiology department of Fuwai Hospital, who performed a quantitative coronary angiography analysis and were blind to the objective of the study.

Stable angina pectoris patients enrolled in this study were further divided into three subgroups based on the tertile of the GS (low GS <18 points, $n = 34$; intermediate GS 18–40 points, $n = 34$; high GS >40 points, $n = 35$).

Laboratory tests

Venous blood was drawn from all individuals after a 12 h overnight fast prior to coronary angiography and was centrifuged immediately at 3000 r/min and 4°C for 10 min. Plasma specimens were then collected and stored at –80°C until further analysis. All specimens were analyzed at the same time to control for testing variability. Plasma AAT and high-sensitivity C-reactive protein (hsCRP) levels were measured by immunoturbidimetry^[10] using an IMMAGE 800 immunochemistry system (Beckman Coulter, USA). The AAT reagent (447740, Beckman Coulter, USA) and hsCRP reagent (474630, Beckman Coulter, USA) were used according to the manufacturer's instructions. Total cholesterol and triglycerides were assayed by routine enzymatic methods (GPO-PAP) using a Beckman DxC800 analyzer (Fullerton, USA). High-density lipoprotein cholesterol (HDL-C) level was measured using a chemical modification and selective melting kit (Kyowa Medex, Tokyo, Japan). The low-density lipoprotein cholesterol (LDL-C) concentration was calculated using the Friedewald equation.^[11] The intra- and inter-assay coefficients of variation for plasma AAT level ranged from 2.1% to 3.1%, and 2.8% to 3.3%, respectively. The AAT level reference range was 88–174 mg/dl.

Statistical analysis

All statistical analyses were performed using the SPSS 17.0 software package (SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was used to determine

the data distribution patterns. Continuous variables are presented as the means \pm SD or medians with the 25th and 75th percentiles, as appropriate. Variables with a skewed distribution were log-transformed for further statistical testing. Differences between groups were compared using the *t*-test or one-way ANOVA. Categorical variables are expressed as frequencies or percentages, and differences were compared with the Chi-square test or Fisher's exact test. Pearson and Spearman correlation coefficients were used to evaluate the correlations between AAT plasma concentration and other variables when appropriate. Subsequently, multiple linear regression analysis was performed to investigate a set of independent risk factors associated with plasma AAT level. Spearman correlation analysis was also used to determine the correlations between plasma AAT levels and GSs in SAP patients. The predictive values of different clinical variables for the SAP risk and a high GS (>40) were determined using the univariate and multivariate logistic regression model. ROC curves were generated to assess the diagnostic value of plasma AAT for SAP and a high GS. And the maximum Youden index was used to determine the optimal cut-off values. The diagnostic values of plasma AAT and hsCRP were compared using *Z* test. A *P* < 0.05 was considered to indicate a statistically significant difference.

RESULTS

Baseline clinical characteristics of the study population

To investigate the relationship between plasma AAT level and SAP, 221 subjects were enrolled in the present study, including 103 SAP patients and 118 non-CAD controls. Because the inflammation-modulating capacity of statins has been confirmed, patients with statin treatment were excluded from our study as previously described. Thus, data regarding the effects of statin use are not presented. The baseline clinical characteristics and biochemical parameters of the study population are summarized in Table 1. Age, gender, BMI, smoking status and the presence of diabetes showed no significant difference between the SAP group and the control group. There were more hypertensive patients in the SAP group than in the control group. As expected, patients in the SAP group had significantly higher mean levels of plasma hsCRP, AAT and LDL-C and a lower mean HDL-C level compared with the control group.

Plasma α 1-antitrypsin concentration assessment

The plasma AAT concentrations for all subjects ranged from 81.15 to 188.10 mg/dl with a median of 133.23 mg/dl. In the total population studied, the plasma AAT concentration was positively correlated with age, smoking status and the plasma hsCRP level, and negatively correlated with the plasma HDL-C level [Table 2]. In covariance analysis, adjusted plasma AAT concentration controlling for these possible confounding factors was still higher in the SAP

Table 1: Baseline characteristics of the study population

Variables	Control group (n = 118)	SAP group (n = 103)	P
Demographic data			
Male, n (%)	79 (66.9)	73 (70.9)	0.563
Age (years)	54.62 \pm 8.35	53.01 \pm 8.75	0.164
BMI (kg/m ²)	25.92 \pm 3.37	26.36 \pm 3.74	0.360
Diabetes, n (%)	18 (15.3)	23 (22.3)	0.225
Hypertension, n (%)	55 (46.6)	73 (70.9)	<0.001
Smoking, n (%)	53 (44.9)	49 (47.6)	0.787
Biochemical parameters			
TC, mmol/L	4.47 \pm 0.70	4.52 \pm 0.89	0.639
TG, mmol/L	1.71 \pm 0.99	1.78 \pm 0.99	0.615
HDL-C, mmol/L	1.18 \pm 0.29	1.06 \pm 0.32	0.005
LDL-C, mmol/L	2.60 \pm 0.60	2.85 \pm 0.76	0.006
hsCRP, mg/L	1.08 (0.62–1.76)	2.02 (1.07–3.38)	<0.001
AAT, mg/dl	125.50 \pm 19.67	142.08 \pm 19.61	<0.001
Medications, n (%)			
Statins	–	–	–
Aspirin	11 (9.3)	15 (14.6)	0.296
CCB	20 (16.9)	20 (19.4)	0.727
ACEI/ARB	13 (11.0)	20 (19.4)	0.254
Beta blocker	27 (22.9)	37 (35.9)	0.123

SAP: Stable angina pectoris; BMI: Body mass index; TC: Total cholesterol; TG: Triglyceride; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; hsCRP: High-sensitivity C-reactive protein, and is presented as the median with 25th and 75th percentiles; AAT: α 1-antitrypsin; CCB: Calcium channel blocker; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin-receptor blocker; *P*: *P* value for SAP group versus control group.

Table 2: Correlations between plasma AAT concentration and other variables

Variables	Univariate analysis		Multivariate analysis		
	r	P	Beta coefficient	B (95% CI)	P
Male	0.068	0.317	–	–	–
Age	0.182	0.007	0.493	0.171–0.815	0.003
BMI	0.669	0.504	–	–	–
Diabetes	0.049	0.469	–	–	–
Hypertension	0.145	0.031	1.324	–4.391–7.038	0.648
Smoking	0.153	0.023	6.238	0.721–11.756	0.027
TC	–0.028	0.690	–	–	–
TG	–0.108	0.114	–	–	–
HDL-C	–0.184	0.006	–9.701	–18.953––0.449	0.040
LDL-C	0.121	0.072	–	–	–
hsCRP	0.297	<0.001	10.691	5.021–16.362	<0.001
Aspirin	0.109	0.105	–	–	–
CCB	0.008	0.902	–	–	–
ACEI/ARB	0.039	0.569	–	–	–
Beta blocker	0.129	0.056	–	–	–

BMI: Body mass index; TC: Total cholesterol; TG: Triglyceride; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; hsCRP: High-sensitivity C-reactive protein; CCB: Calcium channel blocker; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin-receptor blocker; AAT: α 1-antitrypsin.

group than that in the controls (141.17 ± 21.82 mg/dl vs. 126.28 ± 19.88 mg/dl, $P < 0.001$).

Correlations between plasma α 1-antitrypsin concentration and stable angina pectoris

To confirm the predictive value of an increased plasma AAT level for SAP, univariate and multivariate logistic regression analyses were performed. As shown in Table 3, plasma levels of LDL-C, hsCRP and AAT were found to be independent predictors of SAP (LDL-C: Odds ratio (OR) = 1.724, 95% confidence interval (CI): 1.100–2.702, $P = 0.017$; hsCRP: OR = 2.908, 95% CI: 1.402–6.033, $P = 0.004$; AAT: OR = 1.037, 95% CI: 1.020–1.054, $P < 0.001$). To test the diagnostic value of plasma AAT concentration for SAP, ROC curves were established. As shown in Figure 1a, plasma AAT levels were comparable to hsCRP levels for distinguishing patients with SAP from controls (AAT: Area under the curve (AUC) = 0.721, 95% CI: 0.655–0.788, $P < 0.001$; hsCRP: AUC = 0.698, 95% CI: 0.628–0.768, $P < 0.001$; $Z = 0.45817$, $P = 0.105$). The plasma AAT concentration was of certain value in predicting SAP with a sensitivity of 63.4% and a specificity of 67.8%. The best cut-off value calculated using the Youden index was 133.72 mg/dl.

Correlations between plasma α 1-antitrypsin concentration and coronary Gensini score

Gensini score was used to assess the severity of coronary atherosclerotic lesions. SAP patients were divided into three subgroups according to their angiographic results. The baseline characteristics of these subgroups are presented in Table 4. Patients with a high GS had higher plasma AAT levels, whereas those with a low GS had the lowest AAT levels (low GS subgroup <18 : 130.17 ± 15.83 mg/dl; intermediate GS subgroup $18-40$: 137.94 ± 17.73 mg/dl; high GS subgroup >40 : 157.68 ± 13.98 mg/dl).

To further investigate the association between plasma AAT concentrations and coronary severity, a Spearman analysis was performed. As shown in Figure 2, there was a significant positive correlation between plasma AAT levels and GS in patients with SAP ($n = 103$, $r = 0.564$, $P < 0.001$).

Table 3: Univariate and multivariate logistic regression analysis of risk factors and laboratory parameters to identify independent predictors of SAP

Variables	OR	95% CI	P
Univariate analysis			
Male	1.201	0.678–2.130	0.530
Age	0.978	0.948–1.009	0.164
BMI	1.036	0.961–1.117	0.356
Diabetes	1.597	0.807–3.163	0.179
Hypertension	2.787	1.595–4.870	<0.001
Smoking	1.113	0.655–1.891	0.693
TC	1.089	0.771–1.540	0.628
TG	1.073	0.817–1.408	0.613
HDL-C	0.256	0.097–0.677	0.006
LDL-C	1.742	1.161–2.615	0.007
hsCRP	4.395	2.194–8.806	<0.001
AAT	1.044	1.028–1.060	<0.001
Aspirin	1.658	0.725–3.793	0.231
CCB	1.181	0.595–2.343	0.635
ACEI/ARB	1.946	0.915–4.142	0.084
Beta blocker	1.889	1.049–3.404	0.034
Multivariate analysis			
LDL-C	1.724	1.100–2.702	0.017
hsCRP	2.908	1.402–6.033	0.004
AAT	1.037	1.020–1.054	<0.001

BMI: Body mass index; TC: Total cholesterol; TG: Triglyceride; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; hsCRP: High-sensitivity C-reactive protein; AAT: α 1-antitrypsin; CCB: Calcium channel blocker; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin-receptor blocker; OR: Odds ratio; CI: Confidence interval; SAP: Stable angina pectoris.

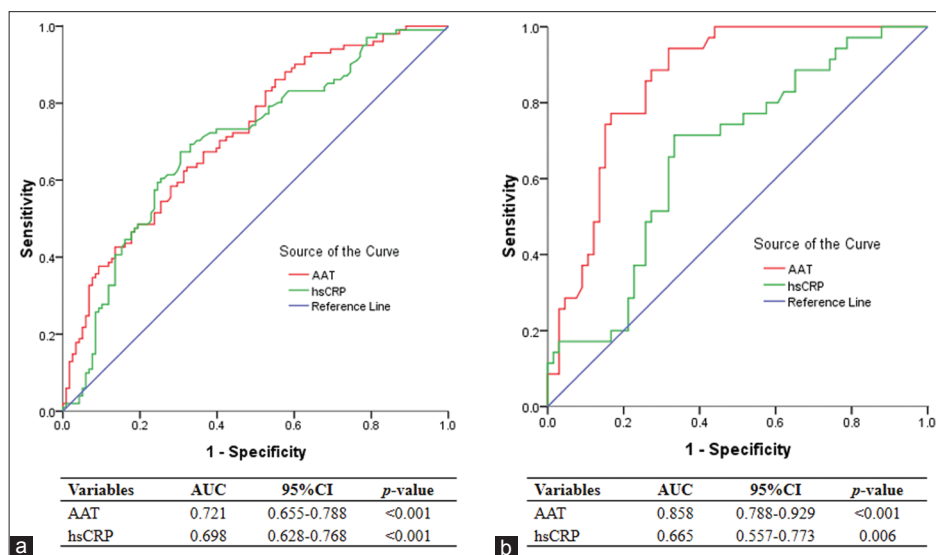


Figure 1: ROC curve analyses of the predictive power of plasma AAT level. (a) ROC curve analysis for SAP diagnosis; (b) ROC curve analysis for a high GS (>40) identification. hsCRP: High-sensitivity C-reactive protein; AAT: α 1-antitrypsin; AUC: Area under the curve; CI: Confidence interval; SAP: Stable angina pectoris; GS: Gensini score; ROC: Receiver operating characteristic.

Additionally, we performed the univariate analysis between the SAP patients with high GS (>40) and those with low and moderate GS (1–40). The data showed that patients with high GS (>40) were more frequently older and had significantly elevated plasma AAT and hsCRP levels. Moreover, the multivariate logistic regression analysis showed that only the plasma AAT level was identified as an independent predictor of a high GS in SAP patients ($OR = 1.087$, 95% CI : 1.051–1.124, $P < 0.001$), which suggests a more severe atherosclerotic lesion.

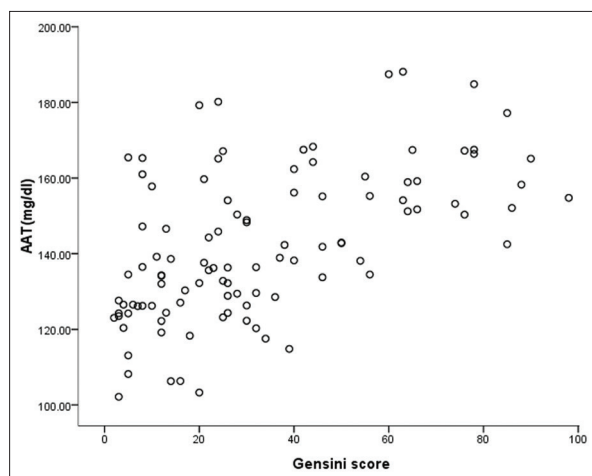


Figure 2: Correlations between the plasma AAT level and the Gensini score in the SAP patients. There was a significantly positive correlation between the plasma AAT level and the Gensini score in SAP patients ($r = 0.564$, $P < 0.001$). AAT: α 1-antitrypsin; SAP: Stable angina pectoris.

Finally, the ROC curve analysis [Figure 1b] showed a moderate diagnostic value of plasma AAT levels for identifying SAP patients with high GS from those with low and moderate GS (AUC = 0.858, 95% CI : 0.788–0.929, $P < 0.001$), and it was better than that of plasma hsCRP levels (AUC = 0.665, 95% CI : 0.557–0.773, $P = 0.006$; $Z = 2.9363$, $P < 0.001$). Additionally, we found that a plasma AAT level of 137.85 mg/dl was an effective cut-off point for differentiating SAP patients with severe atherosclerotic lesions from those without, with a sensitivity of 94.3% and a specificity of 68.2%.

DISCUSSION

Our study demonstrated that plasma AAT levels were significantly higher in patients with SAP than in controls. An elevated plasma AAT level was found to be an independent risk factor for both the presence of SAP and a high GS. The ROC curve analysis indicated that plasma AAT level could be a potential marker of the presence and severity of SAP. In particular, a plasma AAT level of 137.85 mg/dl or higher identified SAP patients with high GSs with a sensitivity of 94.3% and a specificity of 68.2%. All of these findings suggest that plasma AAT levels could serve as a valuable predictor in the screening of SAP patients for more severe coronary stenosis, and these patients would greatly benefit from further examination and treatment, such as percutaneous coronary intervention and stenting.

α 1-antitrypsin is an acute phase protein. The elevation of its plasma level has been well documented in the setting of ACS. In 1983, Gilutz *et al.* first confirmed an elevated plasma AAT

Table 4: Baseline characteristics based on the tertile of the Gensini score

Variables	Low GS (<18, n = 34)	Intermediate GS (18–40, n = 34)	High GS (>40, n = 35)	P
Demographic data				
Male, n (%)	21 (61.8)	23 (67.6)	29 (82.9%)	0.129
Age (years)	52.21 \pm 7.36	51.06 \pm 8.76	55.69 \pm 9.53	0.071
BMI (kg/m ²)	25.48 \pm 3.55	27.05 \pm 4.22	26.54 \pm 3.33	0.214
Diabetes, n (%)	6 (17.6)	9 (26.5)	8 (22.9)	0.699
Hypertension, n (%)	23 (67.6)	25 (73.5)	25 (71.4)	0.893
Smoking, n (%)	14 (41.2)	17 (50.0)	18 (51.4)	0.684
Biochemical parameters				
TC (mmol/L)	4.54 \pm 0.85	4.42 \pm 0.91	4.60 \pm 0.91	0.692
TG (mmol/L)	1.91 \pm 1.17	1.67 \pm 0.90	1.75 \pm 0.91	0.612
HDL-C (mmol/L)	1.06 \pm 0.32	1.09 \pm 0.32	1.02 \pm 0.33	0.640
LDL-C (mmol/L)	2.73 \pm 0.83	2.80 \pm 0.70	3.03 \pm 0.75	0.238
hsCRP (mg/L)	1.83 (0.96–3.62)	1.71 (0.85–2.77)	2.66 (1.67–3.55)	0.013
AAT (mg/dl)	130.17 \pm 15.83	137.94 \pm 17.73	157.68 \pm 13.98	<0.001
Medications, n (%)				
Statins	–	–	–	–
Aspirin	6 (17.6)	3 (8.8)	6 (17.1)	0.605
CCB	6 (17.6)	6 (17.6)	8 (22.9)	0.860
ACEI/ARB	7 (20.6)	6 (14.7)	7 (20)	0.948
Beta blocker	14 (41.2)	10 (29.4)	13 (37.1)	0.619

GS: Gensini score; BMI: Body mass index; TC: Total cholesterol; TG: Triglyceride; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; hsCRP: High-sensitivity C-reactive protein; AAT: α 1-antitrypsin; CCB: Calcium channel blocker; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin-receptor blocker.

level in patients with AMI.^[5] Later, Brunetti *et al.* reported an elevated plasma AAT level in patients with UAP.^[4] Therefore, AAT is considered a marker of ACS. However, different release curves of plasma AAT recently observed in patients with ST-segment elevation myocardial infarction (STEMI), non-STEMI and UAP^[6] indicate an association of the plasma AAT level with different pathological features of atherosclerosis. However, it was previously unclear whether AAT plasma level differs in patients with SAP. The present study is the first to confirm a significantly higher plasma AAT level in SAP patients compared with controls, suggesting that AAT is not only a marker of ACS, but is also involved in the chronic progression of atherosclerosis.

α 1-antitrypsin is an acute phase protein; thus, its plasma level increases rapidly during inflammation due to the stimulation of its over-production by multiple cytokines.^[12-14] CAD is an inflammation-mediated atherosclerotic disease.^[15] Multiple inflammatory cells and mediators have been reported to help sustain and amplify pro-inflammatory signals, leading to the onset and development of atherosclerosis. Therefore, we supposed that the elevation of plasma AAT levels in SAP patients could be the result of the chronic inflammatory status of the disease. This was supported by the positive correlation between plasma hsCRP and AAT levels observed in the total population of our study. In addition to inflammation, plasma AAT levels were also found to be positively correlated with age and smoking status, and negatively correlated with HDL-C plasma levels, and these results were similar to those of previous large-scale population-based studies.^[16-19] Old age, smoking, and low plasma HDL-C level were all related to high plasma AAT levels, and after adjusting for these possible confounders, the plasma AAT level was still associated with SAP. The ROC curve analysis further demonstrated that plasma AAT level was an independent predictor of SAP.

Gensini score has been used to evaluate the severity of CAD. Mori *et al.* observed the plasma AAT level in “chest discomfort” patients without AMI and found a higher plasma AAT level in those patients with a higher GS,^[8] implying a possible association of AAT and coronary lesions. However, whether plasma AAT is a predictive factor of the severity of coronary stenosis was not previously analyzed further. In our study, a positive correlation between plasma AAT levels and GS was confirmed in patients with SAP. After adjusting for other risk factors, plasma AAT levels were still related to a high GS, indicating that the plasma AAT concentration is an independent risk factor for the severity of SAP. In addition, the ROC curve analysis showed that plasma AAT levels could effectively identify SAP patients with severe coronary stenosis from those with low and moderate GS. Increasing evidence has demonstrated that the presence of AAT in atherosclerotic plaques could enhance fibrosis due to its inhibitory effects on collagenase and elastase,^[20] and also suppress the infiltration of inflammatory cells into the arterial walls,^[21-24] and both of these factors are related to the progression of atherosclerosis and the loss of luminal

diameter. All of these findings support the significant association between plasma AAT levels and coronary GS observed in our study.

As a well-known acute phase protein in cardiovascular diseases, hsCRP has been confirmed to be a diagnostic factor for CAD and to be associated with coronary angiographic severity.^[25] Our data showed that plasma AAT levels had a similar diagnostic value to that of hsCRP levels for SAP. However, the plasma AAT level was more powerful than the hsCRP level for identifying SAP patients with a higher GS. Interestingly, plasma AAT levels were better at distinguishing high GS-patients from low and moderate GS-patients than at distinguishing SAP patients from controls. This suggests that measurement of plasma AAT has more value for recognizing severe coronary stenosis in patients with suspected CAD in clinical practice. As there is a need to reduce health care costs, and the risk of cardiovascular events in SAP patients with severe coronary stenosis, plasma AAT levels may be a useful screening tool for clinicians. Therefore, SAP patients with a significantly increased plasma AAT levels are more inclined to receive further evaluation by coronary angiography. In our study, the severity of coronary stenosis was only evaluated by GS. The association of plaque vulnerability and AAT requires further study with intravascular ultrasound and optical coherence tomography. Because of the strong correlation between AAT levels and GS, future studies should evaluate plasma AAT levels in asymptomatic CAD patients.

There are several limitations to our study. First, our sample size was small, and our subjects were obtained from a single center. The diagnostic value of plasma AAT level needs to be further evaluated in a large study population with standardized diagnostic tests. Second, cardiovascular events were not analyzed in this study due to its cross-sectional design, and the value of plasma AAT levels in prognosis prediction must be assessed during patient follow-up.

In conclusion, our study demonstrated a significantly higher plasma AAT level in patients with SAP compared to controls. Plasma AAT levels were an independent risk factor of SAP and a higher GS. Plasma AAT concentrations could be measured in SAP patients to predict the severity of coronary lesions.

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