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# Role of ADAMTS-5 Expression in the Prognosis of Patients with Coronary Artery Disease: A Single Retrospective Analysis

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## Abstract

This study explores the predictive value of plasma a disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS-5) levels for major adverse cardiovascular events (MACE) in patients with coronary artery disease (CAD). 595 patients admitted to our hospital were selected. Initially, the serum ADAMTS-5 levels of subjects were analyzed. Subsequently, a receiver operating characteristic (ROC) curve was constructed. Furthermore, the serum levels of ADAMTS-5 were assessed in patients, and based on CAD severity, they were categorized into stable angina pectoris (SAP), unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) groups, with the aim of examining the relationship between ADAMTS-5 levels and CAD severity. Differences in clinical outcomes between patients with high and low levels of ADAMTS-5 were analyzed during the follow-up period. The study found that the serum levels of ADAMTS-5 were significantly higher in the group of patients with coronary artery disease (CAD) compared to the group without CAD, indicating its potential as a diagnostic marker for CAD. The ADAMTS-5 levels in the serum of STEMI patients were higher than those with SAP, while NSTEMI patients showed higher levels of ADAMTS-5 than the UA group. There was a positive correlation between serum ADAMTS-5 levels and the syntax score in CAD patients, suggesting a potential association with adverse clinical outcomes in patients with acute myocardial infarction (AMI). This study indicates that ADAMTS-5 shows promise as a biomarker for CAD and highlights the need for further research and validation.

## Keywords

Coronary Artery Disease, SYNTAX Score, ADAMTS-5, Prognosis, Diagnosis

## 1. Introduction

Among various atherosclerosis-based cardiovascular diseases (ASCVDs), coronary artery disease (CAD) has emerged as one of the significant clinical burdens threatening human health and longevity [1]. Nevertheless, the early detection of CAD plays a crucial role in patients at a high risk of CAD due to timely interventions concerning dietary and lifestyle changes, pharmacotherapy, and other prevention procedures. Lipid metabolism plays a vital role in the development of atherosclerosis, further implicating CAD. Accordingly, the essential lipoproteins involved in lipid metabolism, such as high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), are well-known risk factors for CAD [2]. However, a study reported that a significant proportion of myocardial infarction (MI) patients showed normal HDL-C concentrations, indicating that increased pharmacologic interventions in HDL-C were not consistently associated with reducing the CAD risk [3]. In addition, the overlap in blood LDL-C distribution between CAD and non-CAD patients led to false-positive and false-negative detection rates [4]. Therefore, identifying new risk factors is of great clinical importance in early prognosis and treatment of CAD.

Over the decades of research, tremendous advancements have indicated that atherosclerosis has been associated with the pathological basis of CAD [5]. Notably, the pathogenesis of atherosclerosis is quite complex, concerning the interactions between multiple genes, environmental, and other associated factors, the damage of endothelial cells from various external causes, the breakage of endothelial barrier function, the invasion of blood-borne lipids, monocytes, lymphocytes, and neutrophils into the subendothelial tissues, and the development of atherosclerotic plaques. These consequences often lead to plaque rupture, hemorrhage, and secondary thrombosis. Accordingly, pathological conditions involve chronic inflammation, abnormal immune responses, and disorders of key enzymes that are involved in lipid metabolism [6]. Among them, a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), a subfamily of matrix metalloproteinases (MMPs) integrated with the extracellular matrix (ECM) or free in plasma, are widely expressed in multiple tissues and organs of the human body. Since the first ADAMTS family member was discovered in 1997, 19 members have been identified [7]. In the atherosclerosis progression, ADAMTS significantly affects neointima formation by regulating the ECM components, such as macrophages and vascular smooth muscle cells [4] [8]. Previous reports indicated that ADAMTS members were highly expressed in the human carotid lesions and advanced coronary atherosclerotic plaques. Among various ADAMTS members, ADAMTS-5 plays a role in the development of atherosclerosis from molecular, cellular, and animal levels [9] [10]. However, the reported data on the effect of ADAMTS members in CAD remained inconsistent. In a case, Didangelos and colleagues demonstrated that reduced levels of ADAMTS-5 were associated with atherosclerosis, accumulating proteoglycans, such as diglycans and nystatin, and mediating lipid re-

tention [9]. In another case, Demet and coworkers observed increased levels of ADAMTS-5 in CAD patients [11]. Anja and colleagues demonstrated high ADAMTS-5 expression in an apoE knockout rabbit model of arteriosclerosis [12].

Considering these findings, in this study, we conducted a retrospective study examining whether ADAMTS-5 is associated with the severity and prognosis of CAD in patients. To explore these aspects, non-CAD and CAD patients admitted to our hospital between June 2021 and March 2023 were selected for this study. Further, the receiver operating characteristic (ROC) curve was plotted. Then, the serum ADAMTS-5 levels were analyzed, and determined their relationship with CAD severity by examining the patients in the subgroups as follows: stable angina pectoris (SAP), unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) groups. Patients with high- and low-ADAMTS-5 expressions were analyzed for differences in clinical outcomes during the follow-up after the study.

## 2. Materials and Methods

### 2.1. Study Population

In this study, 595 patients admitted to our hospital from 2021-06-01 to 2023-03-30 were recruited as subjects. Initially, the routine clinical diagnosis using coronary angiography (CAG) was performed for all patients with suspected CAD. Indeed, the CAD pathological conditions were validated with 50% stenosis of the coronary artery diameter at the time of CAG (corresponding to 75% stenosis in American Heart Association criteria) [13], according to quantitative CAG analysis (CAAS; medical imaging Maastricht, the Netherlands) [14].

All the subjects (n = 595) were recruited by strictly considering the criteria of rearrangement. Considering the clinical information and the results of GAGs, the recruited subjects were further categorized into various groups, such as non-CAD, SAP, UA, NSTEMI, and STEMI groups. The SAP group was refereed according to the 2007 guidelines for diagnosing and treating chronic stable angina published by the Committee for cardiovascular diseases of the Chinese Medical Association [15]. AMI and UA groups were categorized based on the diagnosis according to the European Society of Cardiology ACS criteria [16]. According to the ESC/AHA/ACC guidelines [17], AMI patients were further divided into STEMI and NSTEMI groups.

***Exclusion criteria***

The exclusion criteria were set as follows: 1) Patients taking other lipid-lowering drugs; 2) CAD due to other diseased conditions, such as polycythemia, hypothyroidism, and hereditary hyperlipidemia; 3) Patients with aspartate transaminase (AST)/alanine transaminase (ALT) higher than or equal to 1.5 times of the upper limit of normal, active liver disease, or hepatic insufficiency, as well as renal insufficiency (EGFR < 60 ml/min) or serum creatinine CR greater than 1.5

times the upper limit of normal values; 4) Patients with acute and chronic lung diseases with pulmonary function test, *i.e.*, FEV1 < 50% of the predicted values; 5) Patients with other serious diseases, such as tumors and systemic immune diseases, as well as developmental disorders, severe psychiatric disorders, genetic disorders, and chromosomal-based pathological conditions; 6) Pregnant, lactating women, and recent birth planners; 7) Patients who had participated in other clinical trials within last 3 months before entry into this study. Notably, the informed consent for this study was obtained from all the subjects, along with the approval of the ethics committee of our institution.

***Collection of demographic and baseline data***

After grouping, the demographic characteristics, including age, gender, smoking status, and clinical characteristics (e.g., diabetes and hypertension and medication use), were recorded for all patients through a systematic questionnaire. Further, the baseline data for the enrolled subjects were collected, including lipid levels, body mass index (BMI), type of CAD, extent of coronary disease, and syntax score. Then, the blood samples were collected on day 1 of admission from the recruited subjects for various blood index analyses, such as fasting intravenous glycated hemoglobin, hemoglobin, glomerular filtration rate, AST, lipoprotein (a), total cholesterol (TC), HDL-C, LDL-C, and triglycerides (TG). The biochemical analyses were measured, *i.e.*, blood lipids, by an automatic biochemical analyzer (Tokyo Medical 1024i, Japan). Further, the plasma ADAMTS-5 levels were determined using ADAMTS-5 enzyme-linked immunosorbent assay (ELISA) kit (Beyotime Biotechnology Co. Ltd., Haimen, China), according to the manufacturer's instructions. The testing process for ADAMTS-5 levels in triplicate was performed according to the manufacturer's instructions. The ROC curves were plotted, and the area under the curve (AUC) was compared to evaluate the cut-off value of ADAMTS-5 towards determining the presence and severity of CAD.

***Collection of follow-up data***

The pathological conditions and physical activities of all patients were continuously followed until the first major adverse cardiovascular event (MACE), which was distinguished as: 1) all-cause death, 2) non-fatal myocardial infarction, and 3) unplanned coronary revascularization. Notably, the disease-free survival time was considered before the first MACE. Further, the follow-up data were obtained by outpatient interviews and/or telephone calls by the same physician.

## 2.2. ADAMTS-5 Index Test

Briefly, 4 ml of venous blood was collected early during fasting. Blood was processed by centrifugation at 3000 rpm for 10 min. After 30 min, the upper serum layer was collected to measure the ADAMTS-5 levels using ADAMTS-5 enzyme-linked immunosorbent assay (ELISA) kit (Beyotime Biotechnology Co. Ltd.), according to the manufacturer's instructions. Optical density was measured at 450 nm. The lowest detectable ADAMTS-5 concentration was 1.563

ng/mL, according to the manufacturer's instructions, and the intrassay coefficient of variation was <10%. In addition, 4 ml of venous blood from all study subjects was collected into the anticoagulant tube at an early morning fasting time, mixed well after collection, and subjected to various biochemical analyses.

### 2.3. Follow-Up Investigations

Further, the patients after the study were followed up by telephone and outpatient forms with monthly visits for 2 years to enumerate the patient clinical outcomes. In this study, the attributes of recurrence, acute perforation, and mucosal dysplasia were regarded as poor clinical outcomes.

### 2.4. Statistical Analysis

The measurement data with normal distribution were expressed as mean ± standard deviation (S.D.). The data between the two groups were compared by *t*-test for independent samples and one-way analysis of variance (ANOVA) among multiple groups. The correlation analysis between ADAMTS-5 and traditional indices was performed by Pearson analysis. The ROC curve was used to evaluate the serum ADAMTS-5 levels and other indices for CAD diagnosis and clinical outcomes. The binary and continuous outcomes were assessed using multiple logistical and linear regression analyses, respectively. The data were analyzed by SPSS (v20.0) software, considering $P < 0.05$ as statistically significant.

## 3. Results

### 3.1. General Characteristics and Correlation between ADAMTS-5 with the Clinical-Pathological Characteristics of CAD Patients

Initially, the baseline data characteristics of the patients were collected and statistically analyzed (Table 1). Compared with the non-CAD control subjects, CAD patients (predominantly male subjects) showed a higher BMI, a higher prevalence of hypertensive diabetes mellitus, and a history of more frequent smoking. In addition, the blood levels of white blood cells, monocytes, and neutrophils were significantly higher in the CAD group than in the non-CAD control group. Moreover, other factors, such as hemoglobin and glycated hemoglobin, were also elevated. Interestingly, the lymphocyte count in the serum remained similar in both groups. The clinical data analysis showed that TC, HDL-C, LDL-C, TG, apoB, LVEF, and non-proBNP values were significantly higher in the CAD experimental group than in the non-CAD control group, indicating a worse overall condition in CAD patients over the non-CAD group of patients.

The ADAMTS-5 concentration in the serum of CAD patients was observed to be significantly higher than in the non-CAD control group ($P < 0.001$). To further explore whether ADAMTS-5 was an independent factor of CAD, the univariate logistic regression analysis was employed to evaluate its potential as a CAD

Table 1. Demographic, clinical and laboratory characteristics of the studied groups.

| Variable | Non-CAD | CAD | *P*-value |
|---|---|---|---|
| Gender/Male | 114 | 297 | <0.0001 |
| BMI, kg/m$^2$ | 23.80 (21.90 - 26.10) | 24.60 (22.93 - 26.70) | 0.006 |
| Blood pressure (BP) | 82 | 200 | 0.036 |
| Antihypertension medication | 77 | 191 | 0.026 |
| Diabetes Medication | 22 | 82 | 0.03 |
| Smoking | 38 | 172 | <0.001 |
| Leukocyte, 10$^9$/L | 6.90 (6.00 - 8.10) | 8.15 (6.63 - 10.20) | <0.0001 |
| Monocytes, 10$^9$/L | 0.57 (0.45 - 0.74) | 0.63 (0.49 - 0.81) | 0.026 |
| Neutrophils, 10$^9$/L | 3.75 (2.72 - 4.84） | 5.01 (3.72 - 6.78) | <0.0001 |
| Hemoglobin, g/L | 135.68 ± 15.26 | 138.87 ± 15.02 | 0.015 |
| Glycated hemoglobin, % | 5.60 (5.40 - 6.10) | 6.00 5.50 - 6.55) | <0.0001 |
| AST, U/L | 18 (15 - 22) | 22 (17 - 56) | <0.0001 |
| TC, mmol/L | 4.29 (3.59 - 4.29) | 4.55 (3.82 - 5.37) | 0.012 |
| HDL-C, mmol/L | 1.09 (0.91 - 1.29) | 2.00 (0.87 - 1.27) | 0.007 |
| LDL-C, mmol/L | 2.63 (2.14 - 3.20) | 3.06 (2.31 - 3.74) | <0.0001 |
| TG, mmol/L | 1.31 (0.96 - 1.90) | 1.49 (1.07 - 3.14) | 0.006 |
| ApoA, g/L | 1.29 (0.96 - 1.90) | 1.60 (1.12 - 2.39) | 0.005 |
| ApoB, g/L | 1.29 (1.17 - 1.44) | 1.21 (1.09 - 1.35) | <0.0001 |
| LVEF, % | 68 (50 - 62) | 65.00 (60.00 - 69.90) | <0.0001 |
| non-proBNP, pg/ml | 45.00 (38.00 - 71.00) | 634 (229.50 - 1335.00) | <0.0001 |
| ADAMTS-9 | 12.42 (9.76 - 13.69) | 34.62 (29.80 - 42.96) | <0.0001 |

risk factor between the CAD experimental and non-CAD control groups. Among various recorded factors, several attributes of gender, history of hypertension, smoking, glomerular filtration rate (GFR), and serum levels of ADAMTS-5 were predicted as independent factors of CAD in the univariate multivariate regression analysis (Table 2). Further, the correlation analysis indicated that the ADAMTS-5 expression levels were positively correlated with the age, heart rate, leukocytes, and monocytes along with hemoglobin and glycated hemoglobin, AST, TC, HDL-C, TG, as well as non-proBNP in the serum of CAD group (Table 3). In contrast, the ADAMTS-5 expression was negatively correlated with LVEF values. Moreover, the diagnostic value of ADAMTS-5 expression was evaluated using the ROC curve analysis. The area under the ROC curve (AUC) was recorded as 0.9964 (95% CI: 0.9941 - 0.9987, $P < 0.001$, Figure 1).

Table 2. A summary shows the univariate and multivariate analyses of the reported clinicopathological characteristics.

| Variable | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | OR (95% CI) | *P*-value | OR (95% CI) | *P*-value |
| Age | 1.1010 (0.994 - 1.026) | 0.226 | | |
| Gender (M) | 2.237 (1.558 - 3.211) | <0.001 | 0.02 (0.005 - 0.299) | 0.02 |
| BP-History | 0.693 (0.491 - 0.978) | 0.037 | 0.025 (0.03 - 0.220) | 0.04 |
| Antihypertensive medication history | 0.674 (0.477 - 0.954) | 0.026 | | |
| Type 2 diabetes* | 0.51 (0.31 - 0.83) | 0.07 | | |
| Diabetes Medication | 0.476 (0.287 - 0.789) | 0.04 | | |
| Smoking | 0.307 (0.205 - 0.461) | <0.01 | 0.061 (0.08 - 0.441) | 0.06 |
| Leukocyte, $10^9$/L* | 1.308 (1.203 - 1.422) | <0.01 | | |
| Monocytes, $10^9$/L* | 3.305 (1.591 - 6.868) | 0.01 | | |
| Neutrophils, $10^9$/L* | 1.499 (1.439 - 1.665) | <0.01 | | |
| Hemoglobin, g/L* | 1.014 (1.003 - 1.028) | 0.016 | | |
| Glycated hemoglobin, %* | 1.313 (1.128 - 1.529) | <0.001 | | |
| AST, U/L* | 1.029 (1.017 - 1.040) | <0.001 | | |
| Glomerular filtration rate, ml/min | 0.987 (0.977 - 0.998) | 0.018 | 0.948 (0.930 - 0.995) | 0.017 |
| TC, mmol/L | 1.284 (1.090 - 1.512) | 0.03 | | |
| HDL-C, mmol/L | 0.329 (0.175 - 0.619) | <0.01 | | |
| LDL-C, mmol/L | 1.563 (1.289 - 1.895) | <0.01 | | |
| TG, mmol/L | 1.178 (1.000 - 1.387) | 0.05 | | |
| ApoB, g/L | 2.282 (1.311 - 3.971) | 0.04 | | |

**Continued**

| | | | | |
|---|---|---|---|---|
| LP (a), g/L | 3.910 (1.663 - 9.192) | 0.02 | | |
| LVEF, % | 0.889 (0.857 - 0.922) | <0.01 | | |
| non-proBNP, pg/ml | 1.006 (1.004 - 1.008) | <0.01 | | |
| ADAMTS-9 | 1.959 (1.647 - 2.327) | <0.01 | 2.941 (1.932 - 4.477) | 0.001 |

**Note**: *Residual Chi-Squares are not computed because of redundancies.

**Table 3.** A summary of clinicopathological data for the correlation analysis.

| Variable | r | *P*-value |
|---|---|---|
| Age | 0.299 | <0.001 |
| BMI, kg/m$^2$ | 0.131 | 0.01 |
| Heart rate | 0.135 | <0.001 |
| Leukocytes, 10$^9$/L | 0.399 | <0.001 |
| Monocytes, 10$^9$/L | 0.202 | <0.001 |
| Neutrophils, 10$^9$/L | 0.464 | <0.001 |
| Hemoglobin, g/L | 0.161 | <0.001 |
| Glycated hemoglobin, % | 0.154 | <0.001 |
| AST, U/L | 0.437 | <0.001 |
| TC, mmol/L | 0.189 | <0.001 |
| HDL-C, mmol/L | −0.124 | 0.03 |
| LDL-C, mmol/L | 0.256 | <0.001 |
| TG, mmol/L | 0.110 | 0.007 |
| ApoB, g/L | 0.187 | <0.001 |
| LVEF, % | −0.43 | <0.001 |
| non-proBNP, pg/ml | 0.364 | <0.001 |

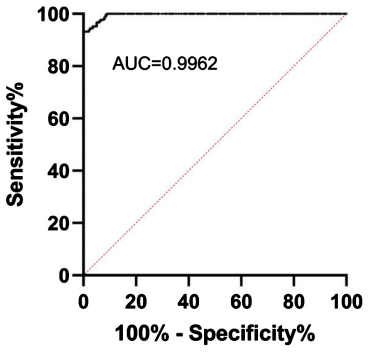


**Figure 1.** ROC curve of plasma ADAMTS-5 in CAD patients.

### 3.2. The Correlation between ADAMTS-5 and CAD Severity

Further, it was observed that the serum levels of ADAMTS-5 were significantly higher in patients with SAP, STEMI, NSTEMI, and UA groups compared to the non-CAD control patients (12.05 ± 3.67 vs. 25.85 ± 5.55, 32.74 ± 3.90, 43.76 ± 2.71, or 43.89 ± 2.73, respectively, $P < 0.0001$) (Table 4). In addition, the serum levels of ADAMTS-5 were significantly higher in the three groups of STEMI, NSTEMI, and UA, compared with SAP. Further analysis indicated that the serum ADAMTS-5 levels were substantially lower in the UA group than in the STEMI or NSTEMI groups (32.74 ± 3.90 vs. 43.76 ± 2.71 or 43.89 ± 2.73, $P < 0.0001$). However, no apparent difference in the serum ADAMTS-5 levels was observed between STEMI and NSTEMI groups. Further, the multiple regression analysis indicated that serum ADAMTS-5 levels remained an independent diagnostic factor for SAP, STEMI, NSTEMI, and UA conditions (Table 5).

### 3.3. ADAMTS-5 Is Positively Correlated with CAD Syntax Scores (SS)

The selected CAD patients (n = 396) were further distributed according to SS values into two groups, *i.e.*, a high-SS group (SS ≥ 22) and a low-SS group (s < 22). The analysis of clinical data from the two CAD cohorts revealed that patients in the high-SS group were older, more male, and more patients with a history of hypertension and medication usage (Table 6). Moreover, other characteristics, such as heart rate, white blood cells, monocytes, lymphocytes, platelets, TC, HDL-C, LDL-C, apoB, LVEF, and non-proBNP levels were higher in the high-SS patients than in the low-SS group. Furthermore, serum ADAMTS-5 level was also higher (38.27 ± 6.55 vs.44.12 ± 8.90) in the high-SS patients than in the low-SS group. The univariate and bivariate regression analyses identified ADAMTS-5 as an independent predictor of the high-SS group (OR = 1.057, 95% CI: 1.028 ± 1.087, $P = 0.04$) (Table 7). The Pearson analysis further validated that ADAMTS-5 was positively correlated with SS in CAD patients (r = 0.498, $P < 0.0001$, Figure 2).

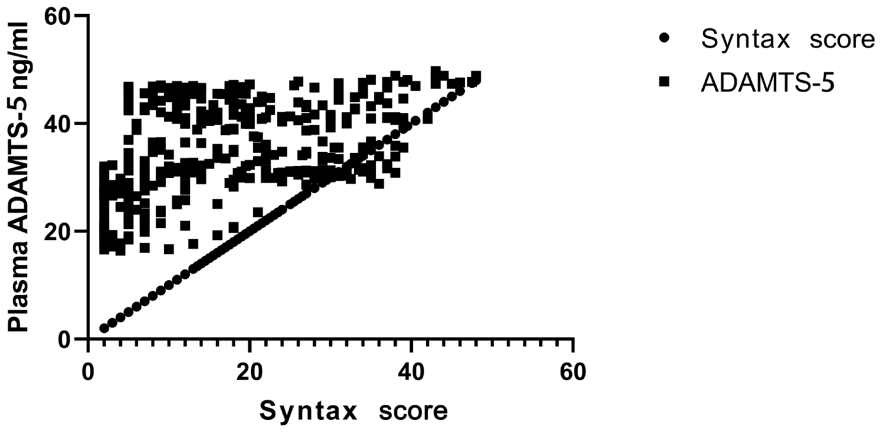


Figure 2. Pearson analysis between ADAMTS-5 and Syntax scores in CAD patients.

Table 4. Demographic, Clinicopathological characteristics of the studied groups.

| Variable | Non-CAD (n = 199) | SAP (n = 103) | UA (n = 132) | NSTEMI (n = 76) | STEMI (n = 85) | *P*-value |
|---|---|---|---|---|---|---|
| Age | 58.30 ± 0.590[b,c,d,e] | 53.91 ± 14.19[a,c,d,e] | 58.77 ± 8.96[b,d,e] | 64.54 ± 8.41[a,b,c,e] | 62.49 ± 8.67[a,b,c] | <0.001 |
| Gender (Male %) | 57.29% (114)[c,d,e] | 59.22% (61)[c,d,e] | 73.48% (97)[a,b,d] | 88.16% (67)[a,b,c] | 84.70% (72)[a,b,c,] | 0.01 |
| BMI, kg/m$^2$ | 24.146 ± 3.274[e] | 24.49 ± 3.00 | 24.574 ± 2.635 | 24.99 ± 2.79[a] | 25.50 ± 2.79 | 0.008 |
| Blood Pressure | 41.21% (82)[b,c,d,e] | 64.08% (66)[a,d,e] | 55.55% (72)[a,d,e] | 35.53% (27)[a,b,c] | 41.18% (35)[a,b,c] | 0.01 |
| Antihypertensive medication history | 41.21% (82)[b,c,d,e] | 64.08% (66)[a,d,e] | 55.55% (72)[a,d,e] | 35.53% (27)[a,b,c] | 41.18% (35)[a,b,c] | 0.01 |
| Type 2 diabetes | 12.06% (24)[c,d,e] | 16.54% (17)[c,d,e] | 23.48% (31)[a,b] | 18.42% (31)[a,b] | 25.88% (22)[a,b] | 0.025 |
| Diabetes Medication | 11.05% (22)[c,e] | 16.51% (17)[c,e] | 22.72 (30)[a,b,d] | 17.10% (13%)[c,e] | 25.88% (22)[a,b,d] | 0.014 |
| Smoking | 19.10% (38)[b,c,d,e] | 37.86% (39)[a,d,e] | 34.09% (39)[a,d,e] | 55.26% (45)[a,b,c] | 54.12% (46)[a,b,c] | <0.01 |
| Heart rate | 76.43 ± 11.575[d] | 77.24 ± 11.36 | 76.77 ± 11.43[b] | 81.21 ± 13.71[a] | 79.04 ± 12.47 | 0.029 |
| Systolic BP, mmHg | 132.49 ± 17.45[d] | 132.98 ± 16.95[d] | 134.61 ± 21.66[d] | 131.34 ± 19.58[d] | 124.80 ± 19.66[a,b,c] | 0.05 |
| Leukocytes, $10^9$/L | 7.159 ± 1.93[c,d,e] | 7.305 ± 1.62[d,e] | 7.823 ± 2.17[a,d,e] | 9.442 ± 3.45[a,c,d,e] | 11.291 ± 3.18[a,c] | 0.00 |
| Monocytes, $10^9$/L | 0.61 ± 0.26[d] | 0.59 ± 0.18[d,e] | 0.66 ± 0.28[e] | 0.74 ± 0.34[a,b,c,e] | 0.80 ± 0.31[c] | <0.01 |
| Neutrophils, $10^9$/L | 3.85 ± 1.80[c,d] | 4.29 ± 1.26[a,d] | 4.68 ± 1.71[a,d] | 6.68 ± 3.30[a,b,c,d] | 8.09 ± 3.13[a,b,c] | <0.001 |
| Lymphocytes, $10^9$/L | 2.06 ± 0.72 | 2.15 ± 0.65[d] | 2.18 ± 0.75[d] | 1.81 ± 0.7[a,b,c,d] | 2.05 ± 0.83 | 0.009 |
| Hemoglobin, g/L | 135.68 ± 15.26 | 136.90 ± 14.99 | 136.11 ± 14.62 | 142.34 ± 13.73[a,b] | 142.45 ± 15.67[a,b] | <0.001 |
| Glycated hemoglobin, % | 5.917 ± 1.08[b,d,e] | 6.086 ± 1.18[a,e] | 6.285 ± 1.39[a,d,e] | 6.436 ± 1.50[a,e] | 6.714 ± 1.91[b] | <0.001 |
| AST, U/L | 21.55 ± 16.83 | 19.22 ± 8.10 | 21.17 ± 12.18 | 79.34 ± 92.36[a,b,c] | 155.79 ± 123.26[a,b,c] | <0.001 |

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|---|---|---|---|---|---|---|
| Glomerular filtration rate, ml/min | 85.786 ± 15.60[b,d] | 82.02 ± 16.74[d] | 79.74 ± 16.97[a] | 85.18 ± 19.01 | 83.95 ± 17.56 | 0.019 |
| TC, mmol/L | 4.34 ± 1.15[d,e] | 4.412 ± 1.004[d,e] | 4.58 ± 1.23 | 4.84 ± 1.146[a,b] | 4.81 ± 1.10[a,c] | 0.001 |
| HDL-C, mmol/L | 4.34 ± 1.145[c,d,e] | 4.412 ± 1.00 | 4.58 ± 1.23[a] | 4.84 ± 1.15 | 4.81 ± 1.10[a] | 0.003 |
| LDL-C, mmol/L | 0.84 ± 0.06 | 0.86 ± 0.09 | 1.13 ± 0.10 | 1.01 ± 0.12 | 0.95 ± 0.104 | <0.001 |
| ApoB, g/L | 0.98 ± 0.35[d,e] | 0.99 ± 0.27[d,e] | 1.06 ± 0.35[d] | 1.17 ± 0.64 | 1.11 ± 0.29 | <0.01 |
| LP (a), g/L | 0.23 ± 0.17 | 0.29 ± 0.29 | 0.31 ± 0.30 | 0.31 ± 0.30 | 0.29 ± 0.28 | 0.04 |
| LVEF, % | 67.50 ± 4.93[c,e] | 67.36 ± 4.07[c,e] | 65.53 ± 7.76[a,b,e] | 60.15 ± 8.78[b,c,e] | 55.07 ± 8.49[a,b,c] | <0.001 |
| non-proBNP, pg/ml | 75.95 ± 155.72[b,c,d,e] | 73.40 ± 140.89[a,c,d,e] | 292.78 ± 720.34[a,b,d,e] | 769.12 ± 1138.59[a,b,c] | 1097.67 ± 1378.45 | <0.01 |
| ADAMTS-5, ng/mL | 12.05 ± 3.67[a,b,c,d,e] | 25.85 ± 5.55[a,c,d,e] | 32.74 ± 3.90[a,b,d,e] | 43.76 ± 2.71[a,b,c,d,e] | 43.89 ± 2.73 | 0.00 |

**Note**: [a]$P < 0.05$ vs. non-CAD group; [b]$P < 0.05$ vs. SAP group; [c]$P < 0.05$ vs. UA group; [d]$P < 0.05$ vs. NSTEMI group; [e]$P < 0.05$ vs. STEMI group.

**Table 5.** Multiple logistic regression analysis of factors in relation to the risk of the SAP, UA, NSTEMI, and STEMI conditions.

| Variable | SAP | | UA | | NSTEMI | | STEMI | |
|---|---|---|---|---|---|---|---|---|
| | OR (95% CI) | *P*-value | OR (95% CI) | *P*-value | OR (95% CI) | *P*-value | OR (95% CI) | *P*-value |
| Age | 0.885 (0.828 - 0.947) | 0.00 | 13.922 (0.0 - 29.578) | 0.928 | 0.804 (0.731 - 0.886) | <0.001 | 0.790 (0.714 - 0.875) | <0.001 |
| Hemoglobin, g/L | 0.988 (0.945 - 1.034) | 0.607 | 0.950 (0.905 - 0.998) | 0.041 | 1.015 (0.950 - 1.085) | 0.655 | 1.003 (0.936 - 1.074) | 0.942 |
| Platelets, $10^9$/L | 0.998 (0.987 - 1.009) | 0.741 | 0.943 (0.900 - 0.989) | 0.015 | 1.003 (0.987 - 1.019) | 0.723 | 1.005 (0.989 - 1.022) | 0.539 |
| Glomerular filtration rate, ml/min | 0.949 (0.910 - 0.990) | 0.015 | 3.711 (0.419 - 32.890) | 0.239 | 0.940 (0.889 - 0.993) | 0.028 | 0.929 (0.878 - 0.983) | 0.011 |
| LP (a), g/L | 15.313 (0.409 - 573.812) | 0.14 | 0.980 (0.157 - 6.099) | 0.983 | 2416.105 (39.135 - 149165.846) | 0.000 | 2.792 (0.015 - 530.473) | 0.701 |
| ADAMTS-5 | 1.697 (1.469 - 1.961) | 0.000 | 2.35 (1.96 - 2.82) | 0.00 | 3.280 (2.641 - 4.074） | 0.000 | 3.40 (2.71 - 4.28) | 0.000 |

**Table 6.** The baseline clinical and biochemical characteristics of the low-SS and high-SS groups[a].

| Variable | High-SS | Low-SS | *P*-value |
|---|---|---|---|
| Age | 61.56 ± 9.118 | 58.40 ± 11.795 | 0.008 |
| Gender % (Male) | 35.2% (104) | 65.00% (193) | 0.019 |
| Blood pressure-History | 54.27% (146) | 42.52% (54) | 0.029 |
| Antihypertensive medication history | 52.78 (142) | 35.58% (49) | 0.013 |
| Heart rate | 82.13 ± 12.77 | 76.39 ± 11.45 | 0.00 |
| Leukocytes, $10^9$/L | 9.30 ± 3.08 | 8.48 ± 2.92 | 0.01 |
| Monocytes, $10^9$/L | 0.75 ± 0.30 | 0.66 ± 0.27 | 0.00 |
| Lymphocytes, $10^9$/L | 2.18 ± 0.85 | 2.02 ± 0.71 | 0.04 |
| Platelets, $10^9$/L | 257.09 ± 62.51 | 244.90 ± 56.27 | 0.05 |
| TC, mmol/L | 4.80 ± 1.20 | 4.56 ± 1.10 | 0.05 |
| LDL-C, mmol/L | 3.25 ± 1.10 | 2.99 ± 0.97 | 0.02 |
| ApoB, g/L | 1.15 ± 0.56 | 1.04 ± 0.29 | 0.01 |
| LVEF, % | 60.89 ± 9.46 | 63.59 ± 8.25 | 0.00 |
| non-proBNP, pg/ml | 731.20 ± 1361.52 | 390.70 ± 731.86 | 0.00 |
| ADAMTS-5 | 38.27 ± 6.55 | 34.12 ± 8.90 | 0.00 |

**Table 7.** Univariate and Bivariate analyses of various clinicopathological factors in relation to CAD Syntax score.

| Variable | Univariate analysis | | Bivariate analysis | |
|---|---|---|---|---|
| | OR (95% CI) | *P*-value | OR (95% CI) | *P*-value |
| Age | 1.03 (1.01 ± 1.05) | 0.01 | 1.00 (0.97 ± 1.02) | 0.83 |
| Gender | 1.78 (1.05 ± 3.01) | 0.03 | 1.29 (0.71 ± 2.36) | 0.40 |
| High blood pressure | 1.60 (1.05 ± 2.46) | 0.03 | 0.58 (0.12 ± 2.90) | 0.51 |
| Antihypertensive medication | 1.76 (1.14 ± 2.70) | 0.01 | | |
| Heart rate | 1.04 (1.02 ± 1.06) | 0.01 | 1.03 (1.01 ± 1.05) | 0.43 |
| Leukocyte, $10^9$/L | 1.09 (1.02 ± 1.17) | 0.01 | 0.94 (0.84 ± 1.04) | 0.20 |
| Monocytes, $10^9$/L | 2.89 (1.37 ± 6.09) | 0.01 | 2.39 (0.92 ± 6.21) | 0.10 |
| Lymphocytes, $10^9$/L | 1.33 (1.01 ± 1.75) | 0.05 | | |
| Platelets, $10^9$/L | 1.00 (1.00 ± 1.01) | 0.05 | | |
| LDL-C, mmol/L | 1.28 (1.04 ± 1.58) | 0.02 | | |
| ApoB, g/L | 2.13 (1.14 ± 3.95) | 0.02 | 2.63 (0.82 ± 8.42) | 0.10 |
| LVEF, % | 0.97 (0.94 ± 0.99) | 0.00 | | 0.48 |
| non-proBNP, pg/ml | 1.00 (1.00 ± 1.00) | 0.00 | 0.99 (0.96 ± 1.03) | 0.75 |
| ADAMTS-5 | 1.06 (1.04 ± 1.09) | 0.00 | 1.057 (1.028 ± 1.087) | 0.04 |

Note: Residual chi-square not calculated due to redundancy.

### 3.4. Correlation between ADAMTS-5 and Disease-Free Survival Rate among AMI Patients

Finally, the clinical significance of ADAMTS-5 in CAD was further determined by analyzing the effect of high ADAMTS-5 expression on clinical outcomes in AMI patients. According to the clinical data analysis results, no difference in the basic information of patients was observed between these two groups. Further, the observation through a 2-year follow-up period revealed that 13 patients in the low-ADAMTS-5 group and 21 patients in the high-ADAMTS-5 group were diseased. The disease-free survival analysis showed that the low-ADAMTS-5 expression group showed a better probability of survival than the high-ADAMTS-5 expression group ($P = 0.0012$, Figure 3).

## 4. Discussion

According to global statistical data, CAD has emerged as the disease with the highest mortality rate among various atherosclerotic cardiovascular diseases (ASCVDs) and other ailments. To explore the relationship between ADAMTS-5 and the prognosis of patients with CAD, this study investigated the predictive value of plasma ADAMTS-5 levels and their correlation with major adverse cardiovascular events (MACE) in patients with CAD. Initially, we observed that serum levels of ADAMTS-5 were significantly higher in the CAD experimental group of patients than in the non-CAD control group. After observing the demographic and clinicopathological data, serum ADAMTS-5 levels were positively associated with the severity of the CAD condition, indicating that the serum ADAMTS-5 level was an independent risk factor for CAD. Further, the plasma ADAMTS-5 levels were also higher in CAD patients with high SS scores than those with low SS scores, indicating a positive correlation between plasma ADAMTS-5 levels and SS scores. Moreover, it acted as an independent prognostic factor for CAD in the high SS group. It was concluded that the high ADAMTS-5 group showed a higher incidence of MACE and worse disease-free survival.

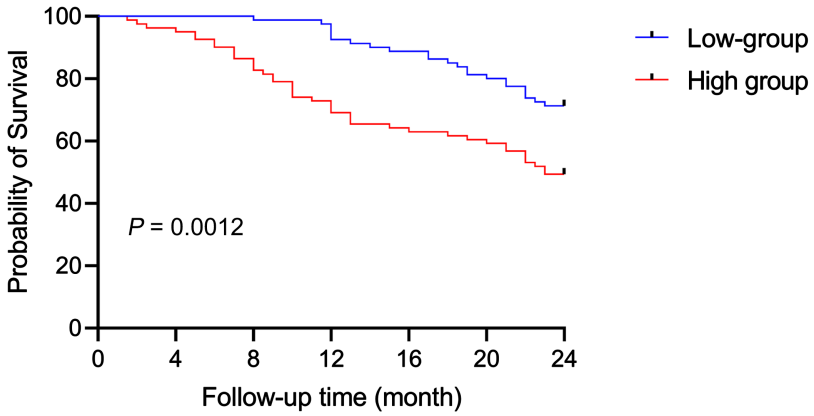


Figure 3. Analysis of prognostic difference between ADAMTS-5 high- and low-expression groups.

The ECM, a major component of the arterial wall, plays a crucial role in remodeling the vascular tissues after injury. Nevertheless, it should be noted that any modification of the ECM might lead to atherosclerosis, restenosis, and eventual heart failure [18]. The fibrous cap-like structures on atherosclerotic plaques are supplemented with the components of ECM, maintaining plaque stability and preventing plaque rupture [19]. In ECM degradation, plaques become unstable and prone to rupture [20]. In addition to protection, the ECM contributes to intimal calcification (5). Accordingly, ADAMTS, a protease, binds to ECM components, such as procollagen and cartilage oligomeric matrix protein (COMP), and leads to ECM degradation [21]. These secretases are structurally related to the matrix-degrading metalloproteinases (MMP) family, which acts by cleaving the vascular proteoglycans to regulate the ECM [22] [23]. Together, these proteins initiate plaque formation, progression, and destruction. Further, the accumulation of fibronectin and collagen leads to fibrous plaques that obstruct blood flow and increase the risk of heart stroke [24]. Previous studies demonstrated the role of ADAMTS in inflammation, atherosclerosis, osteoarthritis, and cancer. For instance, ADAMTS-4 and -7 were stimulated during monocyte-to-macrophage differentiation and were in higher amounts in macrophage-rich areas of the plaques [7] [25]. In addition, the reduced levels of ADAMTS-5 were associated with atherosclerosis, leading to the accumulation of proteoglycans, such as diglycan, and inducing lipid retention [26]. In an apoE knockout atherosclerosis rabbit model, researchers demonstrated a significant increase in ADAMTS-4 and ADAMTS-5 levels [12]. In a retrospective study with 60 patients, the ADAMTS-5 levels in serum were significantly higher in CAD patients relative to the non-CAD control group [11]. Consistent with the reported literature, our experimental results indicated increased ADAMTS-5 levels in CAD patients (n = 296) over the non-CAD control group (n = 199). Wang and colleagues analyzed the serum levels of ADAMTS-5 in CAD patients (n = 6), indicating significantly decreased serum levels [27]. Such discrepancies could be attributed to the two surveys' differing sample sizes. In another instance, it was demonstrated that this enzyme could be involved in the breakdown of structural proteins in the ECM of blood vessels [28]. In CAD, increased ADAMTS-5 expression might lead to excessive degradation of ECM components, weakening the fibrous cap covering the lipid-rich plaques [29]. These consequences could make the plaques more vulnerable to rupture, causing blood clot formation and obstructing blood flow, resulting in acute coronary events like heart attacks. ADAMTS-5 could be associated with dysregulation of cytokines and growth factors, promoting inflammation and smooth muscle cell proliferation in the arterial wall [29]. Subsequently, targeting ADAMTS-5 might hold therapeutic potential in managing CAD by stabilizing vulnerable plaques and inhibiting atherosclerosis progression.

Like the MMPs family, ADAMTS, a family of ECM-degrading enzymes, plays a more active role in unstable plaque lesions [30]. Previous reports indicated that MMP-1, MMP-9, and IL-6 could correlate with the Gensini score [31], indicat-

ing that plasma MMP-9 was associated with CVD-associated mortality in CAD patients at baseline [32]. The upregulated serum levels of ADAMTS-5 could be related to poor disease-free survival in patients with low CAD risk [33]. Thus, we further analyzed the diagnostic and prognostic role of ADAMTS-5 in CAD patients. It was observed that ADAMTS-5 was an independent predictor of the high SS group. Moreover, the disease-free survival analysis showed that the low-ADAMTS-5 expression group showed a better probability of survival than the high-ADAMTS-5 expression group. Noticeably, this study had a relatively small sample size, requiring investigations to explore comprehensively. Despite these limitations, our data demonstrated the diagnostic and predictive potential of serum ADAMTS-5 concentration in CAD patients.

## 5. Conclusion

In this study of CAD patients, ADAMTS-5, a protein, was found to be a promising biomarker. The results revealed that CAD patients exhibited higher levels of ADAMTS-5, demonstrating its promising role in diagnosing CAD. It showed correlations with CAD-related factors and disease severity, particularly in different subtypes of CAD and cases with high CAD Syntax Scores. Additionally, high ADAMTS-5 levels were associated with worse disease-free survival in AMI patients. These findings suggest that ADAMTS-5 has potential as both a diagnostic and prognostic marker for CAD, underscoring the need for further investigation and validation.

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## Availability of Data and Material

The original contributions presented in the study are included in this article; further inquiries can be directed to the corresponding authors.

## Authors' Contributions

Jinguang Liu designed the study. Hailin Pan performed the experiments and analyzed the data. Jinguang Liu supervised the study and drafted the text.

## Conflicts of Interest

All authors declare no conflict of interest.

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