


# Association Between Novel Pro- and Anti- Inflammatory Adipocytokines in Patients with Acute Coronary Syndrome

Clinical and Applied  
Thrombosis/Hemostasis  
Volume 28: 1-11  
© The Author(s) 2022  
Article reuse guidelines:  
sagepub.com/journals-permissions  
DOI: 10.1177/10760296221128021  
journals.sagepub.com/home/cat  


Chen Wei, MM<sup>1</sup>, Yixiang Liu, MM<sup>1</sup> , Enhong Xing, MM<sup>2</sup>,  
Zhenjiang Ding, MM<sup>1</sup> , Yanan Tian, MM<sup>1</sup>, Zhuoyan Zhao, MM<sup>1</sup>,  
Wenjun Fan, MM<sup>1</sup> , and Lixian Sun, MD<sup>1</sup> 

## Abstract

**Background and aims:** Novel pro- and anti-inflammatory adipocytokines affect inflammation, energy metabolism, and insulin signaling. However, their role in acute coronary syndrome (ACS) development is unclear. We evaluated the diagnostic and risk predictive value of such adipocytokines for ACS. **Methods:** We enrolled 168 consecutive inpatients with suspected ACS and detected serum PLIN1, PLIN2, PLIN5, CTRP6, CTRP7, CTRP11, WISPI, FAM19A5, TNF- $\alpha$ , and adiponectin levels. Multivariate logistic regression analysis and Spearman's test were used to assess risk factors for ACS and correlations between serum adipocytokines and continuous variables, respectively. **Results:** Serum levels of the adipocytokines differed between ACS and Non-ACS groups ( $p < 0.05$ ). After adjusting for confounding factors, serum PLIN1, PLIN2, PLIN5, CTRP6, CTRP7, CTRP11, WISPI, and FAM19A5 levels were independently associated with ACS ( $p < 0.05$ ). Increasing tertiles of serum PLIN1, PLIN2, CTRP7, CTRP11, and WISPI levels increased the ACS risk, which decreased gradually with increasing PLIN5 and CTRP6 tertiles ( $p$  for trend  $< 0.05$ ). Serum PLIN1, PLIN5, CTRP6, CTRP7, CTRP11, WISPI, and FAM19A5 levels correlated with ACS severity. **Conclusions:** PLIN1, PLIN2, CTRP7, CTRP11, and WISPI were identified as independent ACS risk factors, whereas PLIN5, CTRP6, and FAM19A5 were independent protective factors for ACS. These serum adipocytokines are novel potential clinical biomarkers of ACS.

## Keywords

serum adipocytokines, acute coronary syndrome, coronary angiography, gensini score, diagnosis

Date received: 4 July 2022; revised: 19 August 2022; accepted: 5 September 2022.

## Introduction

Acute coronary syndrome (ACS) is the leading cause of death worldwide.<sup>1,2</sup> Substantial progress has been made in the diagnosis and treatment of ACS, which is mostly caused by acute thrombosis in coronary arteries due to the rupture or erosion of unstable atherosclerotic plaques.<sup>3</sup> The pro- and anti-inflammatory adipocytokines are classical risk factors associated with ACS.<sup>4-8</sup> Although several biomarkers have emerged as novel risk factors of ACS, their diagnostic and prognostic value has only been assessed in a few studies.<sup>9,10</sup>

Perilipin (PLIN) is lipid droplet (LD) protein that was first identified in adipocytes.<sup>11</sup> As members of the PLIN family, perilipin1 (PLIN1), perilipin2 (PLIN2), and perilipin5 (PLIN5) play their respective roles in lipid metabolism and inflammatory response.<sup>12</sup> PLIN1 is a predominant protein in mature adipocytes and the most abundant protein on the lipid droplet

surface.<sup>13</sup> The C-terminus of PLIN1 has a relatively conserved hydrophobic domain with five cysteine residues. Sulfhydration might stabilize the C-terminal structure of PLIN1 and the distribution of this protein in the lipid droplet, which enhances its inhibitory effect on hormone-sensitive lipase (HSL) and adipose triglyceride lipase (ATGL), thus, inhibiting lipolysis.<sup>13</sup> Overexpression of PLIN2 leads to accumulation of LD in

<sup>1</sup> Department of Cardiology, Chengde Medical University Affiliated Hospital, Chengde, Hebei, China

<sup>2</sup> Central Laboratory of Chengde Medical University Affiliated Hospital, Chengde, Hebei, China

### Corresponding Author:

Lixian Sun, Department of Cardiology, The Affiliated Hospital of Chengde Medical University, Chengde, HeBei, 067000, China.  
Email: lixiansun01@126.com



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use,

reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access page (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

numerous tissues including that of heart.<sup>7</sup> The expression of PLIN2 is also increased in tissues or cells, including foam cell and atherosclerotic plaques, characterized by chronic inflammation.<sup>14</sup> PLIN5 is arguably the most dynamic of the PLIN proteins and is mostly expressed in highly oxidized tissues, such as brown adipose tissue, heart, muscle, and liver tissue.<sup>7</sup> PLIN5 plays an essential role in the regulation of atherogenesis. It might be a new modulator of atherogenesis that suppresses inflammation, apoptosis, and oxidative stress, and thereby, ameliorates the progression of atherogenesis.<sup>15</sup>

Complement component 1q (C1q)/tumor necrosis factor (TNF)-related proteins (CTRPs) are a family of adiponectin (ADP) paralogs, which show the highest expression in adipose tissue around the heart.<sup>16</sup> Recent studies have shown that CTRPs have a role in inflammation regulation, energy metabolism, and insulin signaling.<sup>17</sup> CTRP6, CTRP7, and CTRP11 belong to the same family but each of them has a unique tissue expression profile and assays diverse functions. CTRP6 is a 240-amino acid protein that consists of a signal peptide, a short variable region, a collagen-like region, and a C-terminal globular domain.<sup>18</sup> CTRP6, expressed in adipose tissue, heart, placenta, and brain, modulates metabolism and inflammation.<sup>19</sup> CTRP7 is positively correlated with obesity, glucose and lipid levels, and insulin resistance (IR) and is an independent factor in impaired glucose tolerance (IGT) and type 2 diabetes mellitus (T2DM).<sup>20,21</sup> CTRP11 is highly expressed in the adipose tissue in both human and mice, and is predominantly derived in this tissue from cells of the stromal vascular compartment. CTRP11 can function as an endogenous paracrine regulator of adipocyte differentiation.<sup>22,23</sup>

Wnt1-induced signaling pathway protein 1 (WISP1), a downstream target of Wnt/ $\beta$ -catenin, is a member of the CCN protein family.<sup>24</sup> It plays an important role in the survival, proliferation, and migration of cells.<sup>25,26</sup> In 2015, WISP1 was identified as a novel adipokine secreted from human adipocytes, which was linked to IR and metabolic disorders.<sup>27</sup>

The family with sequence similarity 19 member A5 (FAM19A5) is a novel cytokine that is predominantly expressed in the brain and adipose tissue.<sup>28–30</sup> It can inhibit vascular smooth muscle cell proliferation and migration, and is, therefore, a potential candidate biomarker of cardiovascular diseases.<sup>27</sup>

In this study, we aimed to investigate the association of some new pro- and anti-inflammatory adipocytokines, namely serum PLIN1, PLIN2, PLIN5, CTRP6, CTRP7, CTRP11, WISP1, and FAM19A5 with the development and exacerbation of ACS, and to explore inflammatory biomarkers for diagnosis and risk assessment of ACS in clinical practice.

## Materials and Methods

### Study Population

A total of 168 inpatients with suspected ACS were consecutively enrolled for this study from October 2020 to December 2021 at The Affiliated Hospital of Chengde Medical University, China. They were assigned to the ACS ( $n = 121$ ) and Non-ACS ( $n = 47$ ) groups according to symptoms, and electrocardiography,

laboratory, echocardiography and coronary angiography (CAG) findings. The clinical types of ACS include unstable angina (UA), non-ST-segment elevation myocardial infarction, and acute ST-segment elevation myocardial infarction.

Angiographic ACS is defined as stenosis of  $\geq 50\%$  of one or more of the left main, left anterior descending artery, left circumflex artery, right coronary artery, or their main branches (diameter of vessel  $> 2.0$  mm). This definition also includes patients who underwent previous percutaneous coronary intervention, whereas patients in the Non-ACS group did not have significant luminal stenosis ( $< 50\%$ ) after CAG.<sup>31–33</sup>

The exclusion criteria were as follows: coronary artery spasm or other secondary causes of angina or myocardial infarction, infectious diseases, malignant tumors, severe heart diseases (eg, aortic dissection and hypertrophic cardiomyopathy), muscular disorders (eg, polymyositis and dermatomyositis), encephalitis (eg, viral Encephalitis and autoimmune encephalitis), hepatitis (eg, primary biliary cholangitis and primary sclerosing cholangitis), systemic disease, systemic inflammatory disorders, and hepatic and renal dysfunction. This study was approved by the Institutional Review Board of The Affiliated Hospital of Chengde Medical University, and all participants provided written informed consent before participating.

### Baseline Demographics and Clinical Characteristics

Data on demographics and clinical characteristics, including sex, age, height, weight, body mass index (BMI), history of smoking, dyslipidemia, hypertension, diabetes mellitus (DM), metabolic syndrome (MetS), history of stroke, and family history of coronary artery disease (CAD), were collected by our research team. Systolic blood pressure (SBP), diastolic blood pressure (DBP), routine blood test results, and serum biochemistry parameters, namely total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), albumin (ALB), creatinine (Cr), and homocysteine (Hcy) levels, were also recorded. MetS was defined as the presence of three or more of the following criteria: BMI  $> 30$  kg/m<sup>2</sup>, HDL-C  $< 50$  mg/dL in women and  $< 40$  mg/dL in men, fasting plasma TG  $\geq 150$  mg/dL, SBP  $\geq 130$  mm Hg, DBP  $\geq 85$  mm Hg, fasting plasma glucose (FPG)  $\geq 100$  mg/dL, or previously diagnosed type 2 DM (T2DM).<sup>34</sup>

### Coronary Angiography and Gensini Score

The angiography results were independently evaluated and explained by two experienced interventional cardiologists who were blinded to this study. The severity of coronary artery stenosis was quantitated using the International Gensini score and a guide for score calculation.<sup>35</sup>

### Enzyme-Linked Immunosorbent Assay

Blood samples were drawn from the radial artery of all patients after overnight fasting before the CAR was performed. The blood samples were centrifuged at  $3000 \times g$  for 10 min, and

then stored at  $-80^{\circ}\text{C}$ . The serum levels of PLIN1, PLIN2, PLIN5, CTRP6, CTRP7, CTRP11, WISP1, FAM19A5, TNF- $\alpha$ , and ADP were measured using an enzyme-linked immunosorbent assay (ELISA) kit (Jiangsu Meimian Industrial Co., Ltd, China).

## Statistical Analyses

Statistics analyses were performed using the Statistical Package for the Social Sciences (SPSS) 26.0 (SPSS Inc, Chicago, IL, USA) and GraphPad Prism 8.0 (GraphPad Software Inc., La Jolla, CA). The Kolmogorov–Smirnov test was used to analyze the continuous variables. Continuous variables are expressed as mean  $\pm$  standard deviation (normally distributed data), median and quartile spacing [M (P25–P75)] (non-normally distributed data). To compare the relationship of all continuous variables between the ACS and Non-ACS groups, continuous variables were analyzed using Student's *t*-test in normally distributed data, and Mann–Whitney *U* test in non-normally distributed data. Categorical variables are expressed as frequency and percentages, and were compared using the chi-squared test.

Receiver-operating characteristic (ROC) curves were used to calculate the cutoff value of adipocytokines for diagnosing ACS. Youden's index (sensitivity + specificity – 1) was used to determine the optimal cutoff point. Multivariable logistic regression models were constructed to evaluate the association between serum adipocytokines and ACS in the general population and different subgroups. The odds ratio (OR) was determined based on 1 standard deviation (1-SD) increases in serum adipocytokine levels.

To examine the independent performance of serum adipocytokines for assessing the occurrence of ACS, participants were assigned to three groups (T1, T2, and T3) according to the tertiles of serum adipocytokine levels. We examined the linear trend using *p* for trend, which was calculated using serum adipocytokine tertiles as a continuous variable. Spearman's test was used to analyze the correlations between serum adipocytokines and continuous variables. A Kruskal–Wallis *H* test was used to test for differences between the quartiles groups of the Gensini score. Two-tailed *p*-values  $< 0.05$  were considered significant.

## Results

### Baseline Clinical Characteristics

The baseline clinical characteristics of all the enrolled patients are given in Table 1. The proportion of male patients with dyslipidemia, hypertension, DM, and MetS was higher in the ACS group than that in the Non-ACS group ( $p < 0.05$ ). The percentage of patients with UA (50.4%) was higher in the ACS group than that in the Non-ACS group.

Patients with ACS showed significant differences in white blood cell (WBC) count, TG, HDL-C, ALB, serum uric acid, Hcy, creatine kinase (CK), CK-MB, left ventricular end-systolic diameter (LVESD), and left ventricular ejection fraction (LVEF, all  $p < 0.05$ ). No statistically significant differences were found for other indicators. Coronary stenosis with the involvement of

three-vessels was the most common (present in 38.1% of the patients), as evident from angiographic findings.

Serum levels of PLIN1, PLIN2, CTRP7, CTRP11, WISP1, and TNF- $\alpha$  were significantly higher, whereas those of PLIN5, FAM19A5, CTRP6, and ADP were significantly lower in the ACS group than the corresponding levels in the Non-ACS group (all  $p < 0.05$ , Table 1 and Figure 1).

### ROC Curve Analysis of serum Adipocytokines for Diagnosing ACS

ROC curve analysis was performed to determine the optimal cutoff values of adipocytokines for predicting ACS (Figure 2). The area under the curve (AUC) for PLIN1 was 0.695 (95% confidence interval [CI]: 0.598, 0.793;  $p < 0.05$ ). The optimal diagnostic cutoff value was 373.48 pg/mL, with a sensitivity and specificity of 75.0% and 58.8%, respectively. The AUC for PLIN2 was 0.674 (95% CI: 0.580, 0.768;  $p < 0.05$ ), and the optimal diagnostic cutoff value was 318.20 pg/mL, with a sensitivity and specificity of 32.4% and 100.0%, respectively. The AUC for CTRP7 was 0.662 (95% CI: 0.565, 0.759;  $p < 0.05$ ), and the optimal diagnostic cutoff value was 91.48 pg/mL, with a sensitivity and specificity of 34.3% and 94.9%, respectively. The AUC for CTRP11 was 0.722 (95% CI: 0.629, 0.815;  $p < 0.001$ ), and the optimal diagnostic cutoff value was 45.76 pg/mL, with a sensitivity and specificity of 60.5% and 76.7%, respectively. The AUC for WISP1 was 0.657 (95% CI: 0.556, 0.758;  $p < 0.05$ ), and the optimal diagnostic cutoff value was 222.23 pg/mL, with a sensitivity and specificity of 86.1% and 39.5%, respectively. The AUC for TNF- $\alpha$  was 0.681 (95% CI: 0.565, 0.797;  $p < 0.05$ ), and the optimal diagnostic cutoff value was 285.60 pg/mL, with a sensitivity and specificity of 83.5% and 55.2%, respectively. The AUC of PLIN1, PLIN2, CTRP7, CTRP11, and WISP1 was 0.886 (95% CI: 0.825, 0.947;  $p < 0.001$ ), with a sensitivity and specificity of 71.4% and 96.0%, respectively. The predictive power of these proatherogenic adipocytokines for ACS improved after values for PLIN1, PLIN2, CTRP7, CTRP11, and WISP1 were combined.

The optimal diagnostic cutoff values of PLIN5, CTRP6, FAM19A5, and ADP were 94.43 pg/mL (AUC: 0.682; 95% CI: 0.582, 0.782;  $p < 0.05$ ; sensitivity: 100.0%; specificity: 33.7%), 178.60 pg/mL (AUC: 0.690; 95% CI: 0.600, 0.780;  $p < 0.001$ ; sensitivity: 62.8%, specificity: 70.4%), 208.43 pg/mL (AUC: 0.695; 95% CI: 0.599, 0.792;  $p < 0.001$ ; sensitivity: 37.5%, specificity: 95.8%), 1479.75 pg/mL (AUC: 0.718; 95% CI: 0.622, 0.814;  $p < 0.001$ ; sensitivity: 93.9%; specificity: 43.0%). Furthermore, the predictive power of these antiatherogenic adipocytokines for ACS improved after data for PLIN5, CTRP6, and FAM19A5 were combined (AUC: 0.863; 95% CI: 0.791, 0.934;  $p < 0.001$ ; sensitivity: 75.8%; specificity: 79.5%; Table 2).

### Univariate and Multivariate Logistic Regression Analyses of ACS Risks

Univariate and multivariate analyses were performed using logistic regression models to determine independent predictors

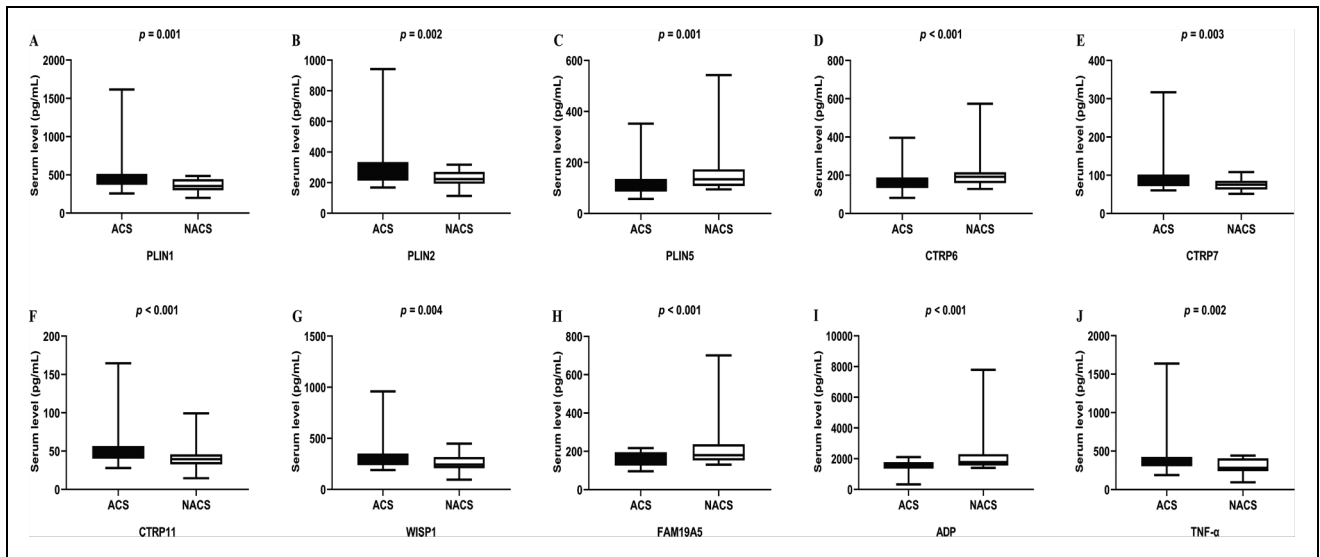
**Table 1.** Baseline Clinical Characteristics of Acute Coronary Syndrome (ACS) and Non-ACS Groups.

Variables	ACS group (n = 121)	Non-ACS group (n = 47)	$\chi^2/Z/t$	p-value
<b>Demographics and clinical data</b>				
Male	76 (62.8)	21 (44.7)	4.559	0.033
Age $\geq 65$ years	34 (28.1)	13 (27.7)	0.003	0.955
BMI	25.48 $\pm$ 3.50	25.39 $\pm$ 2.92	0.155	0.877
Dyslipidemia	72 (64.3)	18 (41.9)	6.417	0.011
Hypertension	97 (80.2)	26 (55.3)	10.656	0.001
Diabetes mellitus	69 (57.0)	10 (21.3)	17.365	<0.001
Smoking	67 (55.4)	20 (42.6)	2.228	0.136
Metabolic syndrome	71 (58.7)	9 (19.1)	21.205	<0.001
History of stroke	26 (21.5)	6 (12.8)	1.670	0.196
Family history of CAD	20 (16.5)	5 (10.6)	0.927	0.336
UA	61 (50.4)			
Non-STEMI	27 (22.3)			
STEMI	33 (27.3)			
<b>Laboratory data</b>				
WBC count ( $10^9/L$ )	8.53 (6.87, 12.10)	7.08 (5.78, 8.93)	-2.964	0.003
Platelet count ( $10^9/L$ )	236.00 (195.00, 289.00)	217.00 (190.25, 269.75)	-1.259	0.208
TC (mmol/L)	3.67 (3.03, 4.45)	3.66 (3.00, 4.24)	-0.264	0.792
TG (mmol/L)	1.49 (0.95, 2.19)	1.13 (0.76, 1.87)	-2.100	0.036
LDL-C (mmol/L)	2.11 (1.59, 2.78)	2.03 (1.54, 2.56)	-0.564	0.573
HDL-C (mmol/L)	1.05 (0.86, 1.25)	1.16 (1.03, 1.38)	-3.296	0.001
ALB (g/L)	40.89 (38.82, 43.19)	42.65 (39.64, 44.96)	-2.401	0.016
Cr ( $\mu\text{mol/L}$ )	68.80 (58.95, 79.43)	63.10 (52.10, 75.40)	-1.651	0.099
Serum uric acid ( $\mu\text{mol/L}$ )	346.75 (279.37, 429.91)	291.43 (256.00, 369.15)	-2.399	0.016
Hcy ( $\mu\text{mol/L}$ )	15.25 (12.08, 18.63)	12.75 (10.15, 16.05)	-2.517	0.012
CK (U/L)	110.00 (70.00, 374.00)	76.00 (57.25, 92.75)	-3.648	<0.001
CK-MB (U/L)	13.24 (9.68, 31.90)	9.89 (8.49, 13.15)	-3.408	0.001
<b>Echocardiography</b>				
LA (mm)	35.0 (33.0, 39.0)	35.0 (32.5, 37.0)	-1.356	0.175
LVEDD (mm)	49.0 (47.0, 54.0)	49.0 (46.0, 51.0)	-1.379	0.168
LVESD (mm)	33.0 (31.0, 37.0)	32.0 (29.0, 34.0)	-2.035	0.042
LVEF (%)	62.0 (55.0, 66.0)	65.0 (59.0, 69.0)	-2.205	0.027
<b>Coronary angiography</b>				
1 vessel	41 (34.8)			
2 vessels	32 (27.1)			
3 vessels	45 (38.1)			
<b>Inflammatory adipocytokines (pg/mL)</b>				
PLIN1	421.48 (370.34, 512.50)	354.43 (298.43, 444.24)	-3.456	0.001
PLIN2	257.85 (213.43, 334.98)	223.00 (193.20, 270.75)	-3.090	0.002
PLIN5	115.70 (86.14, 135.21)	134.23 (107.99, 173.44)	-3.166	0.002
CTRP6	156.95 (133.60, 188.45)	191.50 (158.95, 215.65)	-3.672	<0.001
CTRP7	81.93 (71.84, 101.93)	75.55 (62.80, 85.60)	-2.971	0.003
CTRP11	47.87 (40.33, 56.55)	39.38 (32.78, 45.75)	-4.313	<0.001
WISPI	296.90 (237.65, 350.05)	243.23 (208.26, 316.91)	-2.893	0.004
FAM19A5	158.70 (126.25, 195.70)	179.53 (152.38, 237.05)	-3.578	<0.001
ADP	1544.00 (1362.25, 1781.75)	1779.00 (1550.00, 2292.25)	-3.709	<0.001
TNF- $\alpha$	366.00 (304.68, 424.63)	282.75 (239.25, 405.10)	-3.020	0.003

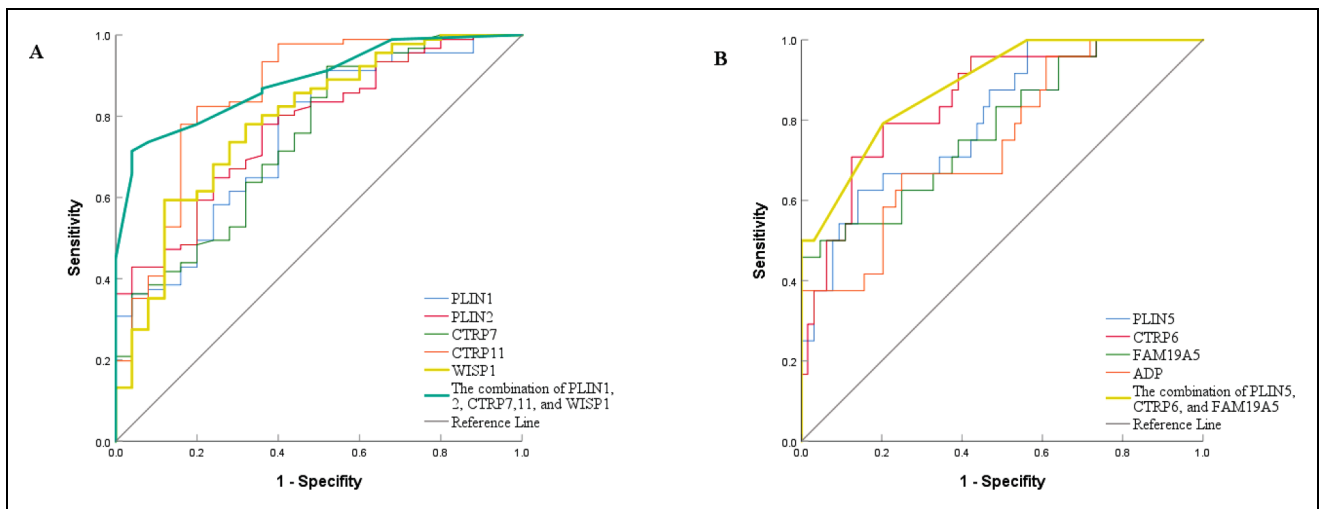
Abbreviations: BMI, body mass index; CAD, coronary artery disease; UA, unstable angina; Non-STEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; WBC, white blood cell; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ALB, albumin; Cr, creatinine; Hcy, homocysteine; CK, creatine kinase; CK-MB, creatine kinase isoenzyme MB; LA, left atrium; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; PLIN, perilipin; CTRP, complement component 1q/tumor necrosis factor-related protein; WISPI, wnt family member 1-inducible signaling pathway protein 1; FAM19A5, family with sequence similarity 19, member A5; ADP, adiponectin; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ .

for ACS, the results of which are presented in Table 3. After adjusting for confounding factors in Model 3, we found that the serum levels of these adipocytokines were independently associated with ACS. The OR of PLIN1, PLIN2, CTRP7,

CTRP11, WISPI, PLIN5, CTRP6, and FAM19A5 expression levels per 1-SD increase were 5.056 (95% CI: 1.266, 20.195;  $p < 0.05$ ), 5.530 (95% CI: 1.418, 21.570;  $p < 0.05$ ), 7.683 (95% CI: 1.604, 36.792;  $p < 0.05$ ), 3.978 (95% CI: 1.528,



**Figure 1.** Comparison of serum adipocytokine levels in acute coronary syndrome (ACS) and Non-ACS groups. (A) PLIN1, (B) PLIN2, (C) PLIN5, (D) CTRP6, (E) CTRP7, (F) CTRP11, (G) WISP1, (H) FAM19A5, (I) ADP, and (J) TNF- $\alpha$ .



**Figure 2.** Receiver operating characteristic (ROC) curves of (A) proinflammatory and (B) anti-inflammatory adipocytokines for predicting acute coronary syndrome (ACS).

10.356;  $p < 0.05$ ), 2.586 (95% CI: 1.048, 6.382;  $p < 0.05$ ), 0.472 (95% CI: 0.232, 0.957;  $p < 0.05$ ), 0.592 (95% CI: 0.361, 0.972;  $p < 0.05$ ), and 0.236 (95% CI: 0.070, 0.800;  $p < 0.05$ ). Surprisingly, CTRP7 and FAM19A5 had a greater impact on ACS than the other serum adipocytokines.

The association between the tertiles of the serum levels of adipocytokines and ACS is shown in Table 4. The risk of ACS increased gradually with rising PLIN1 tertiles (OR [95% CI]: T1: reference, T2: 8.358 [2.005, 34.834], T3: 3.814 [1.118, 13.016];  $p$  for trend  $< 0.05$ ) and CTRP11 tertiles (OR [95% CI]: T1: reference, T2: 4.070 [1.375, 12.046], T3: 6.985 [2.130, 22.906];  $p$  for trend  $< 0.05$ ). Furthermore, the increased risk of ACS was significantly associated with

elevated levels of PLIN2, CTRP7, and WISP1 ( $p$  for trend  $< 0.05$ ). In contrast, the risk of ACS decreased gradually with rising CTRP6 tertiles (OR [95% CI]: T1: reference, T2: 0.220 [0.057, 0.841], T3: 0.093 [0.024, 0.369];  $p$  for trend  $< 0.05$ ). Moreover, increasing PLIN5 levels were significantly associated with reduced risk of ACS ( $p$  for trend  $< 0.05$ ).

### Correlation Analysis of serum Adipocytokines and ACS Severity

The serum levels of PLIN1, CTRP7, CTRP11, and WISP1 were positively correlated, whereas those of PLIN5, CTRP6, and

FAM19A5 were negatively correlated with the Gensini score ( $p < 0.05$ ; Table 5).

The patients were categorized into four quartiles according to the Gensini score (Figure 3), Q1 ( $n = 44$ , Gensini score  $\leq 25.5$ ), Q2 ( $n = 40$ ,  $25.6 < \text{Gensini score} \leq 37.8$ ), Q3 ( $n = 42$ ,  $37.9 < \text{Gensini score} \leq 57.0$ ), and Q4 ( $n = 42$ , Gensini score  $> 57.1$ ). The levels of PLIN1 and CTRP11 were increased

across the quartiles of the Gensini score. In addition, the levels of PLIN5, CTRP6, and FAM19A5 showed a decreasing trend across the quartiles of the Gensini score ( $p < 0.05$ , Figure 3).

## Discussion

In the present study, we investigated the association between serum levels of PLIN1, PLIN2, PLIN5, CTRP6, CTRP7, CTRP11, WISPI, FAM19A5 and ACS. To the best of our knowledge, this is the first study to elucidate and compare the diagnostic performance of these adipocytokines for ACS. The major findings of our study are as follows: (1) The selected serum adipocytokines, as proinflammatory or anti-inflammatory adipokines, are independent predictors for the diagnosis of ACS; (2) Increasing levels of PLIN1, PLIN2, CTRP6, CTRP7, CTRP11, and WISPI show a linear trend with the risk of ACS; (3) Serum levels of PLIN1, PLIN5, CTRP6, CTRP7, CTRP11, WISPI, and FAM19A5 correlate with the severity of ACS.

Atherosclerosis, which is the leading cause of ACS, is a complex process and its development involves lipids, immune cells, vascular smooth muscle cells (VSMCs), and various adipokines.<sup>36</sup> Thus, PLIN1, PLIN2, PLIN5, CTRP6, CTRP7, CTRP11, WISPI, and FAM19A5 can affect atherosclerotic plaques through different mechanisms.

Notably, the major isoforms of PLIN1 (PLIN1a), PLIN2, and PLIN5 preferentially associate with LDs enriched in triacylglycerol (TAG), whereas the minor isoforms of PLIN1 (PLIN1c and PLIN1d) preferentially associate with LDs enriched in cholesterol ester (CE).<sup>12</sup> Under basal conditions, the binding of PLIN1 to CGI58 blocks the access of cytosolic lipases (adipose triglyceride lipase [ATGL] and hormone-sensitive lipase [HSL]) to lipid droplets and interacts with the CIDE-N domain of fat-specific protein 27 to promote lipid-droplet formation, thereby, facilitating TG storage.<sup>13</sup> A key factor in the pathogenesis of atherosclerosis is the modification of macrophages into foam cells due to massive accumulation of LDs).

**Table 2.** Receiver Operating Characteristic (ROC) Curve Analysis of Proinflammatory and Anti-Inflammatory Adipocytokines for Diagnosing Acute Coronary Syndrome (ACS).

Variables	AUC	95% CI	p-value	Se (%)	Sp (%)	Cut-off
<b>Proatherogenic adipocytokines (pg/mL)</b>						
PLIN1	0.695	0.598, 0.793	0.001	75.0	58.8	373.48
PLIN2	0.674	0.580, 0.768	0.002	32.4	100.0	318.20
CTRP7	0.662	0.565, 0.759	0.003	34.3	94.9	91.48
CTRP11	0.722	0.629, 0.815	<0.001	60.5	76.7	45.76
WISPI	0.657	0.556, 0.758	0.004	86.1	39.5	222.23
TNF- $\alpha$	0.681	0.565, 0.797	0.003	83.5	55.2	285.60
Combination of PLIN1, 2, CTRP7, 11, and WISPI	0.886	0.825, 0.947	<0.001	71.4	96.0	–
<b>Anti-atherogenic adipocytokines (pg/mL)</b>						
PLIN5	0.682	0.582, 0.782	0.002	100.0	33.7	94.43
CTRP6	0.690	0.600, 0.780	<0.001	62.8	70.4	178.60
FAM19A5	0.695	0.599, 0.792	<0.001	37.5	95.8	208.43
ADP	0.718	0.622, 0.814	<0.001	93.9	43.0	1479.75
Combination of PLIN5, CTRP6, and FAM19A5	0.863	0.791, 0.934	<0.001	75.8	79.5	–

Abbreviations: PLIN, perilipin; CTRP, complement component 1q/tumor necrosis factor-related protein; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; FAM19A5, family with sequence similarity 19, member A5; WISPI, wnt family member 1-inducible signaling pathway protein 1; ADP, adiponectin; AUC, area under curve; CI, confidence interval; Se, sensitivity; Sp, specificity.

**Table 3.** Logistic Regression Models of Acute Coronary Syndrome (ACS) Risks According to 1-Standard Deviation (SD) Increase in serum Adipocytokine Levels.

Serum adipocytokines (per 1-SD increase)	Model 1		Model 2		Model 3	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
PLIN1	6.040 (2.052, 17.778)	0.001	5.246 (1.339, 20.554)	0.017	5.056 (1.266, 20.195)	0.022
PLIN2	4.433 (1.696, 11.586)	0.002	6.006 (1.545, 23.351)	0.010	5.530 (1.418, 21.570)	0.014
CTRP7	4.984 (1.676, 14.822)	0.004	7.578 (1.655, 34.691)	0.009	7.683 (1.604, 36.792)	0.011
CTRP11	3.679 (1.659, 8.156)	0.001	4.014 (1.557, 10.347)	0.004	3.978 (1.528, 10.356)	0.005
WISPI	2.843 (1.351, 5.986)	0.006	2.695 (1.109, 6.550)	0.029	2.586 (1.048, 6.382)	0.039
PLIN5	0.449 (0.267, 0.756)	0.003	0.496 (0.257, 0.954)	0.036	0.472 (0.232, 0.957)	0.037
CTRP6	0.544 (0.373, 0.792)	0.002	0.616 (0.383, 0.989)	0.045	0.592 (0.361, 0.972)	0.038
FAM19A5	0.213 (0.086, 0.526)	0.001	0.233 (0.069, 0.783)	0.019	0.236 (0.070, 0.800)	0.020

Model 1: Unadjusted.

Model 2: Adjusted for sex, age, BMI, heart rate at admission, blood pressure at admission, smoking, dyslipidemia, hypertension, DM.

Model 3: Adjusted for terms in Model 2 and MetS, history of stroke, family history of CAD.

Abbreviations: SD, standard deviation; CI, confidence interval; OR, odds ratio; PLIN, perilipin; CTRP, C1q/TNF-related protein; WISPI, wnt family member 1-inducible signaling pathway protein 1; FAM19A5, family with sequence similarity 19, member A5; BMI, body mass index; DM, diabetes mellitus; MetS, metabolic syndrome; CAD, coronary artery disease.

**Table 4.** Logistic Regression Models of Acute Coronary Syndrome (ACS) Risks According to Tertiles of serum Adipocytokine Levels.

Serum adipocytokines		Model 1		Model 2		Model 3	
(tertiles 1-3)		OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
PLIN1	T1	1 (Reference)	-	1 (Reference)	-	1 (Reference)	-
	T2	4.000 (1.501, 10.658)	0.006	8.487 (2.042, 35.284)	0.003	8.358 (2.005, 34.834)	0.004
	T3	4.190 (1.576, 11.141)	0.004	3.986 (1.190, 13.356)	0.025	3.814 (1.118, 13.016)	0.033
	p for trend	0.002		0.023		0.029	
PLIN2	T1	1 (Reference)	-	1 (Reference)	-	1 (Reference)	-
	T2	1.346 (0.561, 3.229)	0.505	1.562 (0.515, 4.742)	0.431	1.501 (0.492, 4.575)	0.475
	T3	3.417 (1.200, 9.724)	0.021	5.139 (1.267, 20.847)	0.022	4.759 (1.166, 19.416)	0.030
	p for trend	0.022		0.023		0.032	
CTRP7	T1	1 (Reference)	-	1 (Reference)	-	1 (Reference)	-
	T2	1.133 (0.480, 2.676)	0.775	1.502 (0.454, 4.973)	0.505	1.390 (0.407, 4.752)	0.599
	T3	3.400 (1.254, 9.216)	0.016	6.485 (1.613, 26.077)	0.008	6.615 (1.562, 28.014)	0.010
	p for trend	0.018		0.009		0.012	
CTRP11	T1	1 (Reference)	-	1 (Reference)	-	1 (Reference)	-
	T2	3.055 (1.301, 7.173)	0.010	3.738 (1.293, 10.811)	0.015	4.070 (1.375, 12.046)	0.011
	T3	4.700 (1.869, 11.817)	0.001	6.740 (2.091, 21.722)	0.001	6.985 (2.130, 22.906)	0.001
	p for trend	0.001		0.001		0.001	
WISPI	T1	1 (Reference)	-	1 (Reference)	-	1 (Reference)	-
	T2	2.375 (0.970, 5.817)	0.058	6.015 (1.732, 20.882)	0.005	6.449 (1.832, 22.701)	0.004
	T3	2.837 (1.135, 7.087)	0.026	3.225 (1.080, 9.631)	0.036	2.953 (0.971, 8.985)	0.056
	p for trend	0.021		0.028		0.039	
PLIN5	T1	1 (Reference)	-	1 (Reference)	-	1 (Reference)	-
	T2	0.561 (0.193, 1.632)	0.289	0.957 (0.249, 3.680)	0.950	1.075 (0.270, 4.287)	0.918
	T3	0.252 (0.090, 0.701)	0.008	0.295 (0.082, 1.065)	0.062	0.295 (0.081, 1.078)	0.065
	p for trend	0.007		0.047		0.048	
CTRP6	T1	1 (Reference)	-	1 (Reference)	-	1 (Reference)	-
	T2	0.356 (0.125, 1.013)	0.053	0.270 (0.074, 0.989)	0.048	0.220 (0.057, 0.841)	0.027
	T3	0.161 (0.059, 0.442)	<0.001	0.134 (0.037, 0.486)	0.002	0.093 (0.024, 0.369)	0.001
	p for trend	<0.001		0.002		0.001	
FAM19A5	T1	1 (Reference)	-	1 (Reference)	-	1 (Reference)	-
	T2	0.279 (0.097, 0.800)	0.018	0.382 (0.100, 1.466)	0.161	0.347 (0.089, 1.350)	0.127
	T3	0.231 (0.081, 0.657)	0.006	0.319 (0.088, 1.156)	0.082	0.316 (0.087, 1.146)	0.080
	p for trend	0.007		0.096		0.098	

Model 1: Unadjusted.

Model 2: Adjusted for sex, age, BMI, heart rate at admission, blood pressure at admission, smoking, dyslipidemia, hypertension, DM.

Model 3: Adjusted for terms in Model 2 and MetS, history of stroke, family history of CAD.

Abbreviations: OR, odds ratio; CI, confidence interval; PLIN, perilipin; CTRP, C1q/TNF-related protein; WISPI, wnt family member 1-inducible signaling pathway protein 1; FAM19A5, family with sequence similarity 19, member A5; BMI, body mass index; DM, diabetes mellitus; MetS, metabolic syndrome; CAD, coronary artery disease.

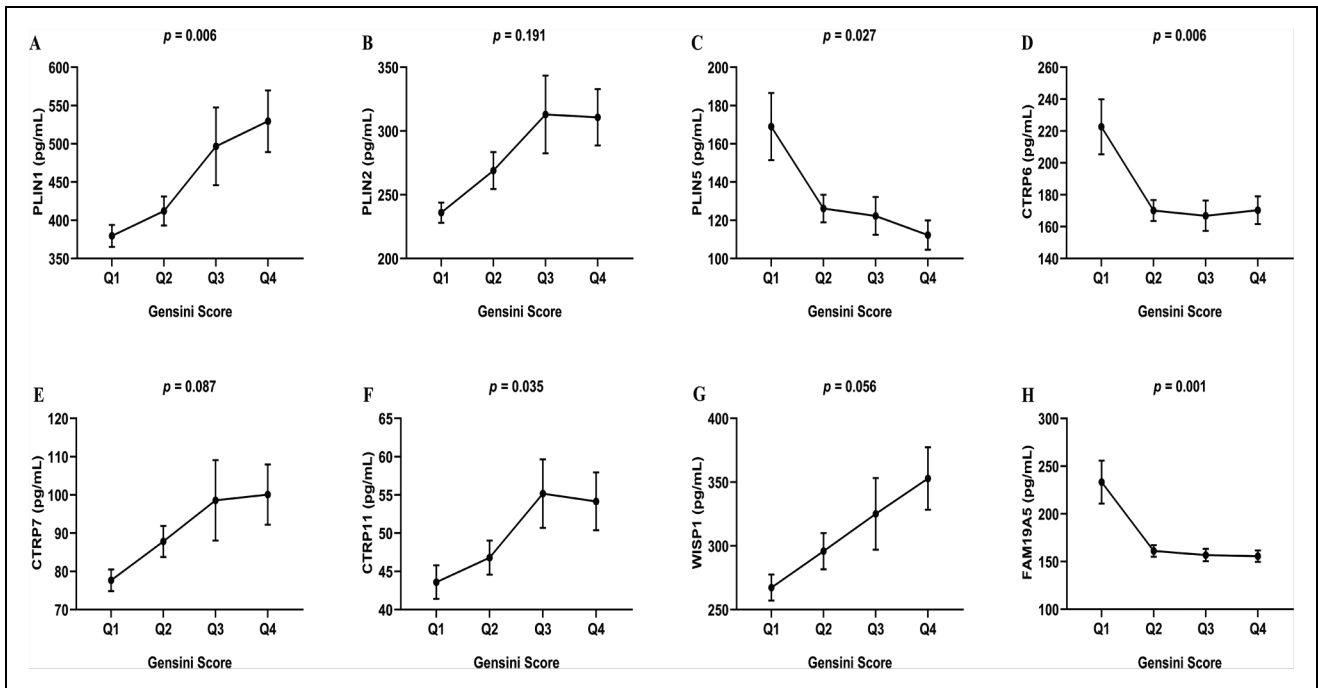
**Table 5.** Correlation Analysis of serum Adipocytokines and Gensini Score.

Serum adipocytokines (pg/mL)	Gensini score	
	r	p-value
PLIN1	0.267	0.001
PLIN2	0.154	0.066
CTRP7	0.184	0.029
CTRP11	0.216	0.006
WISPI	0.182	0.024
PLIN5	-0.275	0.002
CTRP6	-0.257	0.001
FAM19A5	-0.284	0.001

Abbreviations: r, coefficient of correlation; PLIN, perilipin; CTRP, C1q/TNF-related protein; WISPI, wnt family member 1-inducible signaling pathway protein 1; FAM19A5, family with sequence similarity 19, member A5.

Upon the death of foam cells, their atherosclerotic contents are released, which can lead to plaque rupture and thrombotic vessel occlusion. PLIN2 is the main LD-coating protein in macrophages and foam cells, the levels of which are even higher in unstable atherosclerotic plaques.<sup>37</sup> We show that PLIN1 and PLIN2 are independent risk factors for ACS; increasing tertiles of their serum levels, significantly increased the ACS risk, further indicating the proinflammatory effects of these adipocytokines.

We demonstrate that the serum levels of CTRP7 and CTRP11 in the ACS group were higher than those in the Non-ACS group, and their elevated serum levels were associated with an increased risk of ACS. In a previous study, it was shown that CTRP7 deficiency attenuated IR and enhanced glucose tolerance and that these effects were independent of body weight, metabolic rate, and physical activity level.



**Figure 3.** Comparison of serum adipocytokine levels between different groups according to Gensini score quartiles. (A) PLIN1, (B) PLIN2, (C) PLIN5, (D) CTRP6, (E) CTRP7, (F) CTRP11, (G) WISP1, and (H) FAM19A5. Data are means  $\pm$  standard error of the mean (SEM).

Improved glucose metabolism in CTRP7-deficient mice was associated with reduced adipose tissue inflammation, as well as with decreased liver fibrosis and oxidative and endoplasmic reticulum stress. This suggests that CTRP7 is a secreted regulator of inflammation and cellular stress, as well as of whole body insulin sensitivity and glucose metabolism.<sup>21</sup> Ectopic expression of CTRP11 in 3T3-L1 cells inhibited the differentiation of adipocytes by suppressing the expression of peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ) and CCAAT-enhancer binding proteins- $\alpha$  (C/EBP- $\alpha$ ), two critical transcriptional regulators of adipogenesis, and genes involved in the metabolism and formation of LDs.<sup>22</sup>

In this study, we found that the concentration of WISP1 was significantly higher in the ACS group than it was in the Non-ACS group and that the risk of ACS increased with increasing WISP1 levels. Based on the findings in previous studies, this could be attributable to the fact that WISP1 promotes adipose inflammation responses via the regulation of macrophage polarization and migration.<sup>38</sup> Mechanistically, macrophages are by far the most abundant immune cells in the adipose tissue.<sup>39</sup> Epicardial adipose tissue (EAT) is a rich source of macrophages, neutrophils, and lymphocytes. The macrophage population in the fat depot mainly consists of proinflammatory M1 and anti-inflammatory M2 macrophages. Adipokines released from the adipose tissue influence macrophage polarization. EAT can be a major source of M1 macrophages during cardiac injury. Activated M1 macrophages create an inflammatory milieu within the fat pad by secreting proinflammatory cytokines, which compromise the functioning of the adipose tissue. On the contrary, EAT plays a protective

role in a healthy heart by providing it with fatty acids for energy or conversely serves as a buffer for lipid overload. Macrophages polarized toward the M2 phenotype play a role in improving metabolism.<sup>21,40</sup> Notably, we found that the diagnostic performance of CTRP7 as a predictive factor for ACS was significantly higher than that of PLIN1, PLIN2, CTRP11, and WISP1.

CTRP6 is a recently discovered superfamily member of the adipogenic complement C1q/TNF-related protein (CTRP) family, which is structurally homologous to adiponectin.<sup>41</sup> Based on our experimental results, the concentration of CTRP6 was significantly lower in the ACS group than it was in the Non-ACS group and the risk of ACS decreased with increasing CTRP6 levels. Thus, we infer that the biological activities of CTRP6 are similar to those of ADP. In rodents, CTRP6 can improve PPAR- $\gamma$  activation and relieve angiotensin-II-induced hypertension and vascular endothelial dysfunction in spontaneously hypertensive rats.<sup>42</sup> Lei et al reported that CTRP6 was mainly expressed in adult rat cardiomyocytes and that its levels were significantly decreased in the infarct ventricle post-MI.<sup>19</sup> These results suggest that CTRP6 has certain protective anti-inflammatory and antifibrotic effects post-MI. Contrary to our findings, those of Liao et al suggest that overweight/obese (OW/OB) adults have an increased concentration of circulating CTRP6. They observed a positive correlation of circulating CTRP6 with the percentage of fat (Fat%), BMI, and waist hip ratio (WHR) in their study population. The discrepancies between the results of these studies could be attributable to the exclusion of cardiovascular disease (CVD) and T2DM patients in the study of Liao et al<sup>43</sup> Furthermore, the sample size may



be the main reason for the difference. Finally, the discrepancy could also be attributable to the use of different ELISA kits for detection of CTRP6. Thus, more clinical studies are necessary to obtain accurate results.

PLIN5 was reported to be the key factor in regulating the contact of LDs with mitochondria. PLIN5 could reduce cellular levels of reactive oxygen species (ROS) and cell apoptosis.<sup>44</sup> PLIN5 plays an important role in promoting and stabilizing cardiac LDs by increasing the levels of other perilipin proteins.<sup>45</sup> PLIN5 knockout could increase the degree of aortic atherosclerosis in mice.<sup>15</sup> The abovementioned studies indicate that PLIN5 might be involved in the regulation of inflammation and protects against atherogenesis both *in vivo* and *in vitro*. In summary, PLIN5 plays a protective role against atherosclerosis development, which is consistent with our findings that elevated levels of PLIN5 are independent protective factors for ACS.

We also show that elevated serum FAM19A5 level is an independent protective factor for ACS. The diagnostic performance of FAM19A5, which plays an antiatherosclerosis role, was significantly higher than that of CTRP6 and PLIN5. In an *in vitro* test, FAM19A5 was shown to inhibit the proliferation and migration of VSMCs and the formation of neointima via sphingosine-1-phosphate receptor 2-G12/13-RhoA signaling.<sup>28</sup> Furthermore, an association between FAM19A5 and neurodegenerative changes has been reported for major depressive disorder.<sup>46</sup> Interestingly, Lee et al reported that serum FAM19A5 concentrations were greater in patients with type 2 diabetes compared with those in non-diabetic subjects. Mechanistically, we speculated that increased serum FAM19A5 concentrations in DM patients may originate from compensatory upregulation of FAM19A5 to overcome cardiometabolic stress or resistance to FAM19A5, similar to hyperinsulinemia in IR states.<sup>47</sup> Likewise, circulating FAM19A5 concentration may vary with the ACS phase. In summary, additional research is needed to elucidate the association between FAM19A5 and patients with ACS.

To the best of our knowledge, ADP and TNF- $\alpha$  are classical adipocytokines associated with CVD.<sup>4,48–50</sup> The proinflammatory cytokines, PLIN1, PLIN2, CTRP7, CTRP11, and WISP1, and the anti-inflammatory cytokines, PLIN5, CTRP6, FAM19A5, have significant diagnostic and risk predictive value for ACS same as that of TNF- $\alpha$  and ADP.

In this study, the serum levels of PLIN1, PLIN5, CTRP6, CTRP7, CTRP11, WISP1, and FAM19A5 showed a weak correlation with the Gensini score. The proinflammatory cytokines, PLIN1, CTRP7, and CTRP11, and the anti-inflammatory cytokines, PLIN5, CTRP6, and FAM19A5, showed an apparently increasing or decreasing trend with the Gensini score quartiles. In contrast to previous studies, which used the number of lesion vessels, we used the Gensini score to systemically evaluate the association between serum levels of adipocytokines and the severity of ACS. This suggests the potential usefulness of proinflammatory cytokines, PLIN1, CTRP7, and CTRP11, and anti-inflammatory cytokines, PLIN5, CTRP6, and FAM19A5 in assessing the severity of ACS.

## Limitations

Several limitations of this study should be acknowledged. First, in view of the case–control design of this study, clarification of causality was inherently limited. Second, the inpatients were from a single center, and they may not represent the general Chinese population. Third, the serum levels of adipocytokines were evaluated only once after the patients were admitted, and information on the change in levels during hospitalization was limited. More large-scale prospective studies should be conducted to validate the diagnostic significance of PLIN1, PLIN2, PLIN5, CTRP6, CTRP7, CTRP11, WISP1, and FAM19A5 in patients with ACS.

## Conclusion

In this study, we discovered that PLIN1, PLIN2, PLIN5, CTRP6, CTRP7, CTRP11, WISP1, and FAM19A5, as risk or protective factors, are independently associated with ACS. Specifically, PLIN1, PLIN2, CTRP7, CTRP11, and WISP1 were identified as independent risk factors for ACS, whereas PLIN5, CTRP6, and FAM19A5 were independent protective factors for ACS. Moreover, PLIN1, PLIN5, CTRP6, CTRP7, CTRP11, and FAM19A5 were found to be more closely correlated with the severity of ACS than were PLIN2 and WISP1. PLIN1, PLIN2, PLIN5, CTRP6, CTRP7, CTRP11, WISP1, and FAM19A5 have the potential to serve as novel diagnostic biomarkers and future therapeutic targets for ACS in clinical practice.

## Acknowledgments

The authors acknowledge the cardiologists and laboratory staff at the Affiliated Hospital of Chengde Medical University who contributed to this study.

## Authors' Note

Ethical approval was obtained from the Institutional Review Board of The Affiliated Hospital of Chengde Medical University (Number: LL2021036). Written informed consent was obtained from the patients for their anonymized information to be published in this article.


## Declaration of Conflicting Interests


The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.



## Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by Natural Science Foundation of Hebei Province (Grant numbers H2021406071) to Dr. Lixian Sun.

## ORCID iDs

Yixiang Liu  <https://orcid.org/0000-0001-7185-0369>

Zhenjiang Ding  <https://orcid.org/0000-0002-1243-8419>

Wenjun Fan  <https://orcid.org/0000-0002-9760-4331>  
Lixian Sun  <https://orcid.org/0000-0001-9814-0965>

## References

- Bergmark BA, Mathenge N, Merlini PA, Lawrence-Wright MB. Acute coronary syndromes. *Lancet*. 2022;399(10332):1347-1358. doi:10.1016/S0140-6736(21)02391-6
- Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics-2022 update: A report from the American Heart Association. *Circulation*. 2022;145(8):e153-e639. doi:10.1161/CIR.0000000000001052
- Libby P, Buring JE, Badimon L, et al. Atherosclerosis. *Nat Rev Dis Primers*. 2019;5(1):56. doi:1038/s41572-019-0106-z
- Cypess AM. Reassessing human adipose tissue. *N Engl J Med*. 2022;386(8):768-779.
- Neeland IJ, Ross R, Després J-P, et al. Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: A position statement. *Lancet Diabetes Endocrinol*. 2019;7(9):715-725. doi:10.1016/S2213-8587(19)30084-1
- Sakers A, De Siqueira MK, Seale P, Villanueva CJ. Adipose-tissue plasticity in health and disease. *Cell*. 2022;185(3):419-446. doi:10.1016/j.cell.2021.12.016
- Mourouzis K, Oikonomou E, Siasos G, et al. Pro-inflammatory cytokines in acute coronary syndromes. *Curr Pharm Des*. 2020;26(36):4624-4647. doi:10.2174/138161282666200413082353
- Nadimi Shahrazi Z, Azimi H, Ilchi N, et al. Circulating C1q/TNF-related protein-12 levels are associated with the severity of coronary artery disease. *Cytokine*. 2021;144:155545. doi:10.1016/j.cyto.2021.155545
- Rohm TV, Meier DT, Olefsky JM, Donath MY. Inflammation in obesity, diabetes, and related disorders. *Immunity*. 2022;55(1):31-55. doi:10.1016/j.immuni.2021.12.013
- Zorena K, Jachimowicz-Duda O, Ślęzak D, Robakowska M, Mrugacz M. Adipokines and obesity. Potential link to metabolic disorders and chronic complications. *Int J Mol Sci*. 2020;21(10):3570. doi:10.3390/ijms21103570
- Greenberg AS, Egan JJ, Wek SA, Garty NB, Blanchette-Mackie EJ, Londos C. Perilipin, a major hormonally regulated adipocyte-specific phosphoprotein associated with the periphery of lipid storage droplets. *J Biol Chem*. 1991;266(17):11341-11346.
- Najt CP, Devarajan M, Mashek DG. Perilipins at a glance. *J Cell Sci*. 2022;135(5):jcs259501. doi:10.1242/jcs.259501
- Ding Y, Wang H, Geng B, Xu G. Sulfhydration of perilipin 1 is involved in the inhibitory effects of cystathionine gamma lyase/hydrogen sulfide on adipocyte lipolysis. *Biochem Biophys Res Commun*. 2020;521(3):786-790. doi:10.1016/j.bbrc.2019.10.192
- Paul A, Chang BH, Li L, Yechoor VK, Chan L. Deficiency of adipose differentiation-related protein impairs foam cell formation and protects against atherosclerosis. *Circ Res*. 2008;102(12):1492-1501. doi:10.1161/CIRCRESAHA.107.168070
- Zhou PL, Li M, Han XW, et al. Perilipin 5 deficiency promotes atherosclerosis progression through accelerating inflammation, apoptosis, and oxidative stress. *J Cell Biochem*. 2019;120(11):19107-19123. doi:10.1002/jcb.29238
- Si Y, Fan W, Sun L. A review of the relationship between CTRP family and coronary artery disease. *Curr Atheroscler Rep*. 2020;22(6):22. doi:10.1007/s11883-020-00840-0
- Shanaki M, Shabani P, Goudarzi A, Omidifar A, Bashash D, Emamgholipour S. The C1q/TNF-related proteins (CTRPs) in pathogenesis of obesity-related metabolic disorders: Focus on type 2 diabetes and cardiovascular diseases. *Life Sci*. 2020;256:117913. doi:10.1016/j.lfs.2020.117913
- Lee W, Kim MJ, Park EJ, Choi YJ, Park SY. C1q/TNF-related protein-6 mediates fatty acid oxidation via the activation of the AMP-activated protein kinase. *FEBS Lett*. 2010;584(5):968-972. doi:10.1016/j.febslet.2010.01.040
- Lei H, Wu D, Wang JY, et al. C1q/tumor necrosis factor-related protein-6 attenuates post-infarct cardiac fibrosis by targeting RhoA/MRTF-A pathway and inhibiting myofibroblast differentiation. *Basic Res Cardiol*. 2015;110(4):35. doi:10.1007/s00395-015-0492-7
- Li K, Liang Z, Xu W, et al. CTRP7 Is a biomarker related to insulin resistance and oxidative stress: Cross-sectional and intervention studies in vivo and in vitro. *Oxid Med Cell Longev*. 2022;2022:6877609. doi:10.1155/2022/6877609
- Petersen PS, Lei X, Wolf RM, et al. CTRP7 Deletion attenuates obesity-linked glucose intolerance, adipose tissue inflammation, and hepatic stress. *Am J Physiol Endocrinol Metab*. 2017;312(4):E309-E325. doi:10.1152/ajpendo.00344.2016
- Wei Z, Seldin MM, Natarajan N, Djemal DC, Peterson JM, Wong GW. C1q/tumor necrosis factor-related protein 11 (CTRP11), a novel adipose stroma-derived regulator of adipogenesis. *J Biol Chem*. 2013;288(15):10214-10229. doi:10.1074/jbc.M113.458711
- Sarver DC, Xu C, Carreno D, et al. CTRP11 Contributes modestly to systemic metabolism and energy balance. *FASEB J*. 2022;36(6):e22347. doi:10.1096/fj.202200189RR
- Berschneider B, Königshoff M. WNT1 Inducible signaling pathway protein 1 (WISP1): A novel mediator linking development and disease. *Int J Biochem Cell Biol*. 2011;43(3):306-309. doi:10.1016/j.biocel.2010.11.013
- Deng W, Fernandez A, McLaughlin SL, Klinke DJ2nd. WNT1-inducible Signaling pathway protein 1 (WISP1/CCN4) stimulates melanoma invasion and metastasis by promoting the epithelial-mesenchymal transition. *J Biol Chem*. 2019;294(14):5261-5280. doi:10.1074/jbc.RA118.006122
- Venkatachalam K, Venkatesan B, Valente AJ, et al. WISP1, A pro-mitogenic, pro-survival factor, mediates tumor necrosis factor-alpha (TNF-alpha)-stimulated cardiac fibroblast proliferation but inhibits TNF-alpha-induced cardiomyocyte death. *J Biol Chem*. 2009;284(21):14414-14427. doi:10.1074/jbc.M809757200
- Hörbelt T, Tacke C, Markova M, et al. The novel adipokine WISP1 associates with insulin resistance and impairs insulin action in human myotubes and mouse hepatocytes. *Diabetologia*. 2018;61(9):2054-2065. doi:10.1007/s00125-018-4636-9
- Wang Y, Chen D, Zhang Y, et al. Novel adipokine, FAM19A5, inhibits neointima formation after injury through sphingosine-1-phosphate receptor 2. *Circulation*. 2018;138(1):48-63. doi:10.1161/CIRCULATIONAHA.117.032398

29. Zarzour A, Kim HW, Weintraub NL. Understanding obesity-related cardiovascular disease: It's all about balance. *Circulation*. 2018;138(1):64-66. doi:10.1161/CIRCULATIONAHA.118.034454
30. Tom Tang Y, Emtage P, Funk WD, et al. TAFAs: A novel secreted family with conserved cysteine residues and restricted expression in the brain. *Genomics*. 2004;83(4):727-734. doi:10.1016/j.ygeno.2003.10.006
31. Ibanez B, James S, Agewall S, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39(2):119-177. doi:10.1093/eurheartj/ehx393
32. Collet JP, Thiele H, Barbato E, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2021;42(14):1289-1367. doi:10.1093/eurheartj/ehaa575
33. Gulati M, Levy PD, Mukherjee D, et al. 2021 AHA/ACC/AASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain: A report of the American college of cardiology/American heart association joint committee on clinical practice guidelines. *Circulation*. 2021;144(22):e368-e454. doi:10.1161/CIR.0000000000001029
34. Ebrahimi H, Emamian MH, Khosravi A, Hashemi H, Fotouhi A. Comparison of the accuracy of three diagnostic criteria and estimating the prevalence of metabolic syndrome: A latent class analysis. *J Res Med Sci*. 2019;24:108. doi:10.4103/jrms.JRMS\_858\_18
35. Rampidis GP, Benetos G, Benz DC, Giannopoulos AA, Buechel RR. A guide for Gensini Score calculation. *Atherosclerosis*. 2019;287:181-183. doi:10.1016/j.atherosclerosis.2019.05.012
36. Roy P, Orecchioni M, Ley K. How the immune system shapes atherosclerosis: Roles of innate and adaptive immunity. *Nat Rev Immunol*. 2022;22(4):251-265. doi:10.1038/s41577-021-00584-1
37. Conte M, Franceschi C, Sandri M, Salvioi S. Perilipin 2 and age-related metabolic diseases: A new perspective. *Trends Endocrinol Metab*. 2016;27(12):893-903. doi:10.1016/j.tem.2016.09.001
38. Cheng Y, Du X, Zhang B, Zhang J. Increased serum WISP1 levels are associated with lower extremity atherosclerotic disease in patients with Type 2 diabetes mellitus. *Exp Clin Endocrinol Diabetes*. 2022;130(4):248-253. doi:10.1055/a-1474-8220
39. Kohlgruber AC, LaMarche NM, Lynch L. Adipose tissue at the nexus of systemic and cellular immunometabolism. *Semin Immunol*. 2016;28(5):431-440. doi:10.1016/j.smim.2016.09.005
40. Mouton AJ, Li X, Hall ME, Hall JE. Obesity, hypertension, and cardiac dysfunction: Novel roles of immunometabolism in macrophage activation and inflammation. *Circ Res*. 2020;126(6):789-806. doi:10.1161/CIRCRESAHA.119.312321
41. Liu J, Yan X, Wang Z, Zhang N, Lin A, Li Z. Adipocyte factor CTRP6 inhibits homocysteine-induced proliferation, migration, and dedifferentiation of vascular smooth muscle cells through PPARgamma/NLRP3. *Biochem Cell Biol*. 2021;99(5):596-605. doi:10.1139/bcb-2020-0670
42. Chi L, Hu X, Zhang W, et al. Adipokine CTRP6 improves PPARγ activation to alleviate angiotensin II-induced hypertension and vascular endothelial dysfunction in spontaneously hypertensive rats. *Biochem Biophys Res Commun*. 2017;482(4):727-734. doi:10.1016/j.bbrc.2016.11.102
43. Liao X, Liu S, Tang X, et al. Circulating CTRP6 levels are increased in overweight or obese Chinese individuals and associated with insulin resistance parameters: A pilot study. *Exp Clin Endocrinol Diabetes*. 2021;129(7):535-541. doi:10.1055/a-0929-6072
44. Tan Y, Jin Y, Wang Q, Huang J, Wu X, Ren Z. Perilipin 5 protects against cellular oxidative stress by enhancing mitochondrial function in HepG2 cells. *Cells*. 2019;8(10):1241. doi:10.3390/cells8101241
45. Wang H, Sreenivasan U, Gong DW, et al. Cardiomyocyte-specific perilipin 5 overexpression leads to myocardial steatosis and modest cardiac dysfunction. *J Lipid Res*. 2013;54(4):953-965. doi:10.1194/jlr.M032466
46. Han KM, Tae WS, Kim A, et al. Serum FAM19A5 levels: A novel biomarker for neuroinflammation and neurodegeneration in major depressive disorder. *Brain Behav Immun*. 2020;87:852-859. doi:10.1016/j.bbi.2020.03.021
47. Lee YB, Hwang HJ, Kim JA, et al. Association of serum FAM19A5 with metabolic and vascular risk factors in human subjects with or without type 2 diabetes. *Diab Vasc Dis Res*. 2019;16(6):530-538. doi:10.1177/1479164119860746
48. Iwabu M, Okada-Iwabu M, Yamauchi T, Kadowaki T. Adiponectin/AdipoR research and its implications for lifestyle-related diseases. *Front Cardiovasc Med*. 2019;6:116. doi:10.3389/fcvm.2019.00116
49. Karampetsou N, Tzani A, Doulami IP, et al. Epicardial adipocyte-derived TNF-α modulates local inflammation in patients with advanced coronary artery disease. *Curr Vasc Pharmacol*. 2022;20(1):87-93. doi:10.2174/1570161119666211029110813
50. Battineni G, Sagaro GG, Chintalapudi N, Amenta F, Tomassoni D, Tayebati SK. Impact of obesity-induced inflammation on cardiovascular diseases (CVD). *Int J Mol Sci*. 2021;22(9):4798. doi:10.3390/ijms22094798