Diagnostic value and prognostic significance of CTRP9 combined with pentraxin-3 in acute coronary syndrome

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Abstract. The present study aimed to explore the diagnostic value and prognostic significance of C1q/tumor necrosis factor-related protein 9 (CTRP9) combined with pentraxin-3 (PTX-3) in acute coronary syndrome (ACS). A total of 137 patients with coronary heart disease and chest pain were included. Among them, seventy-nine patients with ACS were allocated into a study group and fifty-eight patients with non-cardiac chest pain (NCCP) were allocated into a control group. The serum CTRP9, PTX-3 levels were quantified by ELISA, and their correlation with other ACS-related indexes, diagnostic value for ACS and predictive significance for poor prognosis were analyzed. In addition, the risk factors of the poor prognosis of ACS patients were studied. CTRP9 was lowly expressed and PTX-3 was highly expressed in the serum of ACS patients. CTRP9 was negatively correlated with cardiac troponin I (cTnI), creatine kinase-MB (CK-MB) and high-sensitivity C-reactive protein (hs-CRP) ($P<0.05$), while PTX-3 was positively correlated with them ($P<0.05$). Combined detection of CTRP9 and PTX-3 was of high value in the diagnosis and prognosis of ACS patients. In addition, CTRP9 and PTX-3 were independent risk factors for the poor prognosis of ACS. Patients with ACS had lower CTRP9 expression and higher PTX-3 expression than those without ACS. Moreover, the combined detection of CTRP9 and PTX-3 can better evaluate the diagnosis and prognosis of ACS patients.

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Introduction

Acute coronary syndrome (ACS) is a disease with pathological presentation of complete or incomplete occlusion of the coronary artery lumen caused by thrombosis or sudden hemorrhage in atherosclerotic plaques (1). In addition, it is one of the leading causes of acute cardiovascular events clinically at present, posing a serious threat to the life, health and safety of patients (2). However, approximately 15% of ACS patients cannot be effectively diagnosed at the early stage due to an initially normal electrocardiogram (ECG) (3). Therefore, how to diagnose ACS in a timely and effective manner has important clinical significance for the treatment and prognosis of patients. At present, troponin, myoglobin and brain natriuretic peptide (BNP) are the most commonly used biomarkers in ACS diagnosis. However, these biomarkers are not sensitive to the diagnosis of early ACS (4,5). Thus, finding biomarkers with higher sensitivity is the focus of researches.

C1q/tumor necrosis factor-related protein 9 (CTRP9) is a newly discovered adipocyte factor with similar structure and metabolic regulation function to adiponectin (APN). Moreover, CTRP9 and APN also form heterotrimeric complexes *in vitro* and *in vivo* (6). A study revealed that CTRP9 has an inhibitory effect on systemic inflammatory response, and the reduction of its expression is the start of atherosclerosis as well as other diseases (7). Another study revealed that CTRP9 is an independent risk factor for coronary artery disease and predicts the severity of ACS (8). It is considered that the decrease of CTRP9 is proportional to the incidence, mortality and severity of heart failure (9). Plasma pentraxin-3 (PTX-3) is an acute phase reactant protein with similar structure and function to C-reactive protein (CRP), which is highly expressed in coronary plaques (10). PTX-3, secreted by macrophages and neutrophils, promotes the aggregation of monocytes and the formation of atherosclerotic plaques (11).

Therefore, we suspected that the combined detection of CTRP9 and PTX-3 had a high diagnostic value for ACS and could effectively predict the prognosis of patients. However, there are relatively few studies on CTRP9 and PTX-3 in ACS at present, and thus, we conducted a preliminary study.

Patients and methods

Patient data. A total of 137 patients (71 males and 66 females) with coronary heart disease (CHD) and chest pain admitted to Yidu Central Hospital of Weifang (Weifang, China) from April 2014 to September 2017 were prospectively recruited. According to the results of coronary angiography, 79 patients with early ACS served as the study group, including 40 with unstable angina pectoris (UAP) (12) and 39 with acute myocardial infarction (AMI) (13). Another 58 patients with non-cardiac chest pain (NCCP) served as the control group. The average age of all the patients was (63.71±8.27) years. Inclusion criteria were as follows: Patients with early ACS enrolled in the study group and CHD patients without ACS enrolled in the control group were diagnosed by coronary angiography and MRI (14). Exclusion criteria were as follows: Patients with other malignant tumors, systemic immune system diseases, severe liver and kidney dysfunction; pregnancy patients; and NYHA-IV patients. All participants agreed to participate and signed the informed consent form. The present study was approved by the Ethics Committee of Yidu Central Hospital of Weifang (approval no. SDL201404135).

Index detection. Venous blood was collected from all patients within 24 h after admission and centrifuged at 1,500 x g for 10 min to obtain serum at 4˚C. Enzyme-linked immunosorbent assay (ELISA) was used to detect serum CTRP9 [cat. no. RD191180200R; Seebio Biotech (Shanghai) Co., Ltd.] and PTX-3 (product no. kt99347; MSK Biotechnology Co., Ltd.). In addition, an ECG was carried out, and ACS-related serum indexes cardiac troponin I (cTnI) [FDA registration no. (Wuhan) 20182402369; Wuhan Easydiagnosis Biomedicine Co., Ltd.], creatine kinase-MB (CK-MB) [FDA registration no. (Wuhan) 20192402668; Wuhan Easydiagnosis Biomedicine Co., Ltd.] were detected by chemiluminescence, and high-sensitivity C-reactive protein (hs-CRP) by an immunofluorescence analyzer (product no. YM0061114; i-CHROMA) with a kit from Getein Biotech [FDA registration no. (Suzhou) 20152400403]. The patients with ACS were followed up for 3 months, with the end point of the occurrence of cardiovascular events (cardiac death or readmission for ACS).

Statistical analysis. In the present study, the SPSS 18.0 (SPSS, Inc.) was used for statistical analysis. The categorized data were analyzed using the chi-squared test, and the continuous data were expressed as the mean ± standard deviation. Independent samples t-test was used for comparison between the two groups. GraphPad Prism 6 software (GraphPad Software, Inc.) was used to visualize the data. Pearson's correlation test was applied for correlation analysis, and receiver operating characteristic (ROC) curves were plotted to analyze the diagnostic and prognostic value of CTRP9 and PTX-3 in ACS. The multivariate analysis of prognostic risk factors was carried out with logistic regression model. A value of $P<0.05$ was considered to indicate a statistically significant difference.

Results

Comparison of general data. There was no significant difference in sex, age, body mass index (BMI) and basic diseases between the two groups ($P>0.05$), as revealed in Table I.

Comparison of the expression of CTRP9 and PTX-3. The expression of CTRP9 in the study group was significantly lower than that in the control group, and the expression of PTX-3 was significantly higher than that in the control group ($P<0.05$), as revealed in Table II.

Detection of other relevant indexes. To further analyze the differences between ACS and non-ACS patients, the expression levels of cTnI, CK-MB, and hs-CRP in the two groups were compared. It was revealed that cTnI, CK-MB and hs-CRP in the study group were significantly higher than those in the control group ($P<0.05$), as indicated in Fig. 1.

Correlation of serum CTRP9 and PTX-3 with cTnI, CK-MB and hs-CRP. Serum CTRP9 was negatively correlated with cTnI, CK-MB and hs-CRP in ACS ($P<0.05$), while PTX-3 was positively correlated with them ($P<0.05$), as revealed in Table III and Fig. 2.

Diagnostic values of CTRP9 and PTX-3 in ACS. The sensitivity, specificity, area under curve (AUC), 95% confidence interval (CI), and cut-off value of CTRP9 for ACS diagnosis were 70.69, 72.15%, 0.791, 0.715-0.867, and 3.429 mg/l, respectively, and those of PTX-3 were 68.97, 74.68%, 0.773, 0.692-0.854, and 0.821 μg/l. Whereas the sensitivity, specificity, AUC, and 95% CI of combined diagnosis of CTRP9 and PTX-3 were 86.21, 77.22%, 0.876, and 0.813-0.939, respectively. Therefore, although CTRP9 and PTX-3 each had diagnostic value for ACS, the sensitivity and AUC of combined diagnosis were higher than that of single diagnosis, indicating a higher diagnostic value, as revealed in Fig. 3.

Predictive values of CTRP9 and PTX-3 for cardiovascular events in ACS patients. The patients were divided into a cardiovascular event group (36 cases) and a non-cardiovascular event group (43 cases). Comparison of CTRP9 and PTX-3 between the two groups revealed that CTRP9 in the cardiovascular event group was significantly lower than that in the non-cardiovascular event group, and PTX-3 was significantly higher than that in the non-cardiovascular event group (Table IV). Moreover, the predictive values of CTRP9 and PTX-3 for coronary artery events in ACS patients were analyzed, and the combined detection exhibited higher predictive value for poor prognosis of ACS patients (Fig. 4).

Univariate analysis of risk factors for poor prognosis. Univariate analysis revealed that there was no significant difference in sex, age and CK-MB between the cardiovascular event group and non-cardiovascular event group ($P>0.05$), but there were significant differences in hypertension, diabetes, hyperlipidemia, CTRP9, PTX-3, cTnI and hs-CRP ($P<0.05$), as revealed in Table V.

Multivariate analysis of risk factors for poor prognosis. According to the results from the univariate analysis, hypertension, diabetes, hyperlipemia, low CTRP9, high PTX-3, high cTnI, and high CK-MB that were significant in univariate analysis were included in multivariate analysis and assigned as variables (Table VI). Multivariate analysis

Table I. Comparison of general data.

Factor	Study group n=79	Control group n=58	t/χ^2	P-value
Sex [n (%)]			0.000	0.934
Male	41 (51.90)	30 (51.72)		
Female	38 (48.10)	28 (48.28)		
Age (years) [n (%)]			0.007	0.931
≤63	36 (45.57)	26 (44.83)		
>63	43 (54.43)	32 (55.17)		
BMI (kg/m^2) [n (%)]			0.032	0.858
≤22	41 (51.90)	31 (53.45)		
>22	38 (48.10)	27 (46.55)		
Hypertension [n (%)]			0.008	0.927
Yes	51 (64.56)	37 (63.79)		
No	28 (35.44)	21 (36.21)		
High blood lipid [n (%)]			0.016	0.899
Yes	40 (50.63)	30 (51.72)		
No	39 (49.37)	28 (48.28)		
Alanine aminotransferase (IU/l)	26.34±1.54	26.29±1.61	0.184	0.854
Aspartate aminotransferase (IU/l)	21.26±1.17	21.21±1.13	0.251	0.802
Creatinine (μmol/l)	64.91±4.26	64.81±4.31	0.135	0.893

BMI, body mass index.

Table II. Comparison of the expression of CTRP9 and PTX-3.

Factor	Study group n=79	Control group n=58	t	P-value
CTRP9 (mg/l)	3.31±0.19	3.53±0.20	6.549	<0.001
PTX-3 (μg/l)	0.89±0.15	0.75±0.12	5.861	<0.001

CTRP9, C1q/tumor necrosis factor-related protein 9; PTX-3, pentraxin-3.

Table III. Correlation of serum CTRP9 and PTX-3 with cTnI, CK-MB and hs-CRP.

	CTRP9		PTX-3	
Index	r	P-value	r	P-value
cTnI	-0.735	<0.001	0.626	<0.001
CK-MB	-0.723	<0.001	0.672	<0.001
hs-CRP	-0.686	<0.001	0.774	<0.001

CTRP9, C1q/tumor necrosis factor-related protein 9; PTX-3, pentraxin-3; cTnI, cardiac troponin I; CK-MB, creatine kinase-MB; hs-CRP, high-sensitivity C-reactive protein.

was carried out using logistic regression model to analyze the risk factors of cardiovascular events. The results revealed that hypertension, hyperlipemia, low CTRP9, high PTX-3 were independent risk factors for adverse cardiovascular events (Table VII).

Discussion

ACS is a disease with complicated physiological and pathological processes whose diagnosis and prognosis cannot be predicted by a single index (15). Several myocardial indicators are released into the blood only after necrosis of myocardial cells. If there is still no obvious abnormality in the ECG, it is easy to delay the diagnosis, and therefore delay timely treatment of patients (16). Therefore, more laboratory parameters are required for the diagnosis of ACS.

In the present study, CTRP9 and PTX-3 were selected to diagnose CHD patients with ACS. It was determined that serum CTRP9 in patients with ACS was significantly lower than that in patients without ACS, while the expression of PTX-3 was significantly higher than that of patients without ACS. A previous study demonstrated that CTRP9 was highly expressed in the serum of cardiovascular disease patients with high plaque stability (17). Another study suggested that it contributed to the enhancement of plaque stability by reducing the expression of pro-inflammatory factors in macrophages (7), which confirms our conclusion concerning the low expression of CTRP9 in ACS. However, PTX-3, an inflammatory protein homologous to CRP,

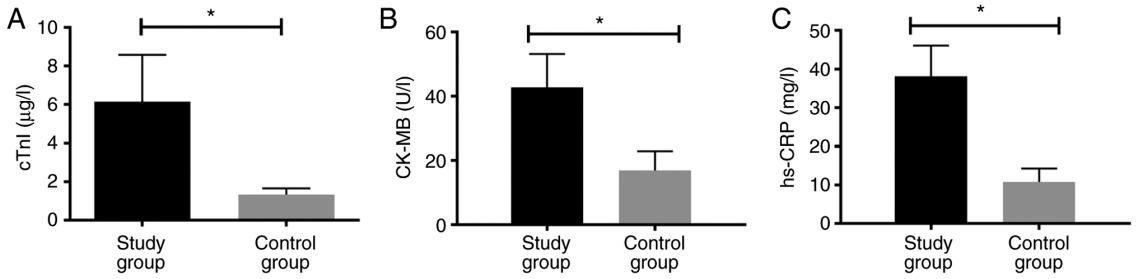

Figure 1. Detection of cTnI, CK-MB and hs-CRP. (A) cTnI expression in the study group was significantly higher than that in the control group. (B) CK-MB expression in the study group was significantly higher than that in the control group. (C) hs-CRP expression in the study group was significantly higher than that in the control group. *P<0.05. cTnI, cardiac troponin I; CK-MB, creatine kinase-MB; hs-CRP, high-sensitivity C-reactive protein.

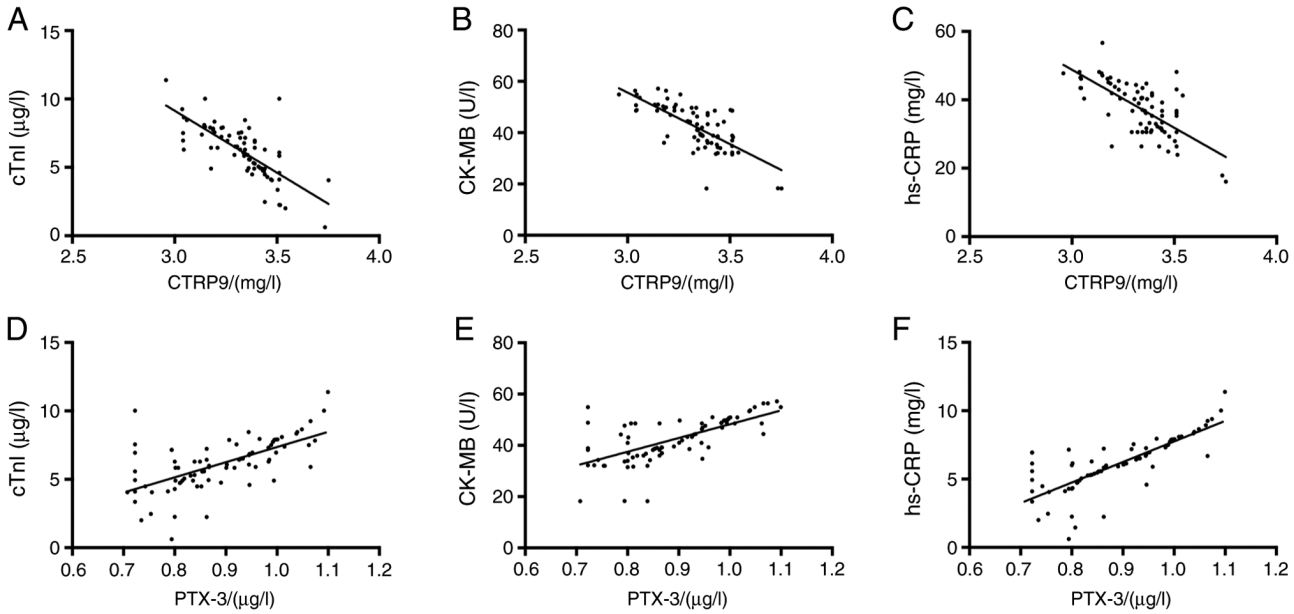

Figure 2. Correlation of serum CTRP9 and PTX-3 with cTnI, CK-MB and hs-CRP. (A) CTRP9 and cTnI are negatively correlated (r=-0.735; P<0.05). (B) CTRP9 and CK-MB are negatively correlated (r=-0.723; P<0.05). (C) CTRP9 and hs-CRP are negatively correlated (r=-0.686; P<0.05). (D) PTX-3 and cTnI are positively correlated (r=0.626; P<0.05). (E) PTX-3 and CK-MB are positively correlated (r=0.672; P<0.05). (F) PTX-3 and hs-CRP are positively correlated (r=0.774; P<0.05). CTRP9, C1q/tumor necrosis factor-related protein 9; PTX-3, pentraxin-3; cTnI, cardiac troponin I; CK-MB, creatine kinase-MB; hs-CRP, hypersensitive C-reactive protein.

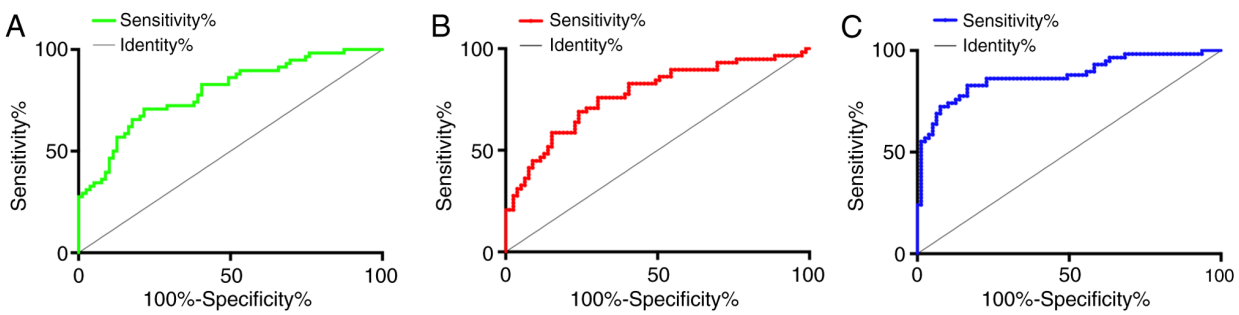

Figure 3. Diagnostic values of CTRP9 and PTX-3 in ACS. (A) The sensitivity, specificity, AUC, 95% CI, and cut-off value of CTRP9 for ACS diagnosis were 70.69, 72.15%, 0.791, 0.715-0.867 and 3.429 mg/l respectively. (B) The sensitivity, specificity, AUC, 95% CI, and cut-off value of PTX-3 for ACS diagnosis were 68.97, 74.68%, 0.773, 0.692-0.854 and 0.821 μg/l, respectively. (C) The sensitivity, specificity, AUC, and 95% CI of combined of CTRP9 and PTX-3 for ACS diagnosis were 86.21, 77.22%, 0.876 and 0.813-0.939 respectively. CTRP9, C1q/tumor necrosis factor-related protein 9; PTX-3, pentraxin-3; ACS, acute coronary syndrome; AUC, area under curve; CI, confidence interval.

significantly increases after infection and its peak expression is higher than of CRP, which indicates that PTX-3 may better reflect the inflammation of blood vessels than CRP (18,19). Other cardiovascular disease-related factors (cTnI, CK-MB and hs-CRP) were detected, and the results revealed that the factors in ACS patients were significantly higher than those in the controls. cTnI,

Table IV. Comparison of serum CTRP9 and PTX-3 in patients with different prognosis.

	Cardiovascular event group (n=36)	Non-cardiovascular event group (n=43)	t	P-value
CTRP9/(mg/l)	3.23±0.11	3.36±0.10	5.498	<0.001
PTX-3/(μg/l)	0.99±0.10	0.84±0.09	7.013	<0.001

Table V. Univariate analysis of the poor prognosis in patients with ACS.

Factor	Cardiovascular event group (n=36)	Non-cardiovascular event group (n=43)	t/χ^2	P-value
Sex [n, (%)]			0.096	0.757
Male	18 (50.00)	23 (53.48)		
Female	18 (50.00)	20 (46.52)		
Age (years)	63.68±8.16	63.75±8.22	0.049	0.961
Hypertension [n, (%)]	28 (77.78)	23 (53.49)	5.052	0.025
Diabetes [n, (%)]	27 (75.00)	20 (46.51)	6.599	0.010
High blood lipid [n, (%)]	25 (69.44)	15 (34.88)	9.364	0.002
CTRP9 (mg/l)	3.23±0.11	3.36±0.10	5.498	<0.001
PTX-3 (μg/l)	0.99±0.10	0.84±0.09	7.013	<0.001
cTnI (μg/l)	7.33±1.26	5.52±1.13	6.728	<0.001
CK-MB (U/l)	49.96±7.34	48.91±6.63	0.668	0.506
hs-CRP (mg/l)	43.51±4.68	36.92±3.47	7.176	<0.001

ACS, acute coronary syndrome; CTRP9, C1q/tumor necrosis factor-related protein 9; PTX-3, pentraxin-3; cTnI, cardiac troponin I; CK-MB, creatine kinase-MB; hs-CRP, high-sensitivity C-reactive protein.

Table VI. Assignment table.

Factor	Assignment
Hypertension	Yes=1, No=2
Diabetes	Yes=1, No=2
High blood lipid	Yes=1, No=2
CTRP9	>3.31 mg/l=1, ≤3.31 mg/l=2
PTX-3	>0.89 μg/l=1, ≤0.89 μg/l=2
cTnI	>6.15 μg/l=1, ≤6.15 μg/l=2
hs-CRP	>38.19 mg/l=1, ≤38.19 mg/l=2

CTRP9, C1q/tumor necrosis factor-related protein 9; PTX-3, pentraxin-3; cTnI, cardiac troponin I; hs-CRP, hypersensitive C-reactive protein.

CK-MB and hs-CRP are sensitive factors to myocardial injury. cTnI has been reported to have a high sensitivity to myocardial infarction, however, due to its insignificant changes in the early stage of ACS, it can only be used to evaluate the severity of myocardial infarction (20). Similarly, although highly sensitive to myocardial infarction, CK-MB has poor specificity for myocardial injury because it is also increased in patients with diabetes and skeletal muscle trauma (21). As the most sensitive factor to the inflammatory response, hs-CRP can predict the occurrence of ACS, but still with poor diagnostic specificity (22). Therefore, the correlation of serum CTRP9 and PTX-3 with cTnI, CK-MB and hs-CRP in ACS patients was analyzed. It was revealed that serum CTRP9 was negatively correlated with cTnI, CK-MB and hs-CRP in ACS patients, while PTX-3 was positively correlated with them, which further suggested that there was a close relationship between CTRP9, PTX-3 and the incidence of ACS.

Subsequently, in order to further clarify the role of CTRP9 and PTX-3 in the pathogenesis and prognosis of ACS, we separately and jointly detected CTRP9 and PTX-3. According to the ROC curve, a common tool for evaluating the diagnostic efficiency, the AUC of combined detection of CTRP9 and PTX-3 for ACS diagnosis and poor prognosis prediction was 0.876 and 0.894 respectively, which indicated that the combined detection had a high predictive value for the onset and prognosis of ACS. Furthermore, a multivariate analysis of risk factors for cardiovascular adverse events was carried out in order to analyze the influencing factors that affect the prognosis of ACS patients. The results revealed that hypertension, hyperlipidemia, low CTRP9 and high PTX-3 were independent risk factors for cardiovascular adverse events in ACS patients. At present, the application of CTRP9 and PTX-3 in ACS diagnosis has seldom been studied. Only a few studies have revealed that low-CTRP9 or high-PTX-3 expression is an important indicator for the pathogenesis of ACS (23,24). However, CTRP9 has been revealed to interfere with insulin-mediated glucose uptake by activating adenosine, thereby inhibiting the proliferation of smooth muscle cells and vascular injury (25). The expression of CTRP9 significantly decreased when patients suffered from myocardial cell injury,

Table VII. Multivariate analysis of the poor prognosis in patients with ACS.

Factor	β	SE	Wald	OR	95% CI	P-value
Hypertension	0.067	0.010	3.173	1.231	1.082-1.403	<0.01
Diabetes	0.009	0.053	3.783	1.431	1.042-1.767	0.052
High blood lipid	0.028	0.114	0.057	1.420	1.109-2.421	<0.01
CTRP9	0.199	0.425	7.183	1.221	1.175-4.418	<0.01
PTX-3	0.205	0.315	4.103	3.017	1.031-8.792	<0.01
cTnI	0.004	0.003	0.289	1.659	1.029-4.121	0.582
hs-CRP	0.124	0.321	0.132	1.312	1.052-2.614	0.730

ACS, acute coronary syndrome; CTRP9, C1q/tumor necrosis factor-related protein 9; PTX-3, pentraxin-3; cTnI, cardiac troponin I; hs-CRP, hypersensitive C-reactive protein; β, beta regression coefficient; SE, standard error; OD, odds ratio; CI, confidence interval.

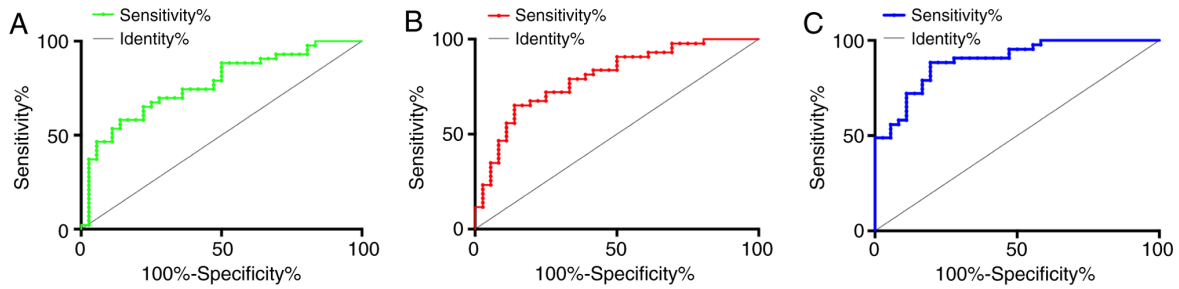

Figure 4. Predictive values of CTRP9 and PTX-3 for cardiovascular events in ACS. (A) The sensitivity, specificity, and AUC of CTRP9 in cardiovascular event prediction were 72.09, 63.89%, and 0.770, respectively. (B) The sensitivity, specificity, and AUC of PTX-3 in cardiovascular event prediction were 74.42, 66.67%, and 0.799, respectively. (C) The sensitivity, specificity, and AUC of combined of CTRP 9 and PTX-3 in cardiovascular event prediction were 88.37, 77.78%, and 0.894, respectively. CTRP9, C1q/tumor necrosis factor-related protein 9; PTX-3, pentraxin-3; ACS, acute coronary syndrome; AUC, area under curve.

thus CTRP9 can better reflect myocardial injury. Myocardial infarction area and apoptosis of myocardial cells in mice were revealed to be increased after CTRP9 knockout, thus it is inferred that low expression of CTRP9 may lead to poor prognosis in ACS mice (26). Moreover, there is evidence that CTRP9 mediates protective effects in cardiomyocytes via AMPK- and adiponectin receptor-mediated induction of anti-oxidant response (27). PTX-3 has been reported to promote the formation of atherosclerotic plaque by accelerating the aggregation of monocytes, and the increase of serum PTX-3 indicates poor prognosis of patients with ACS (28). In addition, it always leads to the increase of fibrinogen and induces a hypercoagulable state of blood vessels; moreover, its interaction with inflammatory reaction may cause unstable atherosclerotic plaque, thereby resulting in the occurrence of ACS; therefore, PTX-3 is considered to be an important predictor of ACS (29). There is a study that specifically revealed that the inclusion of PTX-3 improved the predictive model of cardiovascular complications in patients with myocardial infarction (30). All the aforementioned studies confirmed the conclusions of the present study.

To sum up, CTRP9 was revealed to be lowly expressed and PTX-3 to be highly expressed in the serum of patients with ACS. Combined detection of CTRP9 and PTX-3 can better evaluate and predict the onset and prognosis of ACS. However, there are still several limitations in the present study. Firstly, due to the lack of long-term follow-up, it is impossible to determine the correlation of CTRP9 and PTX-3 with the death of patients. Secondly, the high cardiovascular events in the present study may be a random outcome due to the small sample size included. In a follow-up study, the sample size will be expanded for further exploration. Thirdly, the absence of healthy participants as controls may lead to a lack of data for the assessment of CTRP9 and PTX-3 in CHD. Although this is not our main objective, it will be further explored in future studies.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

NaJ and SZ designed the study and drafted the manuscript. GW and NiJ were responsible for the collection and analysis

of the experimental data. HW and FZ revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Yidu Central Hospital of Weifang, China. Patients who participated in this research, signed the informed consent and had complete clinical data. Signed written informed consents were obtained from the patients and/or guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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