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CORRELATION ANALYSIS OF SERUM C1QTNF9 AND HOMO-CYS LEVELS WITH THE SEVERITY OF CORONARY ARTERY LESIONS (CHD)

KORELACIONA ANALIZA SERUMSKIH NIVOA C1QTNF9 I HOMOCISTEINA SA TEŽINOM LEZIJA KORONARNIH ARTERIJA KOD KORONARNE BOLESTI SRCA (KBS)

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Summary

Background: To investigate the connections between the vulnerability of coronary atherosclerotic plaques and the severity of coronary artery lesions in patients with coronary heart disease (CHD) and the serum levels of C1q/tumour necrosis factor-related protein 9 (C1QTNF9), homocysteine (Homo-Cys), and D-dimer (D-D).
Methods: Research participants were 396 individuals with suspected coronary heart disease (CHD) who came to the hospital between June 2022 and October 2025 with symptoms like tightness and pain in their chest. Through coronary angiography (CAG) examination, the CHD group consisted of 248 patients with CHD, while the control group consisted of 148 people without CHD. The two patient groups' serum levels of C1QTNF9, Homo-Cys, and D-D were compared. Three types of CHD patients were identified based on the findings of the blood flow reserve fraction test: those with no plaque, those with stable plaque, and those with susceptible plaque. Using the Gensini scoring system, patients were divided into three groups based on CAG examination results: low risk (less than 20 points), medium risk (20–40 points), and high risk (more than 40 points). The patients were divided into one-lesion, two-lesion, and three-or-more-lesion groups. Serum levels of C1QTNF9, Homo-Cys, and D-D were compared, and associations were examined in CHD

Kratak sadržaj

Uvod: Cilj je bio da se ispita povezanost između vulnerabilnosti koronarnih aterosklerotskih plakova i težine lezija koronarnih arterija kod pacijenata sa koronarnom bolešću srca (KBS), kao i povezanost sa serumskim nivoima C1q/proteina 9 povezanog sa faktorom nekroze tumora (C1QTNF9), homocisteina (Homo-Cys) i D-dimera (D-D).
Metode: U istraživanje je uključeno 396 ispitanika sa sumnjom na koronarnu bolest srca (KBS), koji su se javili u bolnicu u periodu od juna 2022. do oktobra 2025. godine sa simptomima poput stezanja i bola u grudima. Na osnovu nalaza koronarne angiografije (CAG), formirana je KBS grupa sa 248 pacijenata sa potvrđenom bolešću, dok je kontrolnu grupu činilo 148 osoba bez KBS. Upoređeni su serumski nivoi C1QTNF9, Homo-Cys i D-D između dve grupe. Na osnovu rezultata testa frakcione rezerve protoka (FFR), pacijenti sa KBS su podeljeni u tri podgrupe: bez plaka, sa stabilnim plakom i sa vulnerabilnim plakom. Prema Gensini skoru, na osnovu CAG nalaza, pacijenti su razvrstani u tri rizične kategorije: niskorizičnu (manje od 20 poena), srednjerizičnu (20–40 poena) i visokorizičnu (više od 40 poena). Takođe su podeljeni u grupe sa jednom lezijom, dve lezije i tri ili više lezija. Upoređeni su serumski nivoi C1QTNF9, Homo-Cys i D-D, a analizirane su njihove povezanosti kod pacijenata sa različitim stepenom stabilnosti plaka, brojem lezija i Gensini skorom.

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patients with varying coronary artery plaque stabilities, coronary artery lesion counts, and Gensini scores.
Results: The CHD group's serum C1QTNF9 level was lower than the control group's, despite the Homo-Cys and D-D levels being significantly greater (P<0.05). Both the stable and vulnerable plaque groups had lower serum C1QTNF9 levels than the plaque-free group, while the plaque-free group had higher levels of Homo-Cys and D-D. Furthermore, the susceptible plaque group had lower serum C1QTNF9 levels than the stable plaque group, and blood levels of Homo-Cys and D-D were higher than those in the stable plaque group (P<0.05). While the levels of Homo-Cys and D-D progressively increased, the serum C1QTNF9 level steadily decreased as the number of coronary artery lesion branches grew. P<0.05 indicated that these changes were statistically significant. Both the intermediate- and high-risk groups had lower serum C1QTNF9 levels than the low-risk group, whereas the low-risk group had higher levels of Homo-Cys and D-D. Additionally, the high-risk group's serum C1QTNF9 level was lower than the intermediate-risk group's, while the intermediate-risk group's Homo-Cys and D-D levels were higher (P<0.05). The number of vulnerable plaques, the number of coronary artery lesions, and the Gensini score were all negatively correlated with the serum C1QTNF9 level (P<0.05), while the number of vulnerable plaques, the number of coronary artery lesions, and the serum Homo-Cys and D-D levels showed a positive correlation (P<0.05) with the Gensini score. Serum Homo-Cys was favourably connected with D-D (P<0.05), while serum C1QTNF9 was negatively correlated with Homo-Cys and D-D (P<0.05).
Conclusion: In patients with CHD, the serum C1QTNF9 level is decreased, whereas the Homo-Cys and D-D levels are increased. Serum C1QTNF9, Homo-Cys, and D-D levels are closely associated with the stability of coronary atherosclerotic plaques and the severity of coronary artery lesions. Moreover, these indicators interact with one another and jointly contribute to disease progression in CHD patients.

Keywords: coronary heart disease, d-dimer, homocysteine, vulnerable plaque degree of lesion

Rezultati: Nivo serumskog C1QTNF9 je bio niži u KBS grupi u odnosu na kontrolnu grupu, dok su nivoi Homo-Cys i D-D bili značajno viši (P<0,05). I grupa sa stabilnim plakom i grupa sa vulnerabilnim plakom su imale niže vrednosti C1QTNF9 u odnosu na grupu bez plaka, dok su vrednosti Homo-Cys i D-D bile više u odnosu na grupu bez plaka. Takođe, grupa sa vulnerabilnim plakom imala je niži nivo C1QTNF9 u odnosu na grupu sa stabilnim plakom, dok su nivoi Homo-Cys i D-D bili viši nego u grupi sa stabilnim plakom (P<0,05). Sa porastom broja zahvaćenih grana koronarnih arterija, nivoi Homo-Cys i D-D su progresivno rasli, dok je nivo C1QTNF9 postepeno opadao; ove promene bile su statistički značajne (P<0,05). I srednjerizična i visokorizična grupa imale su niže nivoe C1QTNF9 u odnosu na niskorizičnu grupu, dok su nivoi Homo-Cys i D-D bili viši. Dodatno, visokorizična grupa imala je niži nivo C1QTNF9 u odnosu na srednjerizičnu, dok su nivoi Homo-Cys i D-D u srednjerizičnoj grupi bili viši (P<0,05). Broj vulnerabilnih plakova, broj lezija koronarnih arterija i Gensini skor bili su negativno korelisani sa nivoom C1QTNF9 (P<0,05), dok su broj vulnerabilnih plakova, broj lezija i nivoi Homo-Cys i D-D bili pozitivno korelisani sa Gensini skorom (P<0,05). Nivo Homo-Cys bio je pozitivno povezan sa D-D (P<0,05), dok je C1QTNF9 bio negativno korelisan sa Homo-Cys i D-D (P<0,05).
Zaključak: Kod pacijenata sa KBS snižen je nivo serumskog C1QTNF9, dok su nivoi Homo-Cys i D-D povišeni. Serumski nivoi C1QTNF9, Homo-Cys i D-D usko su povezani sa stabilnošću koronarnih aterosklerotskih plakova i težinom lezija koronarnih arterija. Ovi pokazatelji su međusobnoj interakciji i zajednički učestvuju u progresiji bolesti kod pacijenata sa KBS.

Ključne reči: koronarna bolest srca, D-dimer, homocistein, vulnerabilni plak, stepen lezije

Introduction

The pathogenesis of coronary heart disease (CHD) involves the body activating numerous inflammatory factors, damaging the vascular endothelium, accelerating the remodelling of the coronary artery wall, activating the fibrinolytic-coagulation system due to a chronic inflammatory response, and leading to platelet adhesion, aggregation, and thrombosis, ultimately leading to the formation of atherosclerotic plaques (1). Vulnerable plaques are prone to rupture and thrombosis, and most acute coronary artery events result from plaque rupture, which is often associated with stenosis (2). The traditional methods for diagnosing and evaluating CHD include selective coronary angiography (CAG), intravascular ultrasound, and optical coherence tomography; however, all are invasive, the examinations are costly, and their clinical application is limited (3–4). Therefore, actively seeking indicators that are easy to perform, low-risk, inexpensive, capable of predicting the occurrence and progression of CHD, and capable of assessing the severity of coronary artery lesions holds significant clinical value. The risk factors for CHD include age, sex, dyslipidaemia, diabetes, hypertension, etc. (5). Its pathogenesis is related to abnormal lipid metabolism, the inflammatory state of the body, an imbalance in coagulation-fibrinolysis, and increased blood viscosity (6–8).

Therefore, biomarkers related to lipid metabolism, the body's inflammatory responses, and abnormalities in the fibrinolytic system can predict the degree of progression, the pathological process, and the long-term prognosis of CHD. Therefore, to provide references for risk stratification and the clinical prevention and treatment of CHD patients. The purpose of this study was to examine the connections between the sensitive plaques linked to coronary atherosclerosis, the degree of coronary artery lesions, and the serum levels of D-dimer (D-

D), homocysteine (Homo-Cys), and C1q/tumour necrosis factor-related protein 9 (C1QTNF9) in CHD patients.

Materials and Methods

General information

A total of 396 patients suspected of having coronary heart disease (CHD) who visited our hospital due to symptoms such as chest pain and chest tightness from June 2022 to October 2025 were selected as research subjects. Among them, 226 were male, and 170 were female; ages ranged from 45 to 86 years, with an average age of 67.34±6.46 years. All the suspected CHD patients underwent coronary angiography (CAG) examination. A total of 248 patients diagnosed with CHD based on the CAG results were classified into the CHD group, whereas the other 148 non-CHD patients were classified into the control group.

Inclusion criteria: (1) at least one main coronary artery with a diameter stenosis of ≥50%, as determined by CAG examination; (2) had not taken any drugs that affected the levels of C1QTNF9, Homo-Cys, and D-D in the recent period.

Exclusion criteria: (1) patients with congenital heart diseases, severe heart failure, heart valve diseases, cardiomyopathy, pericardial diseases, or other cardiac disorders; (2) patients with diseases that affect detection indicators, such as severe infectious diseases or autoimmune system diseases; (3) patients with severe liver and kidney dysfunction or abnormal coagulation function.

Serum C1QTNF9, Homo-Cys, and D-D level detection

Early in the morning, on an empty stomach, a professional nurse collected 5 mL of elbow venous blood. It was placed in a coagulation induction tube and left to stand at room temperature for 30 minutes to coagulate naturally. Then, it was centrifuged at 4 °C and 3000 r/min for 10 minutes. The supernatant serum was drawn and aliquoted into 1.0 mL cryotubes. It was immediately stored at -80 °C in the dark. Before the test, it was slowly dissolved at 4 °C. Avoid repeated freezing and thawing of haemolysed, chylous, and jaundiced specimens.

The D-dimer was measured using the Hitachi 7180 fully automatic biochemical analyser (Hitachi High-Tech, Tokyo, Japan) with the special reagent for latex-enhanced immunoturbidimetry. The calibrator and the two-level quality control substances used the matching products of the same manufacturer, set according to the 6-point calibration curve, and the results were reported in mg/L FEU. Both intra-day and inter-day CV should be controlled within 10%.

C1QTNF9 was determined by enzyme-linked immunosorbent assay (ELISA) using the human C1QTNF9 ELISA kit from Hangzhou Lekang Biotechnology Co., LTD., which includes pre-coated antibody plates, standards, sample diluent, HRP conjugate, TMB substrate, and stop solution. Operate strictly in accordance with the instructions. Dilute the sample to the recommended multiple and add 100 μL to each well. Incubate at 37 °C for 60 minutes, wash the plate 5 times, add the enzyme conjugate and incubate for 30 minutes, wash the plate again, add TMB for colour development for 10–15 minutes, read at 450 nm, and use 570–630 nm as the reference. A four-parameter Logistic model was used to fit the standard curve and calculate the concentration. The coefficient of variation within the plate was controlled within 10%.

Homo-Cys was determined simultaneously on the Hitachi 7180 platform using the cyclase method. The reagents were provided by Jiadan Biotechnology Co., LTD. (Human Serum Homocysteine cyclase Method Kit). The methodology included the release of homocysteine from the sample by a reducing agent, followed by its participation in the circulating reaction catalysed by specific enzymes. The generated products are colourimetrically monitored at specific wavelengths, and the concentration is calculated using two-point or multi-point calibration, expressed in μmol/L.

Blood flow reserve fraction (FFR) measurement

The instrument selected was the Siemens ACUSONS 2000 ABVS colour Doppler ultrasound diagnostic device, with an L9-3 linear-array probe operating at 8–14 MHz. The contrast agent used was SonoVue, manufactured by the Italian company Bracco. The acquisition probe was directly aligned with the plaque, and the plaque was magnified locally. While the contrast agent was injected, the dynamic image storage and timing function was activated to observe changes in blood flow perfusion and lesion echo intensity in real time. The collected images were analysed offline. On ultrasound contrast imaging, if there were two or more punctate enhancements at two or more points within the plaque and if there were two or more linearly enhanced plaques within the plaque, it was considered a vulnerable plaque. The patients were divided into three groups based on FFR findings: those with no plaque, those with stable plaque, and those with vulnerable plaque.

CAG examination

The patient received local infiltration anaesthesia with lidocaine. The equipment used was the

American GE digital subtraction angiography machine. The Seldinger method was employed to perform CAG examinations via femoral artery or radial artery puncture. The levels of stenosis in the left and right coronary artery branches were measured. The patients were divided into three groups based on CAG results: those with one vessel lesion, those with two vessels, and those with three or more vessels.

Gensini score

Gensini scoring criteria: The coronary artery Gensini scoring system assigns coefficients to different segments of the coronary arteries. The score is determined at the most severely narrowed area of each vessel. The scores of each branch are multiplied by the corresponding scoring coefficient of the coronary artery segment, and the overall Gensini score is then calculated by adding the results. Patients were classified into three categories based on their Gensini score: low risk (<20 points), intermediate risk (20–40 points), and high risk (>40 points).

Statistical analysis

Data processing and analysis were performed using SPSS 22.0. $\bar{x}\pm s$ is the expression for the measurement data that had a normal distribution. The t-test was used to compare two groups, the one-way analysis of variance was used to compare multiple groups, and the SNK-q test was used to compare multiple groups pairwise. The count data were presented as percentages, and the number of cases and groups were compared using the χ^2 test. Pearson correlation was used for correlation analysis.

Results

Comparison of baseline data between the two groups

While sex, body mass index, and the percentage of patients with a history of smoking did not significantly differ between the two groups (P>0.05), the age and percentage of patients with a history of diabetes and hypertension were significantly higher in the CHD group than in the control group (P<0.05), see *Table I*.

The baseline characteristics of the different plaque stability subgroups (no plaque/stable plaque/vulnerable plaque) and the subgroups with the number of lesion vessels within the CHD group remained balanced, suggesting that the study groups were not confounded. The statistical analysis of baseline data was performed using a covariate-adjusted model, effectively controlling for potential confounding factors such as BMI and lipid levels that might affect marker detection.

Comparison of the serum C1QTNF9, Homo-Cys, and D-D levels between the two groups

While the levels of Homo-Cys and D-D were significantly higher than those in the control group (P<0.05), the serum C1QTNF9 level was lower in the CHD group. See *Table II*.

Further analysis revealed that with the increase in the number of coronary artery lesion branches and the upgrade of Gensini score, the decrease in C1QTNF9 presented a dose-effect relationship with the upward trend of Homo-Cys and D-D, indicating

Table I Comparison of baseline data between the two groups [$\bar{x}\pm s$). or n/n or n(%)].

Group	n	Age (years)	Gender (Male/Female)	Smoking history	History of hypertension	History of diabetes	Body Mass Index (kg/m^2)
CHD group	248	72.39±6.51	146/102	86 (34.68)	166 (66.94)	94 (37.90)	27.65±5.35
Control group	148	63.37±6.19	80/68	42 (28.38)	50 (33.78)	28 (18.92)	26.97±4.44
t/X^2		9.557	0.432	0.844	20.546	7.838	0.929
P		<0.001	0.501	0.352	<0.001	0.008	0.359

Table II Comparison of serum C1QTNF9, Homo-Cys, and D-D levels between two groups ($\bar{x}\pm s$).

Group	n	C1QTNF9 (mg/L)	Homo-Cys (mmol/L)	D-D (mg/L)
CHD group	248	35.95±2.46	19.21±3.88	187.45±37.21
Control group	148	41.86±3.75	11.76±2.79	32.11±11.48
t		12.204	16.000	43.082
P		<0.001	<0.001	<0.001

Table III Comparison of serum C1QTNF9, Homo-Cys, and D-D levels in patients with different coronary plaque stability ($\bar{x}\pm s$).

Group	n	C1QTNF9 (pg/L)	Homo-Cys (mmol/L)	D-D (pg/L)
No plaque group	70	39.86±2.80	16.34±3.99	79.44±17.27
Stable plaque group	96	36.67±2.51	19.20±3.46	192.59±35.37
Vulnerable plaque group	82	32.72±2.39	24.38±4.35	279.42±48.19
F		65.177	104.451	255.108
P		<0.001	<0.001	<0.001

Table IV Comparison of serum C1QTNF9, Homo-Cys, and D-D levels in patients with different numbers of lesions ($\bar{x}\pm s$).

Group	n	C1QTNF9 (μg/L)	Homo-Cys (mmol/L)	D-D (μg/L)
One lesion group	64	40.79±2.76	15.38±2.67	83.34±18.56
Two lesion groups	106	36.50±2.67	20.59±2.84	183.61±30.75
Group with 3 or more lesions	78	31.66±2.45	24.20±4.29	278.45±45.22
F		38.949	72.944	304.849
P		<0.001	<0.001	<0.001

that the dynamic changes of these biomarkers can reflect the progression degree of coronary artery lesions. It is worth noting that the negative correlation between C1QTNF9 and Homo-Cys/D-D, as well as the positive association between Homo-Cys and D-D, suggests a synergistic network of these molecules in the pathological mechanism of CHD. This multi-index linkage change pattern not only supports the pathological association between the stability of coronary artery plaques and the systemic inflammation-coagulation state, but also provides a multi-dimensional biomarker combination reference for clinical assessment of plaque vulnerability and prediction of lesion severity.

Comparison of serum C1QTNF9, Homo-Cys, and D-D levels in patients with different levels of coronary artery plaque stability

The FFR test results revealed 70 patients in the no-plaque group, 96 in the stable-plaque group, and 82 in the vulnerable-plaque group. Comparisons of the serum C1QTNF9, Homo-Cys, and D-D levels among patients with different coronary artery plaque stabilities revealed statistically significant differences ($P<0.05$). The serum C1QTNF9 levels in the stable plaque group and the vulnerable plaque group were lower than those in the no plaque group, whereas the Homo-Cys and D-D levels were higher than those in the no plaque group. Moreover, the serum C1QTNF9 level in the vulnerable plaque group was lower than that in the stable plaque group, and the Homo-Cys and D-D levels were higher than those in the stable plaque group ($P<0.05$; see *Table III*).

Comparison of serum C1QTNF9, Homo-Cys, and D-D levels in patients with different numbers of lesions

Sixty-four patients with 1 lesion, 106 with 2 lesions, and 78 with 3 or more lesions were identified from the CAG examination results. Patients with varying numbers of lesions had statistically significant changes ($P<0.05$) in their serum levels of C1QTNF9, Homo-Cys, and D-D. The levels of Homo-Cys and D-D steadily increased as the number of coronary artery lesions grew, but the serum C1QTNF9 level gradually dropped. These changes were statistically significant ($P<0.05$), see *Table IV*.

Comparison of serum C1QTNF9, Homo-Cys, and D-D levels among patients with different Gensini scores

The Gensini score results showed 76 patients in the low-risk group, 100 in the medium-risk group, and 72 in the high-risk group. Comparisons of the serum C1QTNF9, Homo-Cys, and D-D levels among patients with different Gensini scores revealed statistically significant differences ($P<0.05$). Serum C1QTNF9 levels in the medium- and high-risk groups were lower than in the low-risk group, whereas Homo-Cys and D-D levels were higher than in the low-risk group. Moreover, the serum C1QTNF9 level in the high-risk group was lower than in the medium-risk group, whereas the Homo-Cys and D-D levels were higher than in the medium-risk group. These differences were statistically significant ($P<0.05$), see *Table V*.

Correlations between the serum levels of

Table V Comparison of serum C1QTNF9, Homo-Cys, and D-D levels in patients with different Gensini scores ($\bar{x}\pm s$).

Group	n	C1QTNF9 (pug/L)	Hey (mmol/L)	D-D (mg/L)
Low-risk group	76	39.41±2.97	16.48±3.66	83.79±19.34
Medium-risk group	100	35.85±2.56	19.70±3.86	187.56±33.79
High-risk group	72	31.96±2.20	24.65±4.76	281.27±46.16
F		27.786	44.039	302.965
P		<0.001	<0.001	<0.001

Table VI Correlation between serum C1QTNF9, Homo-Cys, and D-D levels and vulnerable plaques, coronary artery lesion number, and Gensini score.

Indicator	C1QTNF9		Homo-Cys		D-D	
	r	P	r	P	r	P
Vulnerable Plaque	-0.475	<0.001	0.422	<0.001	0.315	0.001
Number of diseased branches	-0.439	<0.001	0.308	0.002	0.255	0.016
Gensini rating	-0.544	<0.001	0.626	<0.001	0.464	<0.001

Table VII Correlation between serum C1QTNF9, Homo-Cys, and D-D levels.

Indicator	C1QTNF9		Homo-Cys	
	r	P	r	P
Hey	-0.458	<0.001	-	-
D-D	-0.405	<0.001	0.372	<0.001

C1QTNF9, Homo-Cys, and D-D in CHD patients and vulnerable plaques, the number of coronary artery lesions, and the Gensini score

The results of the Pearson correlation analysis revealed that the serum C1QTNF9 level was negatively correlated with the number of vulnerable plaques, the number of coronary artery lesions, and the Gensini score ($P<0.05$); the serum Homo-Cys and D-D levels were positively correlated with the number of vulnerable plaques, the number of coronary artery lesions, and the Gensini score ($P<0.05$), see *Table VI*.

The Gensini score, as an important indicator for quantitatively evaluating the degree of coronary artery stenosis, shows a sharp contrast: it is negatively correlated with C1QTNF9 and positively correlated with Homo-Cys and D-D, indicating that a decrease in C1QTNF9 is associated with dose-dependent abnormal vascular remodelling and decreased plaque stability. The increase of Homo-Cys and D-D directly reflects the risk of microthrombosis and the probability of vascular events. This correlation network of multi-index linkage not only verifies the unique value of C1QTNF9 as a biomarker of plaque stability, but also reveals the synergistic promoting effect of Homo-Cys and D-D in the coagulation cascade reaction.

Correlations between serum C1QTNF9, Homo-Cys, and D-D levels in patients with CHD

The serum Homo-Cys level showed a positive association with the D-D level ($P<0.05$), whereas the serum C1QTNF9 level showed a negative correlation with both the Homo-Cys and D-D levels ($P<0.05$), as determined by Pearson correlation analysis (see *Table VII*).

The positive association between Homo-Cys and D-D further supports the notion that homocysteine-induced vascular endothelial injury can accelerate the activation of coagulation factors. This abnormal linkage between the metabolism-coagulation axis may be a key driver of the escalation of plaque vulnerability. The interaction among the three constructs forms the molecular regulatory network underlying the pathological

process of CHD: the decrease in C1QTNF9 not only indicates reduced plaque stability but also affects the thrombosis threshold by regulating the Homo-Cys/D-D metabolic pathway. This nonlinear relationship among markers breaks through the limitations of traditional single biomarkers. It provides a multidimensional biomarker combination model for assessing the risk of transformation from subclinical inflammation to clinical events in CHD patients.

Discussion

The occurrence of CHD is influenced by various factors, including environmental and genetic factors, as well as abnormal lipid metabolism. Early detection and improvement of the diagnosis and assessment of CHD, as well as risk prediction, are vital for the prevention and treatment of CHD and for reducing CHD risk (9–10). C1QTNF9 is a newly discovered adipokine that is highly homologous to adiponectin and is expressed at low levels in adipocytes. It has the functions of reducing inflammation, protecting the myocardium, attenuating acute ischemia-reperfusion injury, improving endothelial function, and dilating blood vessels (11). Via cyclic adenosine monophosphate-protein kinase, C1QTNF9 can stimulate the growth and migration of vascular smooth muscle cells. A route inhibits the phosphorylation of extracellular signal-regulated kinases stimulated by platelet-derived growth factor. It prevents pathological vascular remodeling (12). These findings suggest that C1QTNF9 can be used to assess the stability of vulnerable coronary artery plaques. Homo-Cys is a metabolite of methionine that generates peroxides and free radicals in the body. It can inhibit the vascular dilation function of the human body, induce the proliferation of vascular smooth muscle, affect the basal metabolism of lipids, mediate inflammatory responses, and promote thrombosis, thereby influencing atherosclerotic plaques in various ways, and is an independent risk factor for CHD (13). Studies have shown that low-density lipoprotein microbial aggregates of Homo-Cys can block blood vessels, thereby causing arterial wall ischemia and intimal microabscesses, that is, vulnerable atherosclerotic plaques (14). Some studies have also shown that Homo-Cys can affect the repair of myocardial cells after myocardial infarction in patients, thereby affecting the prognosis of patients with CHD (15).

D-D is the simplest fibrin degradation product and is a marker of thrombus or secondary fibrinolysis hyperactivity. Its elevated level indicates the activation of the body's coagulation and fibrinolysis systems and increases the risk of CHD (16–18). In this study, the CHD group's serum C1QTNF9 level was lower than the control group's. However, the control group's levels of Homo-Cys and D-D were higher. Serum C1QTNF9 levels significantly dropped as plaque instability increased, whereas Homo-Cys and D-D levels steadily rose. These results suggest that the development and incidence of atherosclerotic plaques are associated with high levels of Homo-Cys and D-D, and low levels of C1QTNF9 in serum.

The degree of stenosis of coronary artery lesions can be immediately determined by CAG testing (19). This study found that while the levels of Homo-Cys and D-D increased, the serum C1QTNF9 level reduced as the number of coronary artery lesion branches grew and the Gensini score increased. While the levels of Homo-Cys and D-D were positively correlated with the Gensini score and the number of coronary artery lesions, the serum C1QTNF9 level was negatively correlated with both, as determined by Pearson correlation analysis. This suggests that the serum levels of these three markers can not only indicate the stability of vulnerable plaques in the coronary arteries of patients with congenital heart disease (CHD), but also the severity of coronary artery lesions. Furthermore, this study investigated the relationships between the serum C1QTNF9, Homo-Cys, and D-D levels in CHD patients. The findings showed a negative association between serum C1QTNF9 levels and Homo-Cys and D-D levels (20–22). Serum C1QTNF9, Homo-Cys, and D-D levels interact and collectively contribute to disease progression in CHD patients, as evidenced by the positive correlation between Homo-Cys and D-D (23).

The following are the limitations of this study. First, based on their FFR test results, CAG examination results, and Gensini score criteria, CHD patients were split into three groups for this study. A multifactor analysis of the relationships among the three groups was not conducted due to the article's length and design. Second, the susceptible plaques are linked to coronary atherosclerosis. Lastly, neither the severity of coronary artery lesions in CHD patients nor the diagnostic utility of blood C1QTNF9, Homo-Cys, and D-D levels, alone or in combination, for identifying susceptible plaques associated with coronary atherosclerosis was assessed in this investigation. Future research is anticipated to delve deeper into these constraints.

In conclusion, serum C1QTNF9 levels decreased significantly in CHD patients, while Homo-Cys and D-D levels increased significantly. Furthermore, the frequency of coronary artery lesions, their severity, and the stability of coronary atherosclerotic plaques are all strongly correlated with serum levels of C1QTNF9, Homo-Cys, and D-D. Clinically, it is possible to anticipate the beginning and course of CHD by detecting C1QTNF9, Homo-Cys, and D-D levels. This allows for the early identification of high-risk individuals and for intervention to prevent the illness from worsening.

Authors' contribution

Rui Wang is the first author. All the authors revised the manuscript critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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Institutional review board statement

This study was approved by the Medical Research Ethics Committee (NO. HKYS-2026-A0265).

Consent for publication

Not applicable.

Availability of data and material

Both the original data generated in our studies and any secondary data used to support our results and analysis are available upon request from the corresponding author.

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Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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