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Original Article

Combined detection of homocysteine and hypersensitive c-reactive protein in the risk assessment of coronary heart disease

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Abstract: Objective: The goal of this study was to determine the clinical value of combined detection of homocysteine (Hcy) and hypersensitive C-reactive protein (hs-CRP) in risk assessment of coronary heart disease (CHD). Methods: A total of 182 patients with CHD were enrolled as the CHD group, and 213 healthy people who came to Shenzhen Bao'an Hospital of Traditional Chinese Medicine (Group) for physical examination during the same period were selected as the control group. Baseline data for both groups were analyzed retrospectively, including gender, age, body mass index, systolic blood pressure, diastolic blood pressure, triglyceride, total cholesterol, blood glucose, smoking history, and drinking history. The venous plasma parameters of the two groups such as red blood cells, white blood cells, platelets, low density lipoprotein, uric acid, Hcy and hs-CRP were compared. ROC curve and logistic regression analysis were used to evaluate the results. Results: The baseline data of the two groups were equally comparable ($P > 0.05$). Compared with the control group, the levels of white blood cells, low density lipoprotein, uric acid, Hcy and hs-CRP in the CHD group were significantly increased (all $P < 0.05$). Multivariate logistic regression analysis indicated that low density lipoprotein, Hcy and hs-CRP were independent risk factors for CHD ($P < 0.05$). The area under the ROC curve of the serum Hcy level was 0.791 while the hs-CRP was 0.850, and the combined detection of the two was 0.946. The specificity (85%) and sensitivity (97%) of Hcy combined with hs-CRP detection were better than the single detection, and the differences were statistically significant ($P < 0.05$). Conclusion: Serum Hcy and hs-CRP levels are closely related to CHD. Combined detection of Hcy and hs-CRP can be used as an important indicator for clinical risk assessment of patients with CHD, thereby providing a basis for clinical early diagnosis and contributing to the improvement of the prevention, treatment and prognosis of CHD.

Keywords: Homocysteine, hypersensitive C-reactive protein, coronary heart disease, combined detection

Introduction

Coronary atherosclerotic heart disease is a series of clinical syndromes caused by atherosclerotic lesions in the coronary arteries, leading to cardiovascular stenosis or obstruction, and myocardial hypoxia, ischemia and even necrosis [1-3]. Coronary heart disease (CHD) is one of the most common heart diseases. According to the National Health Service Survey data, compared with 4.6‰ in 2003, the prevalence rate of ischemic heart disease in China was 10.2‰ in 2015, which was increased by more than two times [4, 5]. In 2009, the mortality rate of CHD in Chinese urban residents was about 94.96/100,000, showing an increasing trend year by year [6].

Clinical manifestations of CHD mainly depend on the ischemia degree of the affected myocardium. In mild cases, symptoms such as chest distress, shortness of breath, palpitation and angina pectoris may occur. In severe cases, myocardial infarction, arrhythmia, shock and even sudden death may appear, which seriously endangers the life safety of patients [7, 8]. However, CHD is always too insidious to be discovered. It is less likely to cause the patient's attention until it develops to angina pectoris. At this time, the disease often has developed to a more serious stage, which is difficult to control and has a poor prognosis. Therefore, early screening, diagnosis, and risk assessment of CHD are of great importance for its prevention, treatment, and prognosis.

At present, coronary angiography is commonly used as the gold standard for the diagnosis of CHD in clinical practice, but it is complex and invasive with certain operation taboos and adverse reactions. Therefore, it is not suitable for promotion as a routine examination method for CHD, and cannot reflect the development and change of the disease in real time [9, 10]. Hypersensitive C-reactive protein (hs-CRP) is an inflammatory response marker. Su et al. showed that the level of hs-CRP was positively correlated with the degree and scope of coronary artery lesions [11]. Ridker et al. confirmed that inflammatory response was involved in the occurrence and development of CHD, indicating that hs-CRP was a risk factor and predictor of CHD [12]. Furthermore, abnormal lipid metabolism is one of the important causes of CHD. Studies have shown that low density lipoprotein (LDL) level is not only a key factor in the formation of atherosclerotic plaque, but also one of the crucial indicators to guide the tertiary prevention and treatment of patients with CHD [13, 14]. Currently, detection of serum lipids and hypersensitive C-reactive protein is generally carried out for the diagnosis of CHD in clinical practice. However, in recent years, hyperhomocysteinemia has been shown to be closely related to the severity of CHD. Liu et al. found that the risk of sudden acute myocardial infarction increased significantly in patients with hyperhomocysteinemia (OR (95% CI): 6.38 (1.18-34.46)) [15].

Homocysteine (Hcy) is an important risk factor for the occurrence of cardiovascular disease. The higher the concentration of Hcy is, the greater the risk is. In healthy people, if the blood Hcy concentration continued to rise, CHD would be more likely to occur [16]. Therefore, Hcy has great potential and application value in predicting and assessing the risk of CHD. However, the diagnostic value of single detection for CHD was always limited (sensitivity was 81.1%, specificity was 54.3%), and the combined detection of multiple indicators was more in line with the development direction of clinical needs [17].

In this study, single or combined detection of LDL, Hcy and hs-CRP were used to explore the application value of them in the screening, prevention, diagnosis and risk assessment of CHD. This research aims to improve the detection rate of high-risk patients with CHD, reduce the incidence of cardiovascular accidents, and improve the therapeutic effect and prognosis of patients with CHD. The results are reported below.

Materials and methods

The general information

A total of 182 patients with CHD in Shenzhen Bao'an Hospital of Traditional Chinese Medicine (Group) from June 2017 to June 2018 were enrolled as the CHD group, and 213 healthy people who came to the hospital for physical examination during the same period were selected as the control group. All included research subjects signed the informed consent, and this study was reviewed and approved by the Ethics Committee of Shenzhen Bao'an Hospital of Traditional Chinese Medicine (Group).

Inclusion criteria: All cases met the diagnostic criteria of ischemic heart disease of the American College of Cardiology and the World Health Organization in 2014, and were confirmed by electrocardiogram, echocardiography, coronary angiography, myocardial enzyme and other examination indicators combined with clinical manifestations [18]. Exclusion criteria: Patients with anemia, infection, tumor, liver and kidney dysfunction, abnormal lipid metabolism and congenital heart disease; the patient who took folic acid and vitamin B12, non-steroidal anti-inflammatory drugs, hormones and other drugs in the past 3 months.

Methods

All research subjects in both groups received detection of plasma parameters such as red blood cells, white blood cells, platelets, LDL, uric acid, Hcy and hs-CRP. To be specific, 2 mL of fasting venous blood was extracted from the patients in two groups through the elbow vein in the early morning. Red blood cells, white blood cells, and platelets were measured using a Countess II FL automatic cell counter (American Thermo Fisher Scientific, Inc.). LDL level was detected by direct assay (Hitachi 7600 automatic biochemical analyzer). Blood uric acid level was measured by the uricase method (Hitachi 7600 automatic biochemical analyzer). Hcy level was determined by the en-

Table 1. Comparison of baseline data ($\bar{x}$ ± sd, n, %)

Related factors	CHD group (n = 182)	Control group (n = 213)	t/χ^2	P
Gender			0.127	0.722
Male	101 (55.5%)	122 (57.3%)		
Female	81 (44.5%)	91 (42.7%)		
Age (year)			1.335	0.248
Range	56-72	51-77		
Average	60.9 ± 6.0	59.7 ± 6.3		
BMI	26.00 ± 0.82	25.99 ± 0.82	0.034	0.983
Systolic blood pressure (mmHg)			0.014	0.905
Range	108-124	103-126		
Average	109.3 ± 6.0	110.8 ± 5.9		
Diastolic blood pressure (mmHg)			0.941	0.332
Range	72-91	75-88		
Average	74.6 ± 3.2	78.7 ± 3.1		
Triglyceride (mmol/L)	1.47 ± 0.29	1.51 ± 0.30	-1.242	0.215
Total cholesterol (mmol/L)	4.07 ± 0.30	4.11 ± 0.28	-1.303	0.193
Blood glucose (mmol/L)	6.04 ± 0.29	5.99 ± 0.28	1.516	0.130
Smoking history			0.041	0.839
Yes	95 (52.2%)	109 (51.2%)		
No	87 (47.8%)	104 (48.8%)		
Drinking history			0.096	0.757
Yes	78 (42.9%)	88 (41.3%)		
No	104 (57.1%)	125 (58.7%)		

Note: CHD, coronary heart disease; BMI, body mass index.

Table 2. Comparison of plasma parameters ($\bar{x}$ ± sd)

Parameters	CHD group (n = 182)	Control group (n = 213)	t	P
Red blood cells (*10^6/mL)	4.94 ± 0.60	4.98 ± 0.59	-0.643	0.520
White blood cells (*10^3/mL)	11.77 ± 1.20	6.38 ± 1.25	43.584	< 0.001
Platelets (*10^3/mL)	174.73 ± 14.63	173.66 ± 13.70	0.750	0.454
LDL (mmol/L)	2.51 ± 0.61	2.11 ± 0.62	6.524	< 0.001
Uric acid (μmol/L)	363.26 ± 29.84	346.4 ± 27.78	5.793	< 0.001
Hcy (μmol/L)	17.77 ± 3.54	12.31 ± 4.84	12.897	< 0.001
Hs-CRP (mg/L)	13.1 ± 3.05	7.06 ± 3.56	17.705	< 0.001

Note: CHD, coronary heart disease; LDL, low density lipoprotein; Hcy, homocysteine; Hs-CRP, hypersensitive C-reactive protein.

zyme-linked immunosorbent assay kit (XY-E10836, Shanghai Xinyu Biotechnology Co., Ltd, China). The level of hs-CRP was also determined by the enzyme-linked immunosorbent assay kit (XY-E11183, Shanghai Xinyu Biotechnology Co., Ltd, China). All operations were carried out in strict accordance with the reagent instructions, and the obtained data were recorded in detail.

Statistical analysis

The data were analyzed with SPSS22.0. The measurement data are expressed as mean ± standard deviation ($\bar{x}$ ± sd) and t test was used for intragroup comparison. In addition, the count data were expressed as cases/percentage (n/%) and evaluated by the χ^2 test. Correlation factors were analyzed using logistic regression analysis, with venous plasma parameters as the independent variables and the result of whether or not suffering from CHD as a dependent variable. The ROC curve was used to analyze and compare the area under the curve and the performance parameters of single or combined detection. P < 0.05 was statistically significant.

Results

The comparison of general information

There were no significant differences in the gender composition, age, body mass index, systolic blood pressure, diastolic blood pressure, triglyceride, total cholesterol, blood glucose, smoking history and drinking history between the control group and the CHD group (all P > 0.05). Thus, they were comparable as shown in **Table 1**.

The comparison of plasma parameters

As shown in **Table 2**, the levels of white blood cells, LDL, uric acid, Hcy and hs-CRP in the CHD

Table 3. Univariate logistic repression analysis of CHD plasma parameters

Parameters	χ^2	P	OR (95% CI)
White blood cells (*10^3/mL)	< 0.001	0.984	
LDL (mmol/L)	25.007	< 0.001	2.879 (1.902, 4.359)
Uric acid (μmol/L)	20.547	< 0.001	1.020 (1.011, 1.029)
Hcy (μmol/L)	61.608	< 0.001	1.372 (1.268, 1.485)
Hs-CRP (mg/L)	74.102	< 0.001	1.870 (1.621, 2.156)

Note: CHD, coronary heart disease; LDL, low density lipoprotein; Hcy, homocysteine; Hs-CRP, hypersensitive C-reactive protein; OR, odds ratio; CI, confidence interval.

Table 4. Multivariate logistic repression analysis of CHD plasma parameters

Parameters	β	χ^2	P	OR	95% CI
LDL (mmol/L)	1.336	11.525	< 0.001	3.804	(1.759, 8.227)
Uric acid (μmol/L)	0.322	0.637	0.425	1.380	(0.626, 3.040)
Hcy (μmol/L)	0.310	26.971	< 0.001	1.364	(1.213, 1.533)
Hs-CRP (mg/L)	0.556	52.964	< 0.001	1.743	(1.501, 2.025)

Note: CHD, coronary heart disease; LDL, low density lipoprotein; Hcy, homocysteine; Hs-CRP, hypersensitive C-reactive protein; OR, odds ratio; CI, confidence interval.

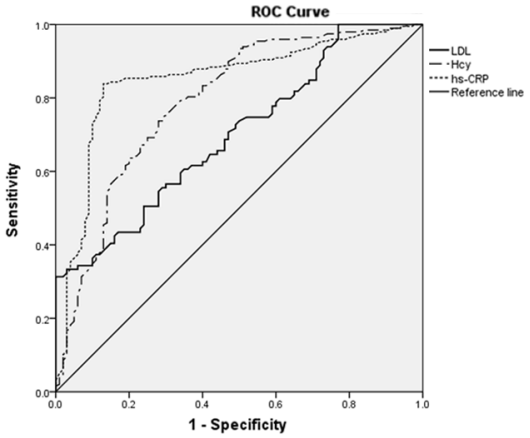

Figure 1. ROC curve for single detection of LDL, Hcy and hs-CRP. LDL: low density lipoprotein; Hcy: homocysteine; hs-CRP: hypersensitive C-reactive protein.

group were significantly higher than the control group (all P < 0.05). However, there was no statistically significant difference in the levels of red blood cells and platelets between the two groups (P > 0.05).

The univariate logistic repression analysis of CHD plasma parameters

According to the univariate logistic regression analysis, white blood cells, LDL, uric acid, Hcy and hs-CRP were used as independent variables and whether or not suffering from CHD was used as a dependent variable. The results showed that LDL, uric acid, Hcy and hs-CRP were closely related to CHD, and the risk degree was ranked as LDL > hs-CRP > Hcy > uric acid (P < 0.05), as shown in **Table 3**. LDL was the most dangerous factor in the occurrence of CHD, and the OR (95% CI) was 2.879 (1.902, 4.359) (P < 0.05). Moreover, the OR (95% CI) of the other three parameters were as follow: hs-CRP: 1.870 (1.621, 2.156), Hcy: 1.372 (1.268, 1.485), uric acid: 1.020 (1.011, 1.029) (P < 0.05).

The multivariate logistic repression analysis of CHD plasma parameters

In order to eliminate the confounding bias among the above possible risk factors, the variables with statistical significance in the univariate analysis were introduced into the multivariate logistic model. LDL, uric acid, Hcy and hs-CRP were taken as independent variables, and whether or not suffering from CHD was used as a dependent variable. The screening was performed at the level of α = 0.05. The results show that LDL, Hcy and hs-CRP were risk factors for the occurrence of CHD (P < 0.05), among which LDL was the most dangerous factor, with OR (95% CI) being 3.804 (1.759, 8.227) (P < 0.05) as shown in **Table 4**.

The single detection performance of LDL, Hcy and hs-CRP

Taking coronary angiography results as the gold standard, the results of ROC curve showed the value of Hcy, hs-CRP and LDL for risk prediction in patients with CHD under the detection of single parameter (P < 0.05), as shown in **Figure 1**. The areas under the curve of Hcy, hs-CRP and LDL were 0.791 (0.735, 0.848), 0.850 (0.801, 0.899) and 0.690 (0.640, 0.759), respectively, and the detection efficiency of hs-CRP was the highest (P < 0.05). The sensitivity and specificity of the three parameters were compared when the Youden index (sensitivity + specificity-1) was the maximum. The sensitivity of hs-CRP detection was the highest (0.84), and the specificity of Hcy detection was the

Table 5. Single detection performance of LDL, Hcy and hs-CRP

Parameters	AUC (95% CI)	P	Sensitivity	Specificity	Youden index (%)
LDL (mmol/L)	0.690 (0.640, 0.759)	< 0.001	0.56	0.69	25.06
Hcy (μmol/L)	0.791 (0.735, 0.848)	< 0.001	0.76	0.79	55.76
Hs-CRP (mg/L)	0.850 (0.801, 0.899)	< 0.001	0.84	0.70	54.84

Note: LDL, low density lipoprotein; Hcy, homocysteine, Hs-CRP, hypersensitive C-reactive protein; AUC, area under the curve; CI, confidence interval.

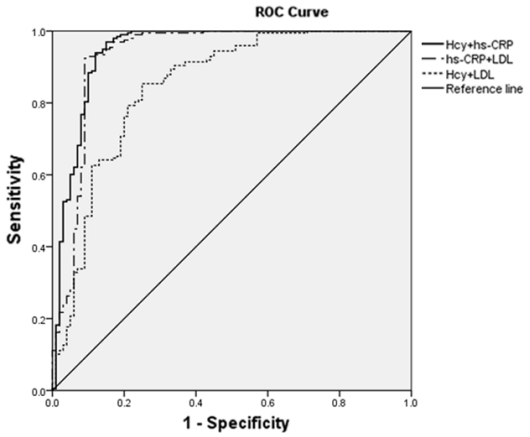

Figure 2. ROC curve for combined detection of LDL, Hcy and hs-CRP. LDL: low density lipoprotein; Hcy: homocysteine; hs-CRP: hypersensitive C-reactive protein.

best (0.79). In addition, the sensitivity and specificity of LDL detection were the lowest (0.56 and 0.69, respectively) as shown in **Table 5**.

The combined detection performance of LDL, Hcy and hs-CRP

The ROC curves of three combined detection methods including Hcy + LDL, hs-CRP + LDL and hs-CRP + Hcy were calculated, and by which the sensitivity and specificity of combined detections in the diagnosis of CHD were evaluated with the results of coronary angiography as the gold standard, as shown in **Figure 2** and **Table 6**. The results showed that the three combined detection methods had risk prediction value for CHD ($P < 0.05$). The area under the curves of Hcy + LDL, hs-CRP + LDL and hs-CRP + Hcy were 0.847 (0.795, 0.898), 0.931 (0.891, 0.971) and 0.946 (0.913, 0.979), respectively, and the detection efficiency of hs-CRP combined with Hcy was the highest ($P < 0.05$). The sensitivity and specificity of the three combined detection methods were compared when the Youden index (sensitivity + specificity-1) was the maximum. The sensitivity of hs-CRP combined with Hcy was the highest (0.97), and the specificity of hs-CRP combined with LDL was the best (0.91). Hs-CRP combined with Hcy had higher area under the ROC curve, sensitivity and specificity o than the single detection of hs-CRP or Hcy separately, which had a better risk assessment value for the diagnosis of CHD.

Discussion

A study showed that high Hcy was an independent risk factor for coronary atherosclerotic heart disease, and elevated serum Hcy level was significantly associated with an increased risk of CHD death (OR (95% CI): 1.66 (1.12-2.47)) [19]. Hcy cannot be synthesized *in vivo* and can only be generated by the hydrolysis of methionine [20]. Excessive intake of high animal protein diet or deficiency of methionine metabolic cofactors such as folic acid, vitamin B6 and B12 can cause the metabolism disorder of methionine and further lead to hyperhomocysteinemia [21].

On the one hand, the increased Hcy in the blood had vascular toxicity. It produced a lot of free radicals through oxidative stress, which damaged vascular endothelial cells, activated platelets and promoted blood coagulation. On the other hand, Hcy could also inhibit the synthesis of nitric oxide and promote its degradation, resulting in decreased endogenous vasoactive substances and abnormal vasodilatory function, thus promoting thrombosis and leading to inflammation and the generation of vascular wall plaques [22].

Hs-CRP was a kind of reactive protein in the acute phase of inflammation and was one of the risk predictors of cardiovascular events [23]. Hs-CRP can bind to lipoprotein, activate the complement system, promote the infiltration of inflammatory cells and have other immune regulatory effects, so as to produce a large number of inflammatory mediators, release oxygen free radicals, and cause vascular injury and vasospasm, plaque formation, lumen

Table 6. Combined detection performance of LDL, Hcy and hs-CRP

Parameters	AUC (95% CI)	P	Sensitivity	Specificity	Youden index (%)
Hs-CRP + Hcy	0.946 (0.913, 0.979)	< 0.001	0.97	0.85	82.69
Hs-CRP + LDL	0.931 (0.891, 0.971)	< 0.001	0.92	0.91	83.92
Hcy + LDL	0.847 (0.795, 0.898)	< 0.001	0.85	0.74	60.64

Note: LDL, low density lipoprotein; Hcy, homocysteine; Hs-CRP, hypersensitive C-reactive protein; AUC, area under the curve; CI, confidence interval.

stenosis, and the occurrence of cardiovascular and cerebrovascular events [24].

Low density lipoprotein (LDL) is a transport carrier for endogenous cholesterol in the blood [25]. LDL level was obviously positively correlated with the incidence of CHD (OR (95% CI): 1.95 (1.31-2.90)), which may be due to the fact that LDL can release various pro-inflammatory factors, recruit inflammatory response cells and damage arterial endothelium [26]. Furthermore, LDL can also promote excessive accumulation of cholesterol in the blood vessel wall, leading to decreased endothelial function and the formation of atherosclerotic plaques [27].

This study shows that the Hcy level of patients in the CHD group was markedly higher than that in the healthy group, which confirmed the close association between hyperhomocysteinemia and CHD. This result was basically consistent with the report of Yeh et al. on the risk ratio of CHD in patients with elevated Hcy level (OR (95% CI): 1.29 (1.02-1.64)) [28]. Furthermore, the hs-CRP level of CHD group was significantly higher than that of the healthy group, indicating that the test of hs-CRP level can provide laboratory basis for the detection and prevention of CHD in high-risk patients, which was the same as Held et al. [29]. The LDL level of patients in the CHD group was clearly higher than that in the healthy group, suggesting that the detection of LDL had certain diagnostic value for CHD, which was in line with the report of Puri et al. on the risk ratio of CHD in patients with elevated LDL level (OR (95% CI): 1.30 (0.93-1.84)) [30].

From the perspective of the sensitivity of single detection, hs-CRP (0.84) > Hcy (0.76) > LDL (0.56). The sensitivity of hs-CRP to the risk assessment of CHD was much higher than that of other parameters, which probably because C-reactive protein was a non-specific indicator reflecting acute inflammatory reaction and closely related to the occurrence, development and deterioration of CHD. From the perspective of the specificity of single detection, Hcy (0.79) > hs-CRP (0.70) > LDL (0.69). The specificity of the detection of hs-CRP was not the highest, which may be inferred although the hs-CRP can reflect the inflammatory response of the whole body, it lacks specificity and directivity. Poisoning, infection, autoimmune reaction, and other factors can cause the rise of hs-CRP level. The specificity of Hcy (0.79) for the risk assessment of CHD was significantly higher than that of other parameters, which may be related to the toxic effect of hyperhomocysteine on cardiovascular and cerebrovascular diseases.

This study confirmed that the combined detection of the two parameters was more valuable for the risk assessment of CHD, among which the detection of hs-CRP combined with Hcy had the highest diagnostic benefit (ROC curve AUC was 0.946 (0.913, 0.979)). From the perspective of sensitivity, hs-CRP + Hcy (0.97) > hs-CRP + LDL (0.92) > Hcy + LDL (0.85). From the perspective of specificity, hs-CRP + LDL (0.91) > hs-CRP + Hcy (0.85) > Hcy + LDL (0.74). Considering the sensitivity and specificity of the detection parameters comprehensively, detection of hs-CRP combined with Hcy has a better reference value for screening, diagnosis, prevention and risk assessment of CHD.

This study still has the following shortcomings. First, this study was a retrospective analysis, and there may be some bias in the inclusion of study subjects and the collection of clinical data. Second, the detection of venous plasma parameters was based on the kit provided by the biological company, and there were some technical problems and possible errors. In addition, this research lacked a stratified study on the subtype and severity of CHD, which will also be the focus of further studies. In future clinical observation, simultaneously combined detection of hs-CRP and Hcy together with coronary angiography will be performed, combined with the comprehensive analysis of clinical characteristics of the patients, and conduct follow-up

to provide more technical support for the diagnosis, treatment and prevention of CHD.

In conclusion, LDL, Hcy and hs-CRP are related to CHD, and all of them can be used as predictors for patients with CHD. In risk assessment of CHD, compared with single parameter detection, combined detection of Hcy and hs-CRP has good specificity and sensitivity, which is more advantageous and worth promoting its use in clinical practice.

Disclosure of conflict of interest

None.

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