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Original Article

Correlation studies of miR-126 and inflammatory factors in peripheral blood of patients with coronary heart disease

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Abstract: Objective: To explore the correlation and the clinical significance of the miR-126 level and the level of inflammatory factor in peripheral blood of patients with coronary heart disease (CHD). Methods: One hundred and seven patients with CHD were selected as the observation group, and 107 healthy people were selected as the control group. The levels of miR-126, C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), matrix metalloproteinase-9 (MMP-9), soluble vascular endothelial cell adhesion molecule-1 (sVCAM-1), N-terminal B-type natriuretic peptide precursor (NT-proBNP) and left ventricular ejection fraction percentage (LVEF%) in peripheral blood were compared between the two groups. According to the Gensini score, the observation group was divided into high and low integral groups, and the index levels of the two groups were compared. And the correlation between miR-126 and serum CRP, IL-6, TNF-α, MMP-9, sVCAM-1, NT-proBNP and LVEF% was analyzed. The patients were followed up for half a year and divided into poor prognosis group and good prognosis group according to the prognosis. The levels of various indexes in the two groups were compared, and the value of miR-126 in predicting the prognosis of patients was analyzed. Results: Compared with the control group, the observation group had lower levels of miR-126 and LVEF%, but higher levels of CRP, IL-6, TNF-α, MMP-9, sVCAM-1, and NT-proBNP (all P<0.001). Compared with the low score group, the high score group had lower levels of miR-126 and LVEF%, and higher levels of CRP, IL-6, TNF-α, MMP-9, sVCAM-1 and NT-proBNP (all P<0.001). Compared with the better prognosis group, the poor prognosis group had lower levels of miR-126 and LVEF%, and higher levels of CRP, IL-6, TNF-α, MMP-9, sVCAM-1, and NT-proBNP (all P<0.001). MiR-126 was positively correlated with LVEF%, and negatively correlated with CRP, IL-6, TNF-α, MMP-9, sVCAM-1 and NT-proBNP (all P<0.001). The results of ROC curve showed that miR-126 was more than 0.800 in evaluating the prognosis of CHD. Conclusion: The level of miR-126 in peripheral blood of patients with CHD decreased significantly, which was negatively correlated with the severity of the disease and inflammatory reaction, and had high clinical value in evaluating the prognosis.

Keywords: Coronary heart disease, miR-126, inflammatory factor, prognosis prediction

Introduction

CHD is one of the common cardiovascular and cerebrovascular diseases. The main pathogenesis of CHD is the coronary atherosclerosis (AS), which usually leads to the accumulation of lipids on the endarterium and the formation of plaques. When the plaque increases continuously, it will further induce arterial stenosis and even obstruction, resulting in obstruction of blood flow, myocardial ischemia, hypoxia or necrosis, and eventually angina pectoris occurs [1, 2]. Epidemiological investigation shows that, with the development of society, the incidence and mortality of CHD are increasing, which is a serious threat to human health [3]. At present, some progress has been made in the clinical treatment of CHD, but the condition of CHD is complex, and some patients have complications, resulting in a poor prognosis. Studies have found that about one-third of patients with CHD still showed cardiac ischemia within 5 years after treatment [4, 5], resulting in a poor prognosis for patients. MicroRNA (miRNA) is a class of endogenous non-coding small RNAs, which is specifically

Table 1. Comparison of two sets of general information

Category	Observation group (n=107)	Control group (n=107)	χ^2/t	P
Gender				
Male	57	59	0.075	0.784
Female	50	48		
Age (years)	57.1±9.4	57.4±9.6	0.231	0.818
BMI (kg/m^2)	24.8±2.5	24.6±2.7	0.562	0.575
Smoking history				
Yes	49	21	16.644	<0.001
No	58	86		
Drinking history				
Yes	46	19	16.108	<0.001
No	61	88		
History of hypertension				
Yes	26	10	8.549	0.004
No	81	97		
Diabetes history				
Yes	21	9	5.583	0.018
No	86	98		

Note: BMI: body mass index.

expressed in cardiomyocytes and is closely related to the occurrence and development of cardiovascular diseases, heart failure, arrhythmia and other cardiovascular diseases [6, 7]. The essence of AS is a chronic inflammatory process, and the inflammatory response is involved in the occurrence, development and coronary artery system of AS and thrombosis [8, 9]. Based on this, the purpose of this study is to explore the correlation and the clinical significance of the miR-126 level in peripheral blood and the level of inflammatory factors in patients with coronary heart disease, aiming to provide relevant basis for clinical treatment of coronary heart disease and evaluation of prognosis.

Materials and methods

General materials

The 107 patients with CHD treated in Hainan Western Central Hospital from April 2017 to April 2019 were selected as the observation group, and 107 healthy people were selected as the control group in the same period. The baseline data of the two groups are shown in **Table 1**. All the study subjects and their families informed and signed the consent form. And this study was approved by the Ethics Committee of Hainan Western Central Hospital.

Inclusion and exclusion criteria

Inclusion criteria of the study group: (1) According to the diagnostic criteria of CHD, it have shown by coronary angiography that the lumen area of any coronary artery is narrowed by more than 50% [10]; (2) It is in a stable period, and the admission time is less than 48 hours; (3) Age ≥18 years old.

Inclusion criteria of the observation group: (1) Physical examination within the past 1 month is healthy; (2) Age ≥18 years old.

Exclusion criteria of the study group and the observation group: (1) Complicated with other serious diseases; (2) Patients that complicated with diseases such as ischemic heart failure and abnormal cardiac conduction; (3) People with neurological or mental disorders; (4) Those who may have other chronic or acute inflammatory disease in the near future; (5) Those who have taken anti-inflammatory drugs, glucocorticoids, immunosuppressants and other drugs that may affect the experimental results in the past 3 months; (6) During pregnancy or lactation.

Methods

The left ventricular ejection fraction percentage (LVEF%) of all the subjects in the two groups before and after treatment was detected by ACUSONS 2000 color Doppler diagnostic instrument (Siemens, Germany) on the next day after enrollment, and 2 tubes of 5 mL/tube of venous blood were drawn in the early morning with fasting or before treatment for the observation group. One of the 2 tubes was centrifuged with 3000 r/min for 5 minutes to separate the serum. The level of N-terminal B-type natriuretic peptide precursor (NT-proBNP) was detected by electro-chemiluminescence (Elecss-2010 electro-chemiluminescence immunoassay, Roche, Switzerland), the level of C-reactive protein was detected by immunoturbidimetry (Roche/Hitachi cobasc501 analyzer, Roche, Switzerland), and the levels of

Table 2. Primer sequences

Primers	Sequences
miR-126 forward Primer	GGGTCGTACCGTT
miR-126 reverse primer	CAGTGCGTGTCGTGGAGT
U6 forward Primer	CTCGCTTCGGCAGCACA
U6 reverse primer	AACGCTTCACGAATTTGCGT

interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), matrix metalloproteinase-9 (MMP-9) and soluble vascular endothelial cell adhesion molecule-1 (sVCAM-1) were detected by enzyme-linked immunosorbent assay (SpectraMaxParadigm multi-function enzyme labeling instrument, Molecular Devices, USA). All the kits were purchased from Beyotime Biotechnology (Shanghai, China). And the other tube was used to extract the RNA from peripheral whole blood by RNA extraction kit, after that the reverse transcription was carried out according to the reverse transcription kit, and then RT-PCR experiment was carried out according to the instructions of SYBR RT-PCR kit (Bioer technology, Hangzhou, China). The reaction system of RT-PCR was performed as follows: Pre-denaturation at 95°C for 30 s, 95°C for 5 s, 60°C for 30 s and cycled for 35 times. The relative expression of miR-126 in each group was determined by $2^{-\Delta\Delta Ct}$ assay with the U6 as internal reference and triplicate for each sample to take the average. The primer was synthesized by Beijing Dingguo Changsheng Biotechnology Co., Ltd., China, and their sequences are shown in **Table 2**.

Outcome measures

Main outcome measures: The levels of miR-126, serum CRP, IL-6, TNF-α, MMP-9, sVCAM-1, NT-proBNP and LVEF% were compared between the control group and the observation group. Follow-up was performed 6 months after enrollment, and the observation group was divided into a poor prognosis group and a better prognosis group according to whether there were adverse events in the observation group. The levels of miR-126, serum CRP, IL-6, TNF-α, MMP-9, sVCAM-1, NT-proBNP and LVEF% in each group were compared. Adverse events are defined as cardiovascular events such as stent thrombosis, vascular restenosis, acute myocardial infarction or death [10]. The receiver operating characteristic (ROC) curve was used to analyze the clinical value of miR-126 in evaluating the prognosis of patients.

Secondary outcome measures: According to Gensini score system, the observation group was divided into low group (n=49) with score ≤30 and high group (n=58) with score >30 [11]. The levels of miR-126, serum CRP, IL-6, TNF-α, MMP-9, sVCAM-1, NT-proBNP and LVEF% were compared in each group. Correlation method was used to analyze the correlation between miR-126 and serum CRP, IL-6, TNF-α, MMP-9, sVCAM-1, NT-proBNP and LVEF% in the observation group.

Statistical analysis

SPSS 22.0 was used for statistical analysis, the counting data were expressed by the number of cases and percentage (n/%), and the measurement data were expressed by mean ± standard deviation ($\bar{x} \pm sd$). The measurement data were compared by t test of independent samples, and the counting data were compared by χ^2 test. Pearson correlation coefficient was used for correlation analysis. P<0.05 indicates that the difference is statistically significant. The ROC curve was drawn to analyze the clinical value of miR-126 level in evaluating prognosis in the observation group.

Results

Comparison of miR-126, serum inflammatory factors, NT-proBNP and LVEF% between the two groups

The results show that the levels of miR-126 and LVEF% in the observation group are lower than those in the control group, while the serum levels of CRP, IL-6, TNF-α, MMP-9, sVCAM-1 and NT-proBNP in the observation group are higher than those in the control group (all P<0.001), as shown in **Table 3**.

Comparison of miR-126, serum inflammatory factors, NT-proBNP levels and LVEF% in patients with different Gensini

Compared with the low score group, the levels of miR-126 and LVEF% in the high group are lower, while the serum levels of CRP, IL-6, TNF-α, MMP-9, sVCAM-1 and NT-proBNP were higher (all P<0.001), as it shows in **Table 4**.

Table 3. Comparison of miR-126, serum inflammatory factors, NT-proBNP levels and LVEF% between the two groups

Groups	Observation group (n=107)	Control group (n=107)	t	P
miR-126	0.37±0.12	1.18±0.24	31.226	<0.001
CRP (mg/L)	5.99±1.26	1.13±0.24	39.194	<0.001
IL-6 (pg/mL)	204.97±38.75	76.47±23.58	29.242	<0.001
TNF-α (pg/mL)	6.44±0.47	2.51±0.32	71.496	<0.001
MMP-9 (pg/mL)	189.22±24.16	101.46±19.57	29.197	<0.001
sVCAM-1 (pg/mL)	155.37±27.66	92.34±21.16	18.722	<0.001
LVEF%	54.21±5.43	63.42±4.41	13.619	<0.001
NT-proBNP (pg/mL)	186.39±22.16	49.27±11.58	56.728	<0.001

Note: IL-6: interleukin-6; TNF-α: tumor necrosis factor-α; MMP-9: matrix metalloproteinase-9; sVCAM-1: soluble vascular endothelial cell adhesion molecule-1; LVEF%: left ventricular ejection fraction percentage; NT-proBNP: N-terminal B-type natriuretic peptide precursor; CRP: C-reactive protein.

Table 4. Comparison of miR-126, serum inflammatory factors, NT-proBNP levels and LVEF% in different Gensini patients

Groups	Low score group (n=49)	High score group (n=58)	t	P
miR-126	0.82±0.13	0.24±0.15	21.168	<0.001
CRP (mg/L)	3.92±1.11	6.91±1.28	12.785	<0.001
IL-6 (pg/mL)	136.41±24.21	276.42±42.16	21.449	<0.001
TNF-α (pg/mL)	3.41±0.35	7.52±0.62	43.019	<0.001
MMP-9 (pg/mL)	129.41±18.49	235.41±22.34	26.430	<0.001
sVCAM-1 (pg/mL)	115.13±21.02	189.34±26.26	15.931	<0.001
LVEF%	58.82±3.84	52.12±4.53	8.166	<0.001
NT-proBNP (pg/mL)	114.34±12.09	232.59±20.11	37.477	<0.001

Note: IL-6: interleukin-6; TNF-α: tumor necrosis factor-α; MMP-9: matrix metalloproteinase-9; sVCAM-1: soluble vascular endothelial cell adhesion molecule-1; LVEF%: left ventricular ejection fraction percentage; NT-proBNP: N-terminal B-type natriuretic peptide precursor; CRP: C-reactive protein.

Table 5. Comparison of miR-126, serum inflammatory factors, NT-proBNP levels and LVEF% in patients with different prognosis

Groups	Group with good prognosis (n=76)	Group with poor prognosis (n=31)	t	P
miR-126	0.68±0.13	0.21±0.09	21.371	<0.001
CRP (mg/L)	3.42±1.24	9.22±1.71	17.136	<0.001
IL-6 (pg/mL)	132.34±25.52	298.71±34.57	24.237	<0.001
TNF-α (pg/mL)	3.22±0.41	9.24±0.45	66.968	<0.001
MMP-9 (pg/mL)	123.58±19.83	271.42±17.22	36.281	<0.001
sVCAM-1 (pg/mL)	113.28±20.05	208.74±25.68	20.541	<0.001
LVEF%	59.22±3.91	48.21±3.76	13.358	<0.001
NT-proBNP (pg/mL)	103.22±12.03	253.38±22.04	35.821	<0.001

Note: IL-6: interleukin-6; TNF-α: tumor necrosis factor-α; MMP-9: matrix metalloproteinase-9; sVCAM-1: soluble vascular endothelial cell adhesion molecule-1; LVEF%: left ventricular ejection fraction percentage; NT-proBNP: N-terminal B-type natriuretic peptide precursor; CRP: C-reactive protein.

Comparison of miR-126, serum inflammatory factors, NT-proBNP levels and LVEF% in patients with different prognosis

Compared with the better prognosis group, the poor prognosis group had lower levels of miR-126 and LVEF%, and higher serum levels of CRP, IL-6, TNF-α, MMP-9, sVCAM-1 and NT-proBNP (all P<0.001), as shown in **Table 5**.

Correlation analysis results

The results show that miR-126 is positively correlated with LVEF%, but it is negatively correlated with CRP, IL-6, TNF-α, MMP-9, sVCAM-1 and NT-proBNP (all P<0.001), as it shows in **Table 6** and **Figure 1**.

ROC curve results

The results show that when the cutoff value of miR-126 was 0.429, the AUC was 0.867 (P<0.001, 95% CI= 0.785, 0.950), the sensitivity was 0.776, and the specificity was 0.903, as shown in **Figure 2**.

Discussion

Inflammatory response plays an important role in the occurrence and development of AS and thrombosis. It has certain clinical significance to evaluate the expression level of inflammatory factors in patients with CHD. As one of the indicators of inflammatory response, the level of CRP is closely related to inflammation. And IL-6 can cause damage to tissue function through humoral immu-

Table 6. Correlation analysis results

Statistical value	r	P
CRP (mg/L)	-0.596	<0.001
IL-6 (pg/mL)	-0.615	<0.001
TNF-α (pg/mL)	-0.742	<0.001
MMP-9 (pg/mL)	-0.599	<0.001
sVCAM-1 (pg/mL)	-0.517	<0.001
LVEF%	0.619	<0.001
NT-proBNP (pg/mL)	-0.572	<0.001

Note: IL-6: interleukin-6; TNF-α: tumor necrosis factor-α; MMP-9: matrix metalloproteinase-9; sVCAM-1: soluble vascular endothelial cell adhesion molecule-1; LVEF%: left ventricular ejection fraction percentage; NT-proBNP: N-terminal B-type natriuretic peptide precursor; CRP: C-reactive protein.

nity and cellular immunity, thereby forming AS, which is closely related to plaque stability. The level of TNF-α is positively correlated with carotid intima thickness and age-related AS [12]. As the main form of VCAM-1 entering the blood after vascular endothelial cell exfoliation, sVCAM-1 plays an important role in inflammatory reaction, endothelial injury and thrombosis [13, 14]. Some studies have shown that the level of serum sVCAM-1 in patients with CHD increased significantly, and was positively correlated with the severity of the disease [15]. As the main enzyme in human body to degrade extracellular matrix, MMPs can degrade the barrier formed by cells, and then destroy the adhesion between cells [16]. Based on this, this study selected IL-6, CRP, TNF-α, sVCAM-1 and MMP-9 as one of the evaluation indicators to explore the relationship between expression of inflammatory factors and CHD. The results showed that the levels of CRP, IL-6, TNF-α, MMP-9 and sVCAM-1 in patients with CHD were significantly higher than those in normal people, suggesting that inflammatory response plays an important role in the occurrence and development of CHD.

As a member of the miRNA family, MiR-126 encodes the genes that located in the 7th intron of a gene that specifically expressed in vascular endothelial cells. It is expressed in multiple systems such as the respiratory system, digestive system, and hematopoietic system, among which the specific expression of cardiovascular system is the highest [17]. Studies have shown that miR-126 is closely related to CHD, hypertension, AS and so on [18, 19]. Previous studies have confirmed that VCAM-1 is the target of miR-126, and miR-126 can negatively regulate the expression of VCAM-1. When the expression of miR-126 decreases, the level of VCAM-1 increases significantly, and the level of corresponding inflammatory factors is also up-regulated, thus enhances the adhesion between leukocytes and endothelial cells [20]. Vascular endothelial cells can promote the secretion of apoptotic bodies in the process of apoptosis, thereby increasing the level of expression of miR-126-mediated chemokine ligand 12, and at the same time, it can also weaken the targeting effect of G protein signal 16 regulator, thus affecting the stable type of AS plaque. Current studies have shown the expression of miR-126 in patients with CHD decreased, but there are few reports about its correlation with inflammatory factors and its value in evaluating the prognosis [21]. The results of this study showed that the level of miR-126 in patients with CHD was significantly lower than that in normal people, and it was negatively correlated with the levels of CRP, IL-6, TNF-α, MMP-9, sVCAM-1 and other factors, but positively correlated with LVEF%, which was consistent with the above results. We further discussed the clinical value of miR-126 in evaluating the prognosis of patients. The results showed that when the cutoff value was 0.429, AUC was 0.867, and both the sensitivity and specificity were higher than 0.700, suggesting that miR-126 has a certain predictive value in evaluating the prognosis of patients with CHD.

The sample selected in this study is a single-center small sample population, and the changes of various indicators have not been dynamically observed, so follow-up studies still need to be further confirmed.

To sum up, the level of miR-126 in peripheral blood of patients with CHD decreased significantly, and it is negatively correlated with the severity of the disease and inflammatory reaction, and can be used as one of the auxiliary indicators to evaluate the prognosis of CHD.

Disclosure of conflict of interest

None.

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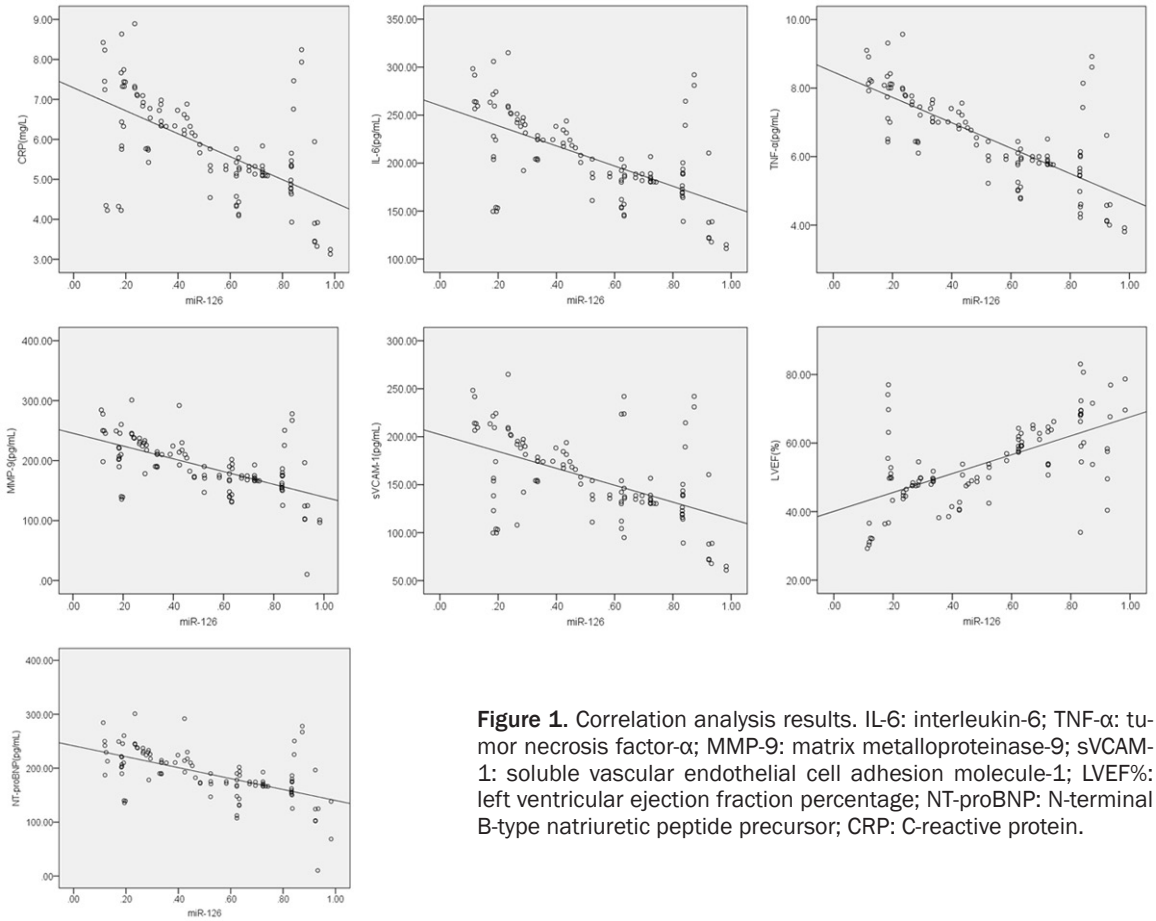

Figure 1. Correlation analysis results. IL-6: interleukin-6; TNF-α: tumor necrosis factor-α; MMP-9: matrix metalloproteinase-9; sVCAM-1: soluble vascular endothelial cell adhesion molecule-1; LVEF%: left ventricular ejection fraction percentage; NT-proBNP: N-terminal B-type natriuretic peptide precursor; CRP: C-reactive protein.

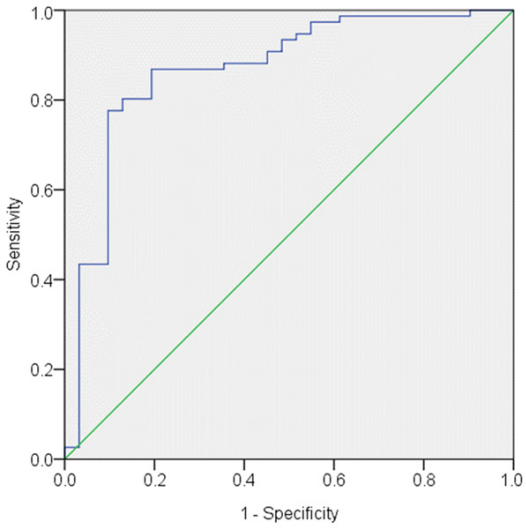

Figure 2. ROC curve results. ROC: receiver operating characteristic.

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