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Original Article

The role of miR-126 in diagnosing coronary heart disease in patients undergoing maintenance hemodialysis

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Abstract: Objective: The goal of this study was to explore the benefits of miR-126 measurement in diagnosis of coronary heart disease in patients undergoing maintenance hemodialysis (HD). Methods: A total of 100 patients underwent maintenance HD in Jiangxi Provincial People's Hospital from June 2018 to December 2018 as the observation group, and 60 underwent physical examination in Jiangxi Provincial People's Hospital during the same period as the control group. Correlations between the relative expression level of miR-126 and the severity of coronary heart disease as well as the level and the degree of coronary artery stenosis in HD patients were analyzed. Results: Relative expression level of miR-126 was significantly lower in HD patients with coronary heart disease than that in the control group and in HD patients without coronary heart disease (both $P < 0.001$). The area under the ROC curve of miR-126 for diagnosis of coronary heart disease in HD patients was 0.879 (95% CI: 82.6%-93.2%), the Youden index was 0.650, the sensitivity was 0.900, and the specificity was 0.750. There was a negative correlation between the degree of coronary artery stenosis and the relative expression level of miR-126 in serum. The relative expression level of miR-126 was low in HD patients with myocardial infarction (MI) and significantly lower in those patients with ST-elevation MI. The area under the ROC curve of miR-126 for diagnosis of MI in HD patients was 0.958 (95% CI: 91.7%-99.9%), the Youden index was 0.856, the sensitivity was 0.889, and the specificity was 0.967. Conclusion: The relative expression level of serum miR-126 has a certain predictive value for coronary artery lesions in HD patients.

Keywords: miR-126, maintenance hemodialysis, coronary heart disease, diagnostic value

Introduction

The incidence of chronic kidney disease (CKD) is on the rise year by year along with economic growth, and its prevalence is now as high as 11% [1]. With the increase of its incidence, a growing number of people have developed the end-stage renal disease (ESRD) and cardiovascular disease [2]. The treatment for patients with ESRD is to choose the appropriate replacement therapy for different patients, including hemodialysis (HD), peritoneal dialysis or kidney transplant [3]. Over two million people need replacement therapy every year in the world, and maintenance hemodialysis is currently the major treatment for ESRD in China [4]. It is found that as increasing number of patients undergoing maintenance hemodialysis, cardiovascular events are the most common causes for their deaths, of which myocardial infarction (MI) is the leading cause of death, accounting for about 50% of all deaths in patients undergoing maintenance hemodialysis [5]. Early prediction of cardiovascular events and active intervention have a positive effect on prognosis in patients. Previous studies have found that when myocardial cells are damaged, some proteins and molecules will leak out from the cells into the blood in large quantity, of which there are such well-known clinical indicators as cardiac troponin I, creatine kinase, creatine kinase isoenzyme, and myoglobin [6]. Of the four indicators, cardiac troponin I is the gold standard biomarker for diagnosis of myocardial infarction (MI), and the other three substances have lower specificity and sensitivity than cardiac troponin I for diagnosis of the disease as they can also be detected in patients without ischemia [7-9]. With development of genetic testing technologies, some non-coding RNAs (microR-

NAs, miRNAs) have been found to be abnormally expressed in the serum of patients with MI [10]. Previous studies reveal that miR-126 mainly plays its role in inhibiting apoptosis and is abnormally expressed in a variety of tumors [11-13]. A previous study associated with the cardiovascular system revealed for the first time a relationship between miR-126 and coronary heart disease, indicating that miR-126 level changed consistent with the changes in cardiac troponin I level in the early-phase of MI, but presented earlier decline to the bottom [14]. Moreover, miR-126 expression was stable in the human body fluid [15]. This study monitored the miR-126 expression in blood of the circulating system of patients undergoing hemodialysis, so as to explore the relationship of miR-126 expression with the presence of coronary heart disease and provide some clinical reference for early assessment of coronary heart disease in patients undergoing maintenance hemodialysis.

Materials and methods

Subjects

A total of 100 patients were recruited for the study and underwent maintenance hemodialysis in Jiangxi Provincial People's Hospital from June 2018 to December 2018 as the observation group. Their age ranged from 40 to 80 years old, with a mean age of 62.5 ± 8.2 years. A total of 60 people who had undergone physical examination in the above-mentioned hospital during the same period were enrolled as the control group, with a mean age of 64.3 ± 7.6 years. This study was approved by the Ethics Committee of Jiangxi Provincial People's Hospital, and informed consents were obtained from all the participants. Patients who had undergone maintenance hemodialysis for more than five months, and aged older than 18 years were included. Exclusion criteria were: (1) patients who had incomplete clinical data; (2) patients who had severe malnutrition, tumors, or other severe diseases; (3) patients with poor treatment compliance due to mental disorders or cerebrovascular diseases; and (4) patients who had been recently given glucocorticoids or immunosuppressant agents.

Grouping

Diagnostic criteria and classification for coronary heart disease were based on the criteria established by the Chinese Society of Cardiology in 2007 [16]. Of the 100 patients underwent maintenance hemodialysis in this study, 25 patients without coronary heart disease were categorized as the observation group 1, and 75 patients with coronary heart disease was set as the observation group 2. Furthermore, the 100 patients were divided into four groups according to the degree of the coronary stenosis (≤ 30% stenosis, 31%-49% stenosis, 50%-69% stenosis, and ≥ 70% stenosis). According to the diagnostic criteria, the 75 patients with coronary heart disease were divided into group A (n = 25, stable angina), group B (n = 20, unstable angina), group C (n = 17, non-ST elevation MI), and group D (n = 13, ST-elevation MI).

Isolation of miRNA

In this study, the TRIzol reagent kits (Molecular Research Center, Inc., USA) were used to isolate total RNA from plasma and to detect the concentration and integrity of RNA. The upstream and downstream primers were purchased from Guangzhou Ruibo Biotechnology Co., Ltd. [17]. The miRNA was reversely transcribed into cDNA using the reverse transcription (RT) kit (Fermentas, Canada). The cDNA was later used as a template to amplify DNA. Finally, quantitative real-time PCR was used to determine the expression levels of miRNA-126 in serum samples [18]. As for samples, 2 mL of peripheral venous blood was collected from all the patients in the morning following overnight fasting from 10 pm. For acute MI patients, 2 mL of peripheral venous blood was drawn from patients before the interventional surgery. EDTA was added to the blood test tubes to keep the cells intact, and then the tubes were gently shaken, so that the blood cells were in full contact with the anticoagulants. These blood samples were then placed in a refrigerator at 4°C and subjected to plasma separation within 2 hours. The plasma was centrifuged for 10 minutes using a high-speed centrifuge, and only the supernatants were aspirated and placed in the Eppendorf tubes. These tubes were then centrifuged for another 10 minutes. After the second centrifugation, the plasma was divided into equal aliquots of 500 μL before placing into a refrigerator at -80°C. The total RNA was extracted by the TRIzol reagent kit and then reversely transcribed using stem-loop RT primers and Moloney Murine Leukemia Virus Reverse Transcriptase. Then, the has-miR-126

Table 1. Comparison of baseline characteristics

Items	Control group	Observation group 1	Observation group 2	χ^2/F	P
Gender (male/female)	32/28	15/10	40/35	0.682	0.711
Age (Years)	64.3 ± 7.6	61.8 ± 9.5	63.4 ± 7.6	0.927	0.398
SBP (mmHg)	107.83 ± 7.65	150.84 ± 8.10	152.93 ± 7.23	658.681	< 0.001
DBP (mmHg)	68.50 ± 5.09	86.84 ± 8.10	89.01 ± 6.98	176.117	< 0.001
TG (mmol/L)	1.14 ± 0.69	1.79 ± 0.66	1.79 ± 0.66	17.542	< 0.001
TC (mmol/L)	4.56 ± 0.44	5.86 ± 0.44	5.86 ± 0.44	168.493	< 0.001
LDL (mmol/L)	1.52 ± 0.44	1.05 ± 0.34	1.12 ± 0.34	23.237	< 0.001
HDL (mmol/L)	2.42 ± 0.42	3.82 ± 0.87	3.82 ± 0.86	69.644	< 0.001
Hb (g/L)	131.68 ± 10.27	102.08 ± 9.57	102.79 ± 10.28	153.097	< 0.001
BMI (kg/m^2)	26.72 ± 1.96	26.99 ± 2.03	27.27 ± 2.13	0.769	0.465
Glu (mmol/L)	5.70 ± 0.78	5.58 ± 0.77	5.56 ± 0.77	0.561	0.572
BUN (mmol/L)	5.88 ± 0.43	17.99 ± 0.66	17.87 ± 0.65	8084.225	< 0.001
sCr (μmol/L)	89.13 ± 1.55	698.30 ± 221.18	683.41 ± 220.75	220.287	< 0.001

Note: SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglyceride; TC: total cholesterol; LDL: low density lipoprotein; HDL: high density lipoprotein; Hb: hemoglobin; BMI: body mass index; Glu: blood glucose level; BUN: blood urea nitrogen; sCr: serum creatinine.

stem-loop primers were used in the process. The upstream and downstream primer sequences were as follows: 5'-TATCCAGTGATTCCGACCGCCGCATGGAGTCTG-3' (miR-126) and 5'-T CCGCTCTTGGTGTGGTGTGAGTCGC-3' (miR-126), and the sequence of reference gene U6 was 5'-TCCGCTCTTGGTGT-GGTGTGAGTCGC-3'. The RT reaction was based on a 25 μL mixture, which included 12.5 μL of SYBR Premix (2x), 0.5 μL of the upstream and downstream primers of a target gene, 2.0 μL of cDNA templates, and 9.5 μL of ddH_2O. The mixture was amplified for 35 cycles, with each cycle consisting of an initial denaturation of 4 minutes at 94°C, a denaturation of 40 seconds at 95°C, an annealing of 30 seconds at 60°C and an extension of 30 seconds at 72°C and were processed with a final extension of 1 minute at 72°C. The PCR products were detected by agarose gel electrophoresis. The relative expression levels of miR-126 were analyzed by the $2^{-\Delta\Delta C(T)}$ method with U6 snRNA expression levels as the standard.

Statistical analysis

Data were analyzed with the use of SPSS 22.0 statistical software. Continuous variables are expressed as mean ± standard deviation ($\overline{x}$ ± sd). When the data were normally distributed and homogeneity of variance assumption was not violated, comparisons within the groups were conducted based on paired t-tests, otherwise, the comparisons were performed based on Wilcoxon rank sum tests. Comparisons among the groups were made based on one-way analysis of variance. When there were significant differences among the groups, the Bonferroni post-hoc test was used for pairwise comparison. Pearson correlation coefficient was used to measure the linear correlation between two variables. *P* value of < 0.05 was considered statistically significant.

Results

Comparison of baseline characteristics

There were significant differences among the three groups in systolic blood pressure (SBP), diastolic blood pressure (DBP), triglyceride, total cholesterol, low-density lipoprotein, high-density lipoprotein, serum creatinine, and blood urea nitrogen (BUN) (all P < 0.05). No significant differences were found among the three groups in age, gender, and body mass index (BMI), and blood sugar level (all P > 0.05) as shown in **Table 1**.

Comparison of relative expression levels of miR-126 based on the complication of coronary heart disease in HD patients

The relative expression level of miR-126 was significantly lower in the observation group 2 than that in the observation group 1 and the control group (both P < 0.001) as shown in **Table 2** and **Figure 1**. The area under the ROC curve of miR-126 for diagnosis of coronary

Table 2. Comparison of relative expression levels of miR-126 based on complication of coronary heart disease in HD patients

Groups	Cases	Relative expression levels of miR-126
Control group	60	0.372 ± 0.046
Observation group 1	25	0.356 ± 0.051
Observation group 2	75	0.232 ± 0.044
F	-	176.183
P	-	< 0.001

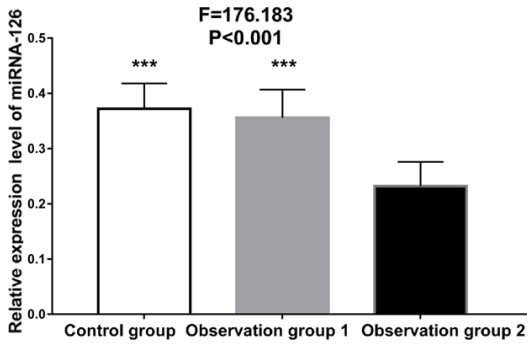

Figure 1. Comparison of relative expression levels of miR-126 based on the complication of coronary heart disease in HD patients. Compared with the observation group 2, ***P < 0.001.

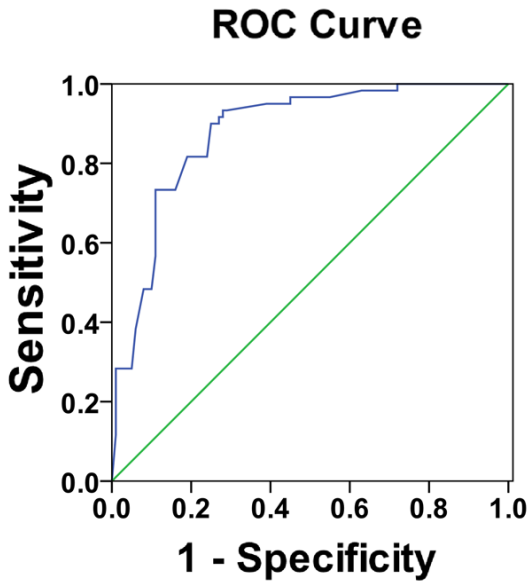

Figure 2. Diagnostic value of miR-126 for coronary heart disease.

heart disease in HD patients was 0.879 (95% CI: 82.6%-93.2%), the Youden index was 0.650, the sensitivity was 0.900, and the specificity was 0.750 as shown in **Figure 2**.

Comparison of relative expression levels of miR-126 based on different degrees of coronary artery stenosis in HD patients

The relative expression level of miR-126 in patients with ≤ 30% stenosis was significantly higher than that in patients with 31-49%, 50-69% and ≥ 70% stenosis (all P < 0.05). The relative expression level of miR-126 in patients with 31-49% stenosis was significantly higher than that in patients with 50-69% and ≥ 70% stenosis (both P < 0.05). The relative expression level of miR-126 in patients with 50-69% stenosis was significantly higher than that in patients with ≥ 70% stenosis (P < 0.05) as shown in **Table 3** and **Figure 3**. There was a negative correlation between the degree of coronary artery stenosis and the relative expression level of miR-126 in the serum (r = -0.358, P = 0.031).

Comparison of relative expression levels of miR-126 based on different coronary heart diseases in HD patients

The relative expression level of miR-126 in group A (stable angina) was significantly higher than that in group C (non-ST-elevation MI) and group D (ST-elevation MI) (both P < 0.001). The relative expression level of miRNA-126 in group B (unstable angina) was significantly higher than that in group D (P < 0.01). See **Table 4** and **Figure 4**. The area under the ROC curve of miR-126 for diagnosis of MI in HD patients was 0.958 (95% CI: 91.7%-99.9%), the Youden index was 0.856, the sensitivity was 0.889, and the specificity was 0.967 as shown in **Figure 5**.

Discussion

The incidence of kidney disease is increasing annually due to a variety of factors such as the changes in diet structure and exercise habits, environmental changes, and accelerated population aging. The number of the patients with end-stage renal disease who need HD is also on the rise. It is estimated that there will be approximately 5.4 million HD patients worldwide by 2030 [19]. The most common cause of death in HD patients is cardiovascular disease [5]. Moreover, patients with uremia have disorders of calcium and phosphorus metabolism. Hyperphosphatemia increases cardiovascular

Table 3. Comparison of relative expression levels of miR-126 based on different degrees of coronary artery stenosis in HD patients

Degrees of coronary artery stenosis	Cases	Relative expression levels of miR-126
≤ 30%	13	0.375 ± 0.034
31-49%	12	0.330 ± 0.063
50-69%	45	0.243 ± 0.051
≥ 70%	30	0.216 ± 0.032
F	-	44.525
P	-	< 0.001

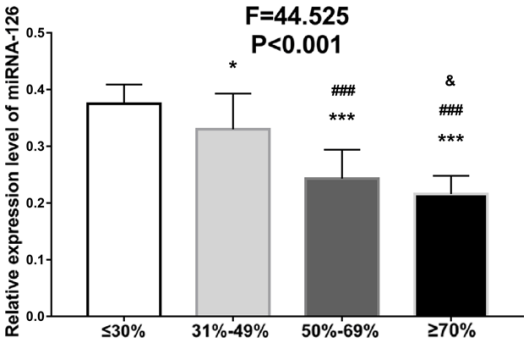

Figure 3. Comparison of relative expression levels of miR-126 based on different degrees of coronary artery stenosis in HD patients. Compared with patients with ≤ 30% stenosis, $^{*}P < 0.05$; compared with patients with ≤ 30% stenosis, $^{***}P < 0.001$; compared with patients with 31%-49% stenosis, $^{###}P < 0.001$; compared with patients with 50%-69% stenosis, $^{\&}P < 0.05$.

events in patients with kidney disease [20]. Patients with uremia are often complicated with secondary hyperparathyroidism. Parathyroid hormone is an independent cardiovascular risk factor as it is associated with the decrease of blood calcium levels due to inhibition of the absorption of active vitamin D [21]. HD also causes damage to the myocardium for such factors as the changes in hemodynamics during dialysis, use of anticoagulants, the occurrence of micro-inflammation, and retention of toxins that causes damages to cardiac function due to inadequate dialysis [22, 23].

Studies on the role of miRNA in the cardiovascular system have found that detection of miRNA expression has a certain diagnostic value for early evaluation and prognosis of coronary heart disease, myocardial infarction, heart failure, and atrial fibrillation [15]. miRNA expression is stable in human body fluid, which presents a great potential for the active exploration of measurement of miRNAs for cardiovascular diseases [24, 25]. In the study of arteriosclerosis, miR-126 is found to inhibit the activation of endothelial cells, leading to damages to the cardiovascular system [26]. When endothelial cells are damaged, the permeability of blood vessels increases and thus causes the deposition of low-density lipoprotein in the vascular wall to promote further progression of arteriosclerosis [27, 28]. This study showed that a higher degree of stenosis was associated with a lower relative expression of miRNA-126, which was consistent with previous studies. miR-126 expression was firstly found to be significantly reduced in patients with coronary heart disease [14]. The substantially decreased release of miR-126 by endothelial cells is due to the role of miR-126 in inhibiting endothelial cell activation and release of apoptotic bodies [29, 30]. In this study, HD patients with coronary heart disease had lower relative expression of miR-126, which is consistent with the findings of previous studies. Furthermore, investigation on miR-126 in diagnosing coronary heart disease in this study reveals that it had good predictive power with a sensitivity of 0.900 and a specificity of 0.750. A previous study showed that miR-126 level changed consistent with the changes in the cardiac troponin I levels in the early-phase of MI, but declined to the bottom earlier [14]. In this study, the relative expression of miRNA-126 was found to be low in MI patients, and that reduction was more evident in ST elevation MI, which are consistent with aforementioned studies. In diagnosis of MI, the sensitivity of miR-126 was 0.889, and the specificity was 0.967, indicating good predictive value.

There are limitations in this study due to the small sample size. Multi-center research with large sample size can be conducted in further studies. However, despite these limitations, this study conclusively reveals that the relative expression level of serum miR-126 has a certain predictive value for coronary artery lesions in HD patients.

Disclosure of conflict of interest

None.

Table 4. Comparison of relative expression levels of miR-126 based on different coronary heart diseases in HD patients

Groups	Cases	Relative expression levels of miR-126
Group A	25	0.264 ± 0.059
Group B	20	0.238 ± 0.015
Group C	17	0.212 ± 0.007
Group D	13	0.185 ± 0.013
F	-	16.396
P	-	< 0.001

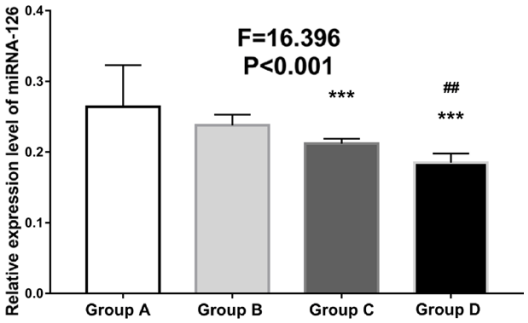

Figure 4. Comparison of relative expression levels of miR-126 based on different coronary heart diseases in HD patients. Compared with group A, ***P < 0.001; compared with group B, ##P < 0.01.

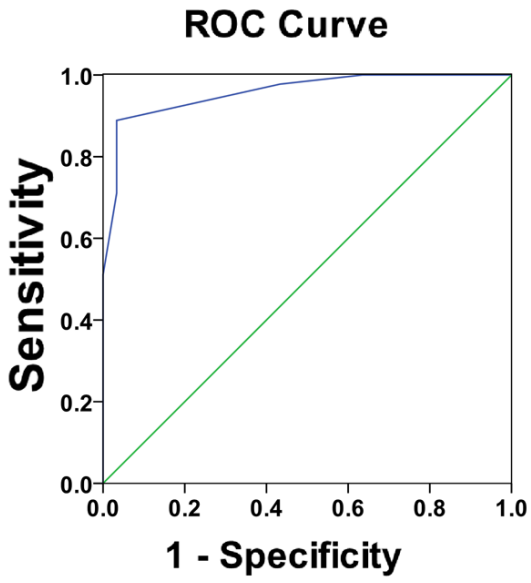

Figure 5. Diagnostic value of miR-126 for MI.

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