

Original Article

Combination of miR-124, miR-188 and MMP-9 in the diagnosis and prognosis assessment of acute cerebral infarction

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Abstract: Objective: To evaluate the use of miR-124 and MMP-9 in combination with miR-188 in the diagnosis and prognosis assessment of acute cerebral infarction (ACI). Methods: One hundred and two patients with ACI and 102 healthy individuals were retrospectively and simultaneously analyzed. The differences in the expressions of miR-124, miR-188, and MMP-9 were compared between the ACI group and the healthy group, as well as among some subgroups of patients with various types and sizes of ACI and different prognoses. The expressions of miR-124 and miR-188 were tested using polymerase chain reaction (PCR), and the expression of serum MMP-9 was determined using an enzyme-linked immunosorbent assay (ELISA). Results: The levels of miR-124 and MMP-9 were elevated, but the levels of miR-188 were significantly decreased in the ACI group compared with the corresponding levels in the healthy group (all $P < 0.05$). With an increase in the sizes of the ACI, the miR-124 and MMP-9 levels were elevated, but the miR-188 levels decreased gradually (all $P < 0.05$). The miR-124 and MMP-9 levels in the patients with good prognoses (the Lh group) were lower than those in the patients with poor prognoses (the BI group), but the levels of miR-188 were higher (all $P < 0.05$). The patients with poor prognoses showed trends of substantial elevation in the miR-124 and MMP-9 levels and a significant decrease in the miR-188 levels when compared with those with good prognoses (all $P < 0.05$). Patients with small-sized and mild ACI were more likely to be in the Lh group than in the BI group (all $P < 0.05$), but the patients with large-sized and severe ACI were much fewer (all $P < 0.05$). Both miR-124 and MMP-9 were independent risk factors for ACI, and miR-188 was a protective factor for ACI. Taking miR-124, miR-188 and MMP-9 as combined variables, the sensitivity and specificity of ACI were determined. The findings showed that the combination of the three types of miRNAs (miR-124, miR-188, and MMP-9) was more useful in the diagnosis of ACI than measuring the miR-124, miR-188, or MMP-9 level alone. Conclusion: miR-124 and MMP-9 were over-expressed, but the miR-188 levels were low in the serum of patients with ACI. Dynamic changes in the miR-124, miR-188, and MMP-9 in the serum were seen in the presence and development of ACI in the patients. The combination of the three factors (miR-124, miR-188, and MMP-9) has important implications in the diagnosis of ACI and the assessment of disease's changes and prognosis in ACI patients.

Keywords: miR-124, miR-188, MMP-9, acute cerebral infarction, prognosis

Introduction

Cerebral infarction (CI) refers to ischemia, necrosis, or a softening of the tissues in the brain that occur when the blood and oxygen supply to the tissues in the brain is interrupted and the blood circulation in the tissues is abnormal. The rates of morbidity, recurrence and mortality of CI are high [1]. According to the findings of *The Third National Retrospective Sampling Survey of Death Causes*, cerebrovas-

cular diseases are the leading cause of death in China, and CI is a single disease associated with a high rate of disability [2]. Without any signs, CI occurs with a rapid onset and at a high mortality rate. Some patients can be cured, but others may have severe sequelae such as brain injury, language disturbance, or limb dyskinesia [3].

Among the miRNAs associated with CI, miR-188 is a newly discovered miRNA. miR-188 has

Table 1. The primer sequences

Gene	RT	Primer sequences
miRNA-124	F	5'-GCTAAGGCACGCGGTG-3'
	R	5'-GTGCAGGGTCCGAGGT-3'
miRNA-188	F	5'-GTCAACGCCGTAGATGACC-3'
	R	5'-TTGTTAGCCCCGTTCTTCAG-3'
U6	F	5'-CTCGCTTCGGCAGCACATATACT-3'
	R	5'-ACGCTTCACGAATTTGCGTGTG-3'

been found to be implicated in the development of cardiovascular and cerebrovascular diseases. In addition to miR-188, MMP-9 is also an independent risk factor for cerebrovascular disorders. MMP-9 is abnormal in patients with cerebrovascular disorders. The levels of MMP-9 are directly related to the risk for CI, as the expression of MMP-9 directly affects the prognosis of patients with CI [4]. miR-124 is a cerebral, tissue-specific miRNA which is involved in the development of nerves in the brain. miR-124 plays a crucial role in the presence and development of CI, and the expression levels of miR-124 are directly associated with the conditions and prognosis of CI [5]. miR-188 is an independent risk factor for cerebrovascular diseases, and miR-124 is implicated in nerve development in the brain. Clinically, testing miR-124 and miR-188 together can be used to diagnose brain diseases and to assess their prognosis, but the sensitivity is low when miR-124 or miR-188 is used to make the determination alone [6]. Therefore, the present study was designed to explore the significance of the combination of miR-124, miR-188, and MMP-9 in the diagnosis of acute cerebral infarction (ACI) and in the prognosis assessment in such patients.

Study subjects and methods

Study subjects and group assignment

A retrospective analysis was performed. In the analysis, 102 ACI patients treated in the hospital from February 2017 to December 2018 were enrolled. Of the 102 ACI patients, 58 were male and 44 were female, with a mean age of 60.01 ± 9.65 years; mild ACI occurred in 31 patients, moderate ACI in 43, and severe ACI in 28; 53 had poor prognoses (the B1 group), 49 had good prognoses (the Lh group); 34 had small-sized ACI; 43 had medium-sized ACI, and 25 large-sized ACI. In the same period, 102

healthy volunteers were enrolled as controls. Of the 102 healthy volunteers, 57 were male, and 45 were female, with a mean age of 59.87 ± 10.03 years.

Exclusion and inclusion criteria

The inclusion criteria were patients with ACI as confirmed by CT or MRI, and their family members were informed and gave consent to participate in the study [7]. Patients who met any of the following conditions were excluded from the study: severe cerebral hemorrhage caused by trauma, pregnancy, cardiac disease, renal disorder, or unstable blood flow.

Outcome measures and methods

Testing methods: Venous blood samples were collected from the patients with ACI and the healthy controls. The expression of miR-124 and miR-188 was tested using polymerase chain reaction (PCR), and the expression of MMP-9 in the serum was determined using an enzyme-linked immunosorbent assay (ELISA). The kits were purchased from Shanghai Hengyuan Biological Technology (Shanghai, China). The experiments were carried out strictly in accordance with the kit's instructions.

Determination of the serum miR-124 and miR-188 expressions using PCR: A fasting venous blood sample was collected from each patient. After a 10-minute centrifugation at 2500 r/min, serum was taken and put into a centrifuge tube. Total RNA was extracted using a Trizol-based method and reversely transcribed into cDNA. The experiments were conducted according to the instructions. The miR-124 and miR-188 levels were determined using the DNA fluorescent dye SYBR Green I. U6 was used as the internal reference gene. The reactions were carried out with an initial denaturation at 60°C for 10 min, followed by 40 cycles of 95°C for 30 s, 72°C for 30 s, and 95°C for 5 min. The experiment was repeated at least three times. The relative quantifications of the miR-124 and miR-188 expressions were calculated using the $2^{-\Delta\Delta CT}$ method. The primer sequences are provided in **Table 1**.

Outcome measures

One outcome was the expressions of miR-124, miR-188, and MMP-9 compared between the

Table 2. The expressions of miR-124, miR-188, and MMP-9 in the ACI group and the healthy group

Group	n	miRNA-124	miRNA-188	MMP-9
Cerebral infarction group	102	2.91±1.16	0.52±0.19	432.21±72.06
Healthy group	102	1.13±0.52	1.12±0.11	156.56±16.23
t		14.14	27.60	37.69
P		<0.001	<0.001	<0.001

Note: ACI: acute cerebral infarction.

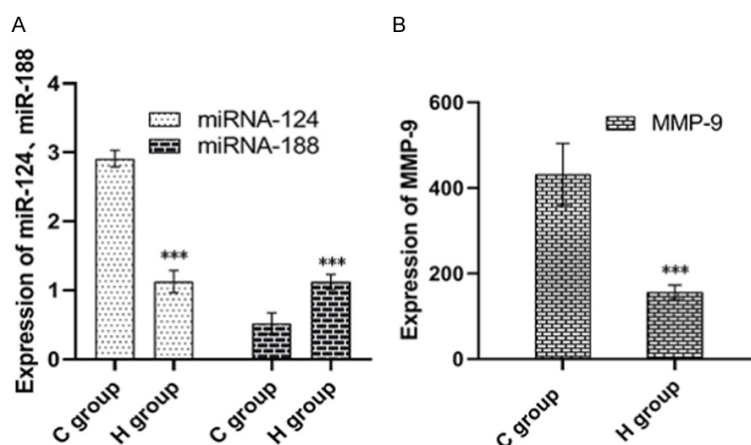


Figure 1. A indicates the expression of miR-124 and miR-188 in each group; B indicates the expression of MMP-9 in each group; C Group indicates acute cerebral infarction group, H Group indicates healthy group; *** indicates compared with acute cerebral infarction, there was a statistical difference, $P < 0.001$.

acute CI group and the healthy group. Other outcomes included the expressions of miR-124, miR-188, and MMP-9 in the patients with different types of ACI, the differences in the miR-124, miR-188, and MMP-9 expressions in the patients with ACI of various sizes, the serum expressions of miR-124, miR-188, and MMP-9 in the Lh and BI groups, the sizes and types of ACI compared between the Lh and BI groups, and a regression analysis on the quantification results of miR-124, miR-188, and MMP-9 for ACI.

Criteria for severity grading and prognosis assessment

The Modified Rankin Scale (mRS) was used to evaluate the neurological functions of the ACI patients three months after discharge, that is, an mRS score for which no more than 2 indicates a good prognosis, and an mRS score for which more than 2 indicates a poor prognosis [8]. The National Institutes of Health Stroke Scale (NIHSS) was utilized as an evaluation cri-

terion for measuring infarct severity [9]. A score between 16 and 40 indicates severe ACI; a score between 4 and 15 indicates moderate ACI; a score between zero and 3 indicates mild ACI. The sizes of ACI were adjudicated according to the following description [10]: a large-sized ACI $>10 \text{ cm}^3$, a medium-sized ACI ranges from 4 to 10 cm^3 , and a small-sized ACI $<4 \text{ cm}^3$.

Statistical analysis

The expression levels of miR-124, miR-188, and MMP-9 were analyzed using SPSS software, version 22.0. The measurement data were expressed as the means \pm standard deviations; comparisons among three groups were performed using one-way ANOVA, while the pairwise comparisons between groups were made using least-significant difference (LSD) t-tests or a Bonferroni test. The Count data were expressed as n (%)

and measured with the use of a chi-squared test, and a P value <0.05 was considered statistically significant.

Results

Differences in the expression of miR-124, miR-188, and MMP-9 between the ACI group and the healthy group

Compared with the healthy group, the expression levels of miR-124 and MMP-9 in the ACI group were elevated, but the expression levels of miR-188 (0.52 ± 0.19) were significantly decreased. There were significant differences between the two groups (all $P < 0.05$; **Table 2** and **Figure 1**).

The expression levels of miR-124, miR-188, and MMP-9 in patients with different types of ACI

The lowest levels of miR-124 and MMP-9 and the highest levels of miR-188 were reported in

Table 3. The expression levels of miR-124, miR-188, and MMP-9 in patients with different types of ACI

Type of infarction	n	miRNA-124	miRNA-188	MMP-9
Light	31	1.42±0.12	0.94±0.11	261.42±102.03
Medium-sized	43	2.45±0.56*	0.74±0.08*	409.85±126.31*
Heavy	28	2.96±1.03* [#]	0.41±0.05* [#]	516.54±157.65* [#]
F		43.49	297.2	29.22
P		<0.001	<0.001	<0.001

Note: *indicates compared to the mild ACI group, P<0.05; [#]indicates compared to the moderate ACI group, P<0.05; ACI: acute cerebral infarction.

Table 4. The expression levels of miR-124, miR-188, and MMP-9 in patients with ACI of various sizes

Infarct size	n	miRNA-124	miRNA-188	MMP-9
Large area	26	2.86±0.82	0.52±0.04	495.23±85.62
Medium area	42	2.35±0.36*	0.75±0.06*	329.32±63.69*
Small area	34	1.32±0.11* [#]	0.97±0.09* [#]	227.91±56.25* [#]
F		83.93	326.3	129.0
P		<0.001	<0.001	<0.001

Note: *indicates compared to the large-sized ACI group, P<0.05; [#]indicates compared to the medium-sized ACI group, P<0.05; ACI: acute cerebral infarction.

Table 5. Expression of miR-124, miR-188, and MMP-9 in the Lh and BI groups

Group	n	miRNA-124	miRNA-188	MMP-9
Lh group	49	1.26±0.12	0.69±0.07	209.32±53.69
BI group	53	2.25±0.29	0.46±0.05	245.23±85.62
t		22.2	19.2	2.558
P		<0.001	<0.001	0.012

Note: Lh group: patients with good prognoses; BI group: patients with poor prognoses.

patients with mild ACI; the highest levels of miR-124 and MMP-9 and the lowest level of miR-188 were reported in those patients with severe ACI; the levels of miR-124 and MMP-9 in patients with moderate ACI were higher than those with mild ACI but lower than those with severe ACI (all P<0.05; **Table 3**).

The expression levels of miR-124, miR-188, and MMP-9 in patients with ACI of various sizes

The lowest levels of miR-124 and MMP-9 and the highest levels of miR-188 were found in patients with small-sized ACI; the highest levels of miR-124 and MMP-9 and the lowest levels of miR-188 were found in those with large-sized ACI; the levels of miR-124 and MMP-9 were higher in the patients with medium-sized ACI

than in those with small-sized ACI (all P<0.05; **Table 4**).

Expressions of miR-124, miR-188, and MMP-9 in the Lh and BI groups

When compared with the Lh group, the expression levels of miR-124 and MMP-9 were elevated significantly, but the expression level of miR-188 was markedly decreased in the BI group (all P<0.05; **Table 5**).

Types and sizes of ACI in the Lh and BI groups

More patients with small-sized ACI were in the Lh group, but more patients with medium-sized ACI were in the BI group. The number of patients with severe ACI was small in the Lh group (only 8 patients), as was the number of patients with mild CI in the BI group (only 10). In the Lh group, the difference between the number of patients with mild ACI and the number of patients with moderate ACI was one; in the BI group, the difference between the number of patients with severe ACI and the number of patients with moderate ACI was 3. The number of patients

with small-sized and mild ACI in the Lh group was significantly larger than it was in the BI group, but the number of patients with large-sized and severe ACI was significantly smaller (all P<0.05; **Table 6**).

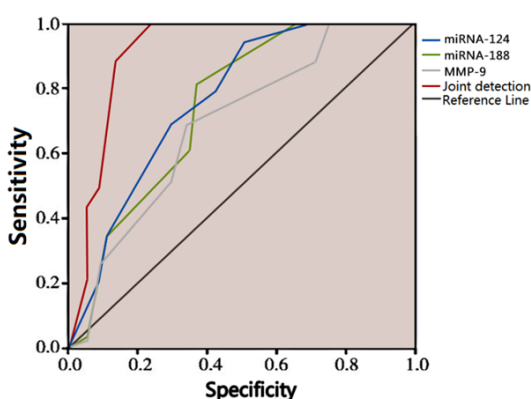
Regression analysis on miR-124, miR-188 and MMP-9 detection for ACI

Considering miR-124, miR-188, and MMP-9 as variables, the sensitivity and specificity of ACI detection were more valuable than the detection with miR-124, miR-188, or MMP-9 alone. The results from the logistic regression analysis showed that both miR-124 and MMP-9 were independent risk factors for ACI, and miR-188 was a protective factor for ACI, as shown in **Figure 2** and **Table 7**.

Table 6. Comparison of the clinical data of the patients in the Lh and BI groups

Clinical data	Lh group (n=49)	BI group (n=53)	χ^2	t
Infarct size				
Large area	8 (16.3%)	17 (32.1%) [#]	10.456	0.015
Medium area	17 (34.7%)	26 (49.0%)		
Small area	24 (49.0%)*	10 (18.9%)		
Type of infarction				
Heavy	8 (16.3%)	20 (37.7%) [#]	9.113	0.027
Medium-sized	20 (40.8%)	23 (43.4%)		
Light	21 (42.9%)*	10 (18.9%)		

Note: *indicates compared to the BI group, $P < 0.05$; [#]indicates compared to the Lh group, $P < 0.05$; Lh group: patients with good prognoses; BI group: patients with poor prognoses.

**Figure 2.** Regression analysis on miR-124, miR-188, and MMP-9 detection for acute cerebral infarction (ROC curve).

Discussion

Patients with CI are on the increase in China, with a trend of the prevalence changing from middle-aged and old populations to the young population. Data from *The Third national retrospective sampling survey of death Causes* shows that nearly 2.3 million cases of cerebral stroke are caused by CI per year in China. Among them, 1.7 million patients could not be completely cured or even died, so CI has adversely affected humans' health and quality of life [12]. Clinicians have recently conducted multiple profound studies on the pathological mechanisms of CI patients, and have found that several miRNAs play important roles in ischemic injuries of the central nervous system in CI patients [13]. Of the miRNAs, miR-124, miR-151, and miR-210 are closely associated with the neurological deficits in the patients

with CI [14]. CI not only affects the patients' quality of life, but it also seriously threatens their safety. Therefore, a good understanding of the relationship between CI and miRNAs in advance has become a hotspot in exploring how to prevent and manage CI. It is of great value to the development of treatment regimens and the improvement of patient prognosis [15].

In the present study, comparisons of the expression levels of miR-124, miR-188, and MMP-9

between the ACI group and the healthy group, and among the subgroups with different types of ACI showed that as CI deteriorated, the levels of miR-124, MMP-9 became elevated, but the levels of miR-188 decreased in the ACI patients. A previous study demonstrated that the levels of miR-124 are elevated during ischemic stress in the body, which might be a protective response of the body; additionally, the time-and-space-specific distribution of miR-124 in various cells and tissue types affects a wide range of biological functions in the central nervous system [16]. In another study, a trend of elevated levels of MMP-9 in serum was observed in patients with CI; the risk of CI was reduced significantly when MMP-9 in the serum remained at a low level [17]. The serum levels of miR-124 are elevated in CI patients, so the level of miR-124 is positively correlated with CI and is one of the independent risk factors for CI [18]. In the case of hypoxia or ischemia in the brain, antigen stimulation increases substantially and the levels of MMP-9 in patients elevate abnormally. The elevated MMP-9 levels may result in damage to the vascular intima, hence aggravating the death of brain cells and deteriorating the conditions of CI patients [19]. This is consistent with the findings in the present study.

In the present study, the serum levels of miR-124, miR-188, and MMP-9 were compared among subgroups of patients with ACI of various sizes, as well as between the Lh group and the BI group, and the sizes and types of CI were also compared. The findings revealed that with an increase in the ACI sizes, the levels of miR-

Table 7. Logistic regression analysis results

Factor	β	SE	OR	95% CI	P
miRNA-124	1.819	0.485	7.691	3.109-31.752	P<0.001
miRNA-188	-1.832	0.743	0.117	0.034-0.428	P<0.001
MMP-9	1.396	0.588	9.522	2.163-37.415	P<0.001

Note: CI: Cerebral Infarction.

124 and MMP-9 were elevated gradually, but the levels of miR-188 decreased; the expression levels of miR-124 and MMP-9 were lower in patients with good prognoses than in those with poor prognoses, and the expression levels of miR-188 in patients with poor prognoses was higher than they were in the patients with poor prognoses; both miR-124 and MMP-9 were independent risk factors for CI, and miR-188 was a protective factor for CI. According to published studies, miR-188 precludes the improvements in synaptic plasticity and cognitive function resulting from the inhibition of 2-Ag metabolism, and miR-188 is also implicated in the pathophysiological mechanism for CI, so it is a potential biological marker for CI [20]. In a clinical trial, the injuries in the brain deteriorated when the levels of miR-188 were reduced in the serum. miR-188 activated the oxidative reaction of the body, acted on the related pathways, and ultimately alleviated the nervous and vascular injuries in the brain [21]. The over-expression of MiR-124 down-regulates the endothelial cell-related signaling pathways and inhibits the repair of tissues in the brain after CI in patients. The neurons remain in an ischemic status, and the CI patients' conditions are worsened [22]. An ROC curve analysis indicated that the specificity and sensitivity and the area under ROC curves of CI detected by miR-124, miR-188, and MMP-9 in combination were higher than those determined by miR-124, miR-188 or MMP-9 alone, suggesting the combination of the three factors (miR-124, miR-188, and MMP-9) is more beneficial in clinical practice.

However, there are still some limitations to the present study, such as the big differences in time, sample size, detection methods and performers. Thus, more experimental methods should be added into future research to explore miR-124, miR-188, and MMP-9, and the pathogenesis of CI, so as to provide more favorable evidence for the treatment of CI.

In conclusion, miR-124 and MMP-9 are over-expressed in the serum of patients with ACI, but miR-188 is low-expressed, and dynamic changes in the levels of miR-124, miR-188, and MMP-9 in serum are observed during the presence and development of ACI in such patients. The combination of the three factors (miR-124, miR-188, and MMP-9) is of significance in the diagnosis of ACI and in assessing the changes in the conditions and prognoses of ACI patients.

Disclosure of conflict of interest

None.

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