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Original Article

miR-195 and miR-497 in acute stroke and their correlations with post-stroke cognitive impairment

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Abstract: Objective: To quantify the expression of miR-195 and miR-497 in acute stroke and to evaluate their correlations with post-stroke cognitive impairment. Methods: A total of 108 patients with acute stroke admitted to our hospital from January, 2019 to June, 2020 were enrolled as a patient group, and 76 healthy volunteers were recruited as a normal group. Levels of serum miR-195 and miR-497 in the two groups were quantified. Neurological and cognitive functions were tested by National Institutes of Health Stroke Scale (NIHSS) and Montreal Cognitive Assessment (MoCA), respectively. Diagnostic value of serum miR-195 and miR-497 in acute stroke was evaluated by receiver operating characteristic (ROC) curve, and independent risk factors were determined by multivariate logistic regression. Results: Levels of serum miR-195 and miR-497 increased in acute stroke. The area under the curve (AUC) of serum miR-195 in the diagnosis of acute stroke was 0.901, while that of serum miR-497 was 0.922. Levels of miR-195 and miR-497 were positively correlated with NIHSS score and negatively correlated with MoCA score. Logistic regression analysis demonstrated that family history of stroke, diabetes, hypertension, NIHSS score, MoCA score, miR-195, and miR-497 were independent risk factors for acute stroke. Conclusion: Serum miR-195 and miR-497 are elevated in acute stroke and associated with the loss of neurologic and cognitive functions. They may be biomarkers for diagnosis and prognosis of acute stroke.

Keywords: Acute stroke, miR-195, miR-497, diagnosis, prognosis

Introduction

Acute stroke, a common clinical acute cerebrovascular dysfunction, is a consequence of ischemia induced by occlusion or rupture of cerebral blood vessels, or tissue damage induced by acute hemorrhagic cerebral circulation disorder, making patients more vulnerable to long-term disability and cognitive dysfunction [1, 2]. Although magnetic resonance imaging (MRI) and computed tomography (CT) are preferred options for the diagnosis of acute stroke, they are generally time-consuming and expensive [3]. Therefore, there is an urgent need to develop serum/plasma biomarkers to accurately predict and diagnose acute stroke.

There is accumulating evidence that miRNAs play a pivotal role in vascular diseases, metabolic diseases and cancer, and may be novel biomarkers and therapeutic targets under various pathologic conditions [4]. Circulating miRNAs in the serum of patients with ischemic stroke are highly stable and detectable, with up- or down-regulated expression in stroke patients, indicating that they may be biomarkers and targets for stroke [5]. Serum miR-126 is upregulated in patients with vascular dementia, and its downregulation reduces the risk of cognitive impairment [6]. Highly expressed in acute stroke, serum miR-124-3p can be used for early prediction of mortality and modified Rankin Scale after stroke [7]. miR-195 and miR-497, are also strongly related to stroke. High expression of serum miR-195 is revealed in patients with ischemic stroke; moreover, it inhibits neuronal apoptosis by down-regulating KLF5 and blocking the JNK signaling pathway [8]. Serum miR-497 has been found to participate in the pathogenesis of ischemic stroke and other nervous system diseases. It is highly expressed in ischemic stroke, and inhibiting its expression enhances neuronal autophagy and relieves cerebral ischemic injury [9]. However,

Table 1. Primer sequences

Gene	Upstream primer sequence	Downstream primer sequence
miR-195	5'-ACACTCCAGCTGGGTAGCAGCACAGAAATATT-3'	5'-CTCAACTGGTGTCGTGGAGTCGGCAATTCAGTTGAGGCCAATA-3'
miR-497	5'-ACAGTGCCGTACAAACCACA-3'	5'-GTCTTCCCAGCACTGCTATGT-3'
U6	5'-CTCGCTTCGGCAGCACA-3'	5'-AACGCTTCACGAATTTGCGT-3'

Table 2. General data [n (%), mean ± SD]

Factor	Patient group (n=108)	Normal group (n=76)	χ^2/t	P
Sex			2.100	0.147
Male	67 (62.04)	39 (51.32)		
Female	41 (37.96)	37 (48.68)		
Average age (years)	53.78±11.32	54.07±11.18		
Onset time (h)	29.68±4.54	-	-	-
Infarct size (mm)	9.57±2.79	-	-	-
Body mass index	22.15±2.34	22.53±2.28		
History of alcohol drinking			0.414	0.519
Yes	69 (63.89)	45 (59.21)		
No	39 (36.11)	31 (40.79)		
History of smoking			2.893	0.089
Yes	73 (67.59)	42 (55.26)		
No	35 (32.41)	34 (44.74)		
Family history of stroke			29.201	<0.001
Yes	63 (58.33)	14 (18.42)		
No	45 (41.67)	62 (81.58)		
Diabetes			5.998	0.014
Yes	68 (62.96)	34 (44.74)		
No	40 (37.04)	42 (55.26)		
Hypertension			5.036	0.025
Yes	65 (60.19)	33 (43.42)		
No	43 (39.81)	43 (56.58)		

the diagnostic value of miR-195 and miR-497 as serum markers in acute stroke is uncertain.

Therefore, the present study analyzes the diagnostic value of serum miR-195 and miR-497 for acute stroke, the correlations between them and post-stroke cognitive impairment, as well as the risk factors for acute stroke, hoping to provide a reference for the prevention and diagnosis of this disease.

Materials and methods

General data

A total of 108 patients with acute stroke admitted to Taizhou People's Hospital from January, 2019 to June, 2020 were enrolled as a patient group, and 76 healthy volunteers were recruited as a normal group. Inclusion criteria: patients diagnosed with acute stroke [10]; patients with complete general clinical data; patients with onset within 72 hours; patients receiving no hormones or anti-inflammatory drugs in the past 3 months; patients without cognitive and communication barriers. This study was granted ethical approval by the hospital ethics committee. All participants signed a fully informed consent. Exclusion criteria: patients with hemorrhagic cerebral infarction, other malignant tumors, severe liver and kidney dysfunctions, or a history of cerebral hemorrhage or head trauma surgery; patients with acute or chronic infection and trauma, or a history of cerebral infarction or myocardial infarction within 3 months before admission, as well as those who were not willing to cooperate or withdrew from the experiment, or those who had undergone surgery or did not cooperate with follow-up and omitted visits.

Sample collection

Venous blood (5 mL) sampled from all participants, was centrifuged (1500 × g) at 4°C for 10 min to obtain supernatants.

miR quantification

RT-qPCR was used to quantitate the relative expression of miR-195 and miR-497. Total RNA in serum was extracted by Trizol reagent (GenMed Technology Co., Ltd., Shanghai, China, GMS12279), and the concentration and purity were tested by a spectrophotometer (Pubiao Equipment Technology Co., Ltd., Dongguan,

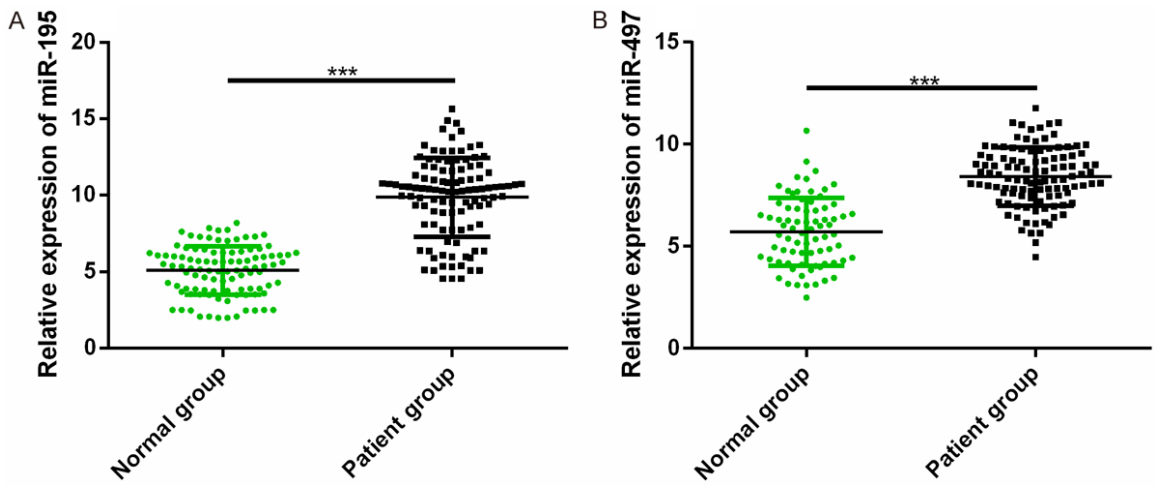

Figure 1. Quantification of serum miR-195 and miR-497. A. Expression of serum miR-195 in patient group is much higher than that in control group. B. Expression of serum miR-497 in patient group is much higher than that in control group. Note: ***P<0.001.

Table 3. ROC parameters of miR-195 and miR-497 in diagnosing acute stroke

Source	AUC	95% CI	Standard error	Cutoff value	Sensitivity (%)	Specificity (%)
miR-195	0.901	0.859-0.944	0.022	6.541	91.67	76.32
miR-497	0.922	0.887-0.958	0.018	7.720	80.56	97.03

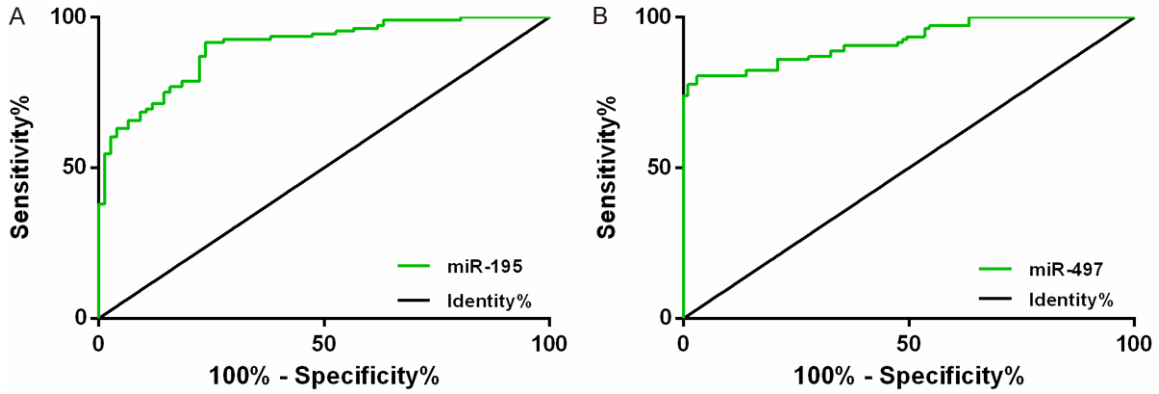

Figure 2. ROC curve of miR-195 and miR-497 in diagnosing acute stroke. A. AUC of serum miR-195 in diagnosing acute stroke is 0.901; sensitivity and specificity are 91.67% and 76.32%, respectively. B. AUC of serum miR-497 in in diagnosing acute stroke is 0.922; sensitivity and specificity are 80.56% and 97.03%, respectively.

Guangdong, China, SPCC). cDNAs were synthesized by a reverse transcription kit (Taize Technology Co., Ltd., Beijing, China, PHG6054). U6 served as an internal reference gene of miR-195 and miR-497, and primer sequences were all designed by Shanghai Daixuan Biotechnology Co., Ltd., (**Table 1**). PCR amplification (Tianlong Technology Co., Ltd., Xi'an, Shaanxi China, TL988) was carried out under conditions of 40 cycles of 95°C for 15 sec, 60°C for 30 sec, 72°C for 30 sec. Each sample was tested in 3 replicate wells. The relative expression of miR-195 and miR-497 was analyzed by $2^{-\Delta\Delta CT}$ [11].

Assessment of neurologic and cognitive functions

Neurologic and cognitive functions were scored by National Institutes of Health Stroke Scale (NIHSS) [12] and Montreal Cognitive

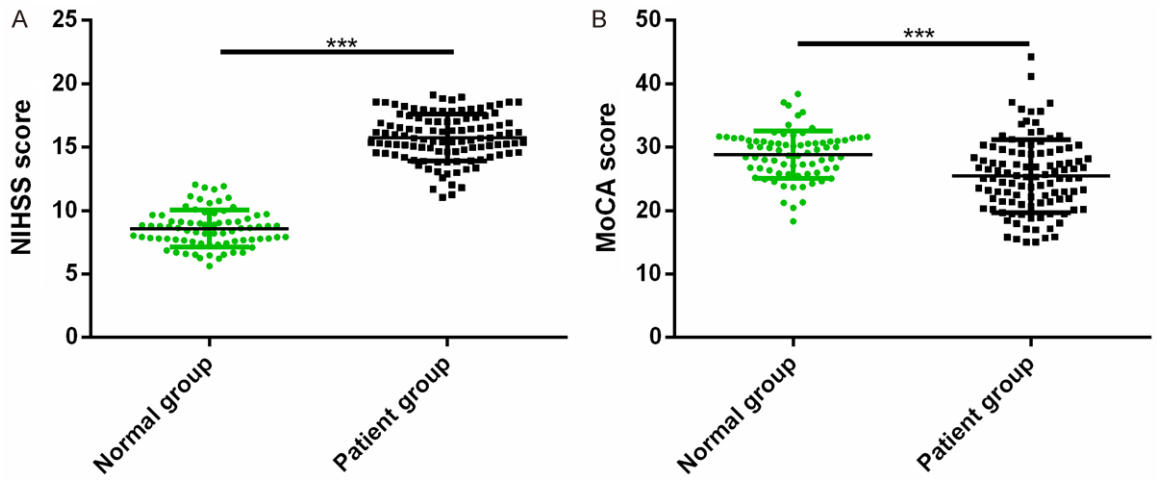

Figure 3. Evaluation of NIHSS score and MoCA score. A. NIHSS score in patient group is significantly higher than that in normal group. B. MoCA score in patient group is significantly lower than that in normal group. Note: ***P<0.001.

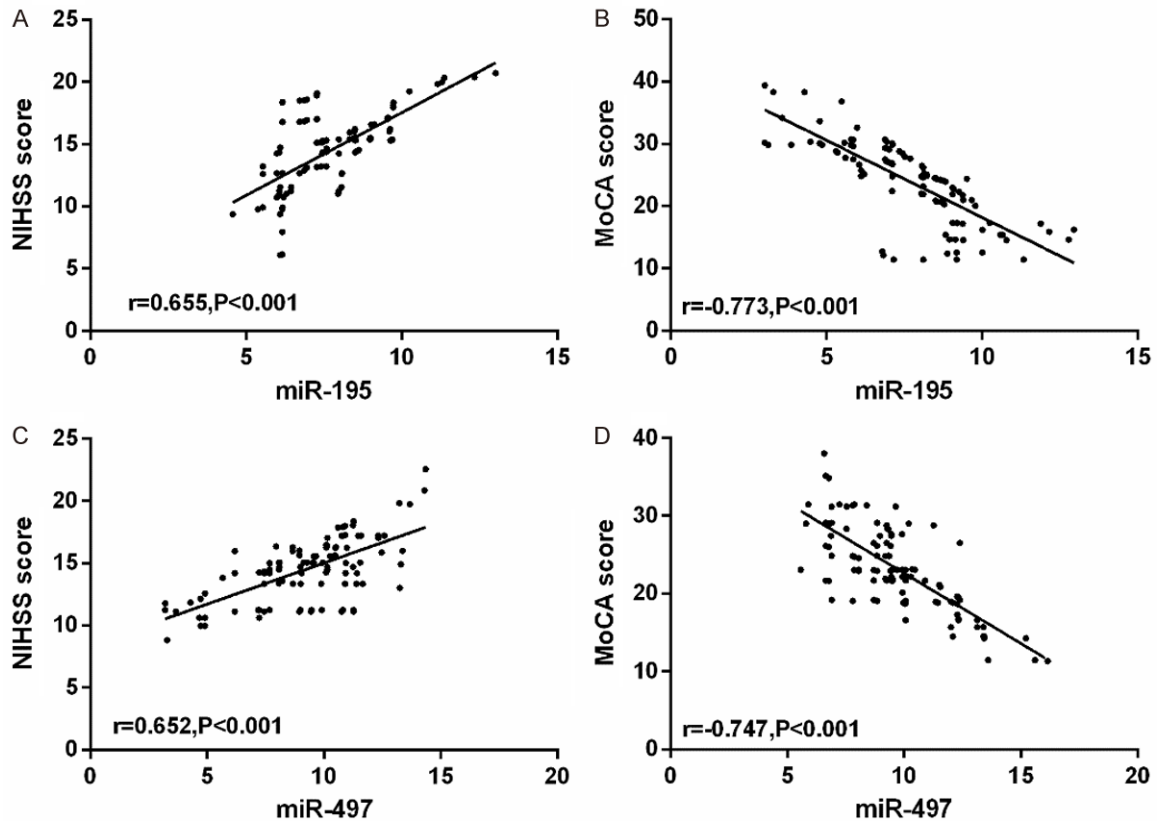

Figure 4. Correlation analysis of miR-195 and miR-497 with NIHSS and MoCA. A. Serum miR-195 is positively correlated with NIHSS score in acute stroke (r=0.655, P<0.001). B. Serum miR-195 is negatively correlated with MoCA score in acute stroke (r=-0.773, P<0.001). C. Serum miR-497 is positively correlated with NIHSS score in acute stroke (r=0.652, P<0.001). D. Serum miR-497 is negatively correlated with MoCA score in acute stroke (r=-0.747, P<0.001).

Assessment (MoCA) [13], respectively. Lower NIHSS scores indicated better neurologic function, and higher MOCA scores indicated better cognitive function.

Table 4. Multivariate logistic regression assignment

Factor	Variable	Assignment
Family history of stroke	X1	No =0, Yes =1
Diabetes	X2	No =0, Yes =1
Hypertension	X3	No =0, Yes =1
NIHSS score	X4	Continuous variable
MoCA score	X5	Continuous variable
miR-195	X6	Continuous variable
miR-497	X7	Continuous variable

Statistical analysis

SPSS22.0 (EasyBio Technology Co., Ltd., Beijing, China) was employed for statistical analysis. Counted data expressed as number/percentage (n/%) were compared by chi-square test. Measured data expressed by mean ± standard derivation (SD) were compared by independent samples t test. The receiver operating characteristics (ROC) curve assessed diagnostic values of miR-195 and miR-497 in acute stroke. Pearson coefficient identified correlations between miR-195, miR-497 and NIHSS and MoCA. Multivariate logistic regression analyzed risk factors for acute stroke. Values of $P<0.05$ were considered significant.

Results

General data

There was no significant difference in sex, average age, body mass index, alcohol drinking and smoking history between the patient group and normal group (P>0.05), but there were significant differences in family history of stroke, diabetes and hypertension (P<0.05) (**Table 2**).

Quantification of serum miR-195 and miR-497

To explore whether miR-195 and miR-497 were abnormally expressed in acute stroke, we quantified their levels in patient and normal groups. It turned out that serum miR-195 and miR-497 were markedly upregulated in the patient group (P<0.001) (**Figure 1**).

miR-195 and miR-497 have a high value in diagnosing acute stroke

ROC curves of miR-195 and miR-497 in diagnosing acute stroke were plotted. Serum miR-195 had an area under the curve (AUC) of 0.901 (95% CI: 0.859-0.944), an optimal cut-off value of 6.541, a sensitivity of 91.67%, and a specificity of 76.32%. Those of miR-497 were 0.922 (95% CI: 0.887-0.958), 7.720, 80.56%, and 97.03%, respectively (**Table 3** and **Figure 2**).

Evaluation of NIHSS score and MoCA score

NIHSS score in the patient group was higher than that in the normal group (P<0.05), and MoCA score was lower than that in the normal group (P<0.05) (**Figure 3**).

Correlations of miR-195 and miR-497 with NIHSS and MoCA

Correlation analyses showed that both serum miR-195 and miR-497 were positively correlated with NIHSS score (r=0.655, P<0.001; r=0.652, P<0.001) and negatively correlated with MoCA score (r=-0.773, P<0.001; r=-0.747, P<0.001) (**Figure 4**).

Prognostic factors of post-stroke cognitive impairment

Factors with differences (family history of stroke, diabetes, hypertension, NIHSS score, MoCA score, miR-195, and miR-497) were analyzed by multivariate logistic regression. It turned out that family history of stroke (P=0.008), diabetes (P=0.027), hypertension (P=0.013), NIHSS score (P=0.002), MoCA score (P=0.003), miR-195 (P=0.001), and miR-497 (P=0.001) were independent risk factors for acute stroke (**Tables 4**, **5**).

Discussion

Stroke is a cerebrovascular disease and the second leading cause of death, accounting for 9.6% of global mortality [14]. Following changes in environment and the aging of the population, the number of patients with acute stroke has been increasing, and most of them suffer from repeated attacks and are at a higher risk of dementia, disability, and death [15]. Stroke is the main inducer of cognitive impairment and dementia, which poses a serious threat to rehabilitation and quality of life [16, 17].

Serum miRNAs participate in pathologic processes of stroke because of their differential expression during ischemic preconditioning

Table 5. Multivariate analysis of independent risk factors for acute stroke

Factor	β	S.E.	Wald	P	OR	95% CI
Family history of stroke	0.482	0.216	4.428	0.008	1.632	1.036-2.783
Diabetes	0.639	0.304	7.372	0.027	1.796	1.368-3.967
Hypertension	0.753	0.803	6.261	0.013	2.652	1.903-4.068
NIHSS score	1.127	0.374	8.328	0.002	3.032	1.749-6.904
MoCA score	1.002	0.326	8.732	0.003	2.793	1.572-5.283
miR-195	0.725	0.267	8.396	0.001	3.397	2.036-6.835
miR-497	0.673	0.327	8.894	0.001	3.382	2.163-6.984

and postconditioning, and they also participate in the regulation of molecular processes after stroke [18, 19]. miR-195 is associated with the pathogenesis of stroke and other cerebrovascular diseases. It directly decreases the apoptosis of injured nerve cells by inhibiting Sema3A/Cdc42/JNK signaling in acute stroke, and induces nerve regeneration by promoting proliferation and migration of neural stem cells, and directly blocks the NF-kB pathway to exert an anti-inflammatory effect and effectively enhance endothelial function [20]. Serum miR-497 alleviates ischemic cerebral infarction and enhances the neurological function of mice after focal cerebral ischemia by negatively regulating the levels of bcl-2 and bcl-w [21]. Moreover, miR-497 has been reported to be highly expressed in ischemic stroke [22], which is consistent with our findings. In this present study, serum miR-195 and miR-497 presented at higher levels in patients than those in controls, suggesting their role in pathologic regulation of acute stroke. ROC curves demonstrated that AUC, sensitivity, and specificity of serum miR-195 in diagnosing acute stroke were 0.901, 91.67%, and 76.32%, while those of serum miR-497 were 0.922, 80.56% and 97.03%, respectively. Therefore, both serum miR-195 and miR-497 have excellent performance in the diagnosis of acute stroke.

Neurological deficits and cognitive impairments (hemiplegia, aphasia) are likely to occur after stroke [23]. NIHSS and MoCA were employed in this study to assess patients' neurologic and cognitive functions. NIHSS is widely used to evaluate severity of neurologic deficit in stroke patients [24], and MoCA is used clinically to predict functional dependence in late stroke [25]. The patient group showed higher NIHSS score and lower MoCA score than the normal group, indicating that the neurologic and cognitive functions of patients with acute stroke were damaged. Serum miR-195 and miR-497 were positively correlated with NIHSS score but negatively correlated with MoCA score, suggesting that they can reflect neurologic impairment and cognitive dysfunction of patients with acute stroke. Previous studies have shown that serum miR-195 is related to cognitive impairment and functions as a novel therapeutic target for neuropathic pain [26, 27]. Moreover, miR-497 induces ischemic neuron death by negatively regulating anti-apoptotic proteins, while its inhibition exerts a neuroprotective effect [28]. We noticed that a family history of stroke, diabetes, hypertension, NIHSS score, MoCA score, miR-195 and miR-497 were all risk factors for acute stroke. This is similar to Alloubani's finding that diabetes and hypertension are independent risk factors for acute stroke [29]. We revealed that patients with family history of stroke, diabetes, hypertension, high NIHSS score, low MoCA score, high miR-195, and high miR-497 were more likely to develop acute stroke, validating Alloubani's finding.

Although this present study confirms that serum miR-195 and miR-497 have a high diagnostic value for acute stroke, there is still room for improvement. More basic research is required to explore the relationship between miR-195 and miR-497 and pathologic data, to figure out their molecular mechanism in acute stroke or their influence on cellular biologic functions, and to develop more effective treatments for acute stroke. We will gradually address these limitations to supplement our conclusions.

To sum up, serum miR-195 and miR-497 are elevated in acute stroke and associated with the loss of neurologic and cognitive functions. They may become biomarkers for diagnosis and prognosis of acute stroke.

Disclosure of conflict of interest

None.

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