

Circulating miR-505-5p as a Diagnostic Marker for Acute Cerebral Infarction and Its Predictive Value for Clinical Outcomes After Endovascular Mechanical Thrombectomy

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This study aimed to evaluate the diagnostic significance of miR-505-5p in Acute cerebral infarction (ACI) and its prognostic utility following endovascular mechanical thrombectomy. A total of 138 patients with ACI and 120 healthy controls participated. RT-qPCR quantified miR-505-5p levels in serum and cerebrospinal fluid (CSF). The National Institutes of Health Stroke Scale (NIHSS) scores assessed the severity of the disease. Furthermore, the modified Rankin Scale (mRS) score evaluated the prognosis one year after endovascular mechanical thrombectomy. The Pearson coefficient analyzed the correlation between miR-505-5p and NIHSS or mRS scores. Logistic regression determined risk factors associated with poor outcomes. The receiver operating characteristic (ROC) curve assessed diagnostic and prognostic accuracy. miR-505-5p levels in serum and CSF were significantly elevated in ACI patients compared to controls (P < 0.05). A positive correlation existed between serum miR-505-5p and NIHSS score, which increased with disease severity. miR-505-5p demonstrated 81.88% sensitivity and 85.83% specificity in identifying ACI patients, with levels correlated to mRS scores. Higher levels of miR-505-5p indicated a poor prognosis in ACI patients, suggesting its role as a potential biomarker for adverse outcomes and mortality. Both miR-505-5p and NIHSS scores emerged as risk factors for negative outcomes. Serum miR-505-5p serves as a biomarker for predicting poor prognosis and mortality in patients. In conclusion, elevated serum miR-505-5p may act as a diagnostic biomarker for ACI and correlates with unfavorable prognoses a worse prognosis in patients having endovascular mechanical thrombectomy.

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Introduction

Acute cerebral infarction (ACI) represents a common stroke subtype, comprising over 85% of cases (Cao et al. 2024). It arises from the narrowing or blocking of blood vessels supplying the brain, resulting in brain damage (Du et al. 2023a). Individuals with ACI often suffer from hemiparesis, facial paralysis, and in severe cases, total body paralysis or even death. Prompt medical intervention, whether through medication or surgery, is essential to restore blood flow. Diagnosis currently relies on symptoms and imaging tests (like MRI and CT scans) but can be

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costly and time-consuming, potentially leading to missed treatment opportunities (Wang et al. 2022). Previously, thrombolysis existed with a low success rate and the limitation of a short time window (3-4.5 h) (Feng and Gong 2022). With the advancement of minimally invasive procedures, endovascular mechanical thrombectomy has gained significant attention (Wang et al. 2023). Yet, it has been reported to affect neurological recovery. Therefore, swiftly identifying effective diagnostic markers for ACI and predicting unfavorable prognosis post-endovascular mechanical thrombolysis is essential.

MicroRNAs (miRNAs) are small non-coding RNAs that play a role in transcriptional regulation (Zhang et al. 2024). The molecules are prevalent in the brain and contribute to the development of several conditions, including ACI. Given their accessibility, non-invasiveness, stability, and affordability, extensive attention has been devoted to exploring their potential as clinical biomarkers (Long et al. 2024; Ren et al. 2024). For instance, the elevation of miR-411-5p acts as an independent predictor of outcomes following thrombolysis in patients with ACI (Lin et al. 2023). Serum miR-106a-5p is a diagnostic biomarker for ACI (Du et al. 2023b). Among the miRNAs, miR-505-5p showed increased levels in the cerebrospinal fluid of Parkinson's patients (Denk et al. 2015). Furthermore, miR-505-5p rises in athletes with concussions and impacts brain injury (Papa et al. 2019). Atherosclerosis (AS) underlies cerebral infarction and peripheral vascular lesions, and low-density lipoprotein-treated vascular endothelial cell exosome miR-505-5p exacerbates AS progression (Chen et al. 2019). Furthermore, miR-505-5p levels increase in patients with degenerative aortic stenosis (Zhang et al. 2023). Interestingly, Abe et al. (2020) compared miRNA expression profiles through microarray analyses among healthy subjects and ACI patients, as well as those in patients before and after treatment, identifying common miRNAs, including miR-505-5p. However, the expression patterns and clinical relevance of miR-505-5p in ACI patients remain unclear.

Based on the aforementioned background, we postulated that miR-505-5p is implicated in the progression of ACI. In this exploratory study, we assessed the expression of miR-505-5p in patients with ACI and explored its clinical diagnostic and prognostic implications following mechanical thrombectomy.

Materials and Methods

Ethics Statement

Approval (Ethics approval number was PTEC-A-2020-45-1) was obtained from the Putuo People's Hospital, Tongji University Medical Ethics Committee and the study followed the ethical standards outlined in the 1964 Declaration of Helsinki and its revisions. Informed consent was obtained from all subjects.

Patient recruitment

A total of 138 patients suffering from ACI were admitted to Putuo People's Hospital, Tongji University from June 2020 to December 2022. The inclusion criteria encompassed: 1) first onset; 2) meeting the diagnostic criteria of ACI and confirmed diagnosis by crania CT or MRI; 3) comprehensive clinical data available; 4) age > 18 years; and 5) onset within 24 h of symptoms, including individuals concurrently treated with mechanical thrombus extraction. Exclusion criteria: 1) history of previous cerebral hemorrhage; 2) recurrent ACI cases; 3) acute and chronic infectious; 4) pregnant and lactating women; 5) individuals on glucocorticoids or immunosuppressants. Additionally, 120 individuals who underwent health screening during the same period served as the control group (Controls). The controls matched ACI patients based on age and gender and were free of stenosis, atherosclerosis, transient ischemic attack, hemorrhagic stroke, neoplasm, and acute infection. Furthermore, 15 control subjects and 32 patients provided cerebrospinal fluid (CSF) samples for additional analysis.

Clinical data collection and serum preparation

Venous blood was collected from the patients and controls upon admission. Baseline clinical characteristics of patients including age, gender, underlying diseases, time of onset and admission, and biochemical indices were collected. What's more, according to previous studies, the National Institutes of Health Stroke Scale (NIHSS) assessed patients' severity based on criteria established in prior studies, classifying NIHSS scores as follows: NIHSS < 4 for mild, $4 \le$ NIHSS \le 15 for moderate, and NIHSS > 15 for severe (Chalos et al. 2020).

Endovascular mechanical thrombectomy

According to previous studies (Narsinh et al. 2021), patients underwent continuous monitoring of vital signs and establishment of venous access. The Seldinger technique evaluated access to the femoral artery, concurrently inserting a 6F catheter sheath upon successful access. A 6F catheter was then guided into the artery via a guidewire for angiography, verifying vascular occlusion at distal and proximal locations. A Solitaire stent was positioned at the site of embolism, followed by catheter removal while retaining the stent. Then, the fully released stent was withdrawn along with simultaneous extraction of the thrombus. Arteriography was utilized to observe blood flow at the lesion site to prevent thrombus displacement. Postoperatively, a daily dose of 100 mg aspirin was administered for one month.

RNA extraction and Real-time quantitative reverse transcription PCR (*RT-qPCR*)

miRNeasy micro-Kit (Qiagen, USA.) was employed to extract total RNA from the subjects' serum. RNA quality and concentration were assessed using a NanoPhotomer NP80 spectrophotometer and met acceptable standards with a 260/280 ratio of 1.8-2.2. The Taqman microRNA Reverse Transcription kit converted 500 ng of RNA into complementary DNA (cDNA). Subsequently, the cDNA was amplified utilizing the TaqMan miRNA assay kit along with primers in an ABI7500 thermal cycler. The relative levels of miRNA were normalized using U6 as internal references for standardization and analyzed using the cycling threshold method (2^{-dACT}). The primers used for RT-qPCR followed: miR-505-5p forward primer: 5'-GTAATCGGGAGCCAGGAAGT-3', and reverse primer: 5'-ATTGGAACGATACAGAGAAGATT-3', and reverse primer: 5'-ATTGGAACGATACAGAGAAGATT-3', and reverse primer: 5'-AGGAACGATACAGAGAAGATT-3', The following cycling parameters were determined according to the primer sequence: 95°C for 1 min; 40 cycles of 95°C for 20 s, 60°C for 30 s, and 68°C for 45 s.

Prognosis evaluation methods

A one-year postoperative follow-up study was conducted on patients with ACI using outpatient and telephone methods (Eugene et al. 2015; Man et al. 2023). Neurological recovery of patients was assessed using the Modified Rankin Scale (mRS) ranging from 0 to 6 grade. Grade 0 had no symptoms at all; Grade 1 had no visible disability despite symptoms; Grade 2 had a mild disability; Grade 3 had a moderate disability; Grade 4 had a severe disability; Grade 5 had a severe disability; and Grade 6 was dead. Prior research categorizes mRS scores of ≤ 2 as having a good prognosis, while scores > 2 are classified as a poor prognosis (Chang et al. 2023).

Statistical analysis

For statistical analysis, SPSS (Version 23.0) and GraphPad Prism (version 9.0) were employed. Normally distributed parametric variables were presented as mean \pm

SD, while non-normally distributed parameters were represented as median and interquartile range (IQR). T-tests were utilized to compare variations between two groups, while one-way ANOVA with Tukey's multiple comparison tests was employed to compare three groups. Percentages were utilized for tally data, and the chi-square test was utilized to compare group variations. Pearson correlation analysis was conducted for correction assessment. P < 0.05indicated that the differences were statistically significant.

Results

Baseline characteristics of the participants

The clinical baseline characteristics of the subjects in both groups were recorded in Table 1. No significant differences were found regarding age, gender, BMI, drinking, smoking, hypertension, diabetes mellitus, and hypercholesterolemia (P > 0.05). However, ACI patients exhibited increased platelet count, fibrinogen, and homocysteine levels, along with prolonged activated partial thromboplastin time (APTT) compared to controls (P < 0.05).

The expression of miR-505-5p in patients with ACI

Serum miR-505-5p was elevated in patients with ACI compared with controls (P < 0.05, Fig. 1A). Furthermore, miR-505-5p levels in the CSF were also notably higher in ACI patients than in controls (P < 0.05, Fig. 1B). A strong positive correlation existed between serum miR-505-5p and CSF miR-505-5p in ACI patients (r = 0.899, P < 0.001, Fig. 1C). The ROC curve confirmed that miR-505-5p with 81.88% sensitivity and 85.83% specificity, which illustrates high diagnostic significance (ROC = 0.908, Fig. 1D).

MiR-505-5p was associated with ACI severity

The clinical significance of miR-505-5p in ACI

Parameters	Controls $(n = 120)$	ACI patients $(n = 138)$	P values
Age, years	61.47 ± 7.27	60.70 ± 7.00	0.392
Gender, male, n (%)	63 (52.50)	71 (51.45)	0.901
BMI, kg/m ²	24.94 ± 3.28	24.81 ± 3.13	0.727
History			
Drinking, n (%)	61 (50.83)	72 (52.17)	0.901
Smoking, n (%)	63 (52.50)	73 (52.90)	0.949
Hypertension, n (%)	59 (49.17)	83 (60.14)	0.081
Diabetes Mellitus, n (%)	55 (45.83)	68 (49.28)	0.618
Hypercholesterolemia, n (%)	58 (48.33)	79 (57.25)	0.170
Biochemical indexes			
Platelet count, \times 10 ⁹ /L	170.70 ± 20.19	$178.51{\pm}28.62$	0.013
Fibrinogen, g/L	3.13 ± 0.37	3.87 ± 1.17	0.000
APTT, s	34.57 ± 4.82	36.37 ± 6.14	0.010
Homocysteine, µmol/L	9.26 ± 2.54	11.09 ± 2.93	0.000

Table 1. Clinical baseline characteristics of subjects.

APTT, activated partial thromboplastin time; Date was presented as mean \pm SD, or N (%).



Fig. 1. The expression of miR-505-5p in subjects. A. The serum levels of miR-505-5p in the subjects. B. The cerebrospinal fluid (CSF) miR-505-5p in the subjects. C.

A. The serum levels of mix-505-5p in the subjects. B. The cereorospinal nuld (CSF) mix-505-5p in the subjects. C. Pearson coefficient correlation was conducted on the correlation between serum miR-505-5p and CSF miR-505-5p in the patients with ACI. D. Diagnostic significance of serum miR-505-5p in patients with ACI as determined by plotting ROC curve. Comparisons were performed using unpaired student's t-test, ****P < 0.0001.

patients was further investigated. Serum miR-505-5p demonstrated a significant positive correlation with NIHSS score (r = 0.632), as illustrated in Fig. 2A. The NIHSS score serves as an indicator of ACI severity, categorizing patients into 14 mild cases, 85 moderate cases, and 39 severe cases based on this score. RT-qPCR assays confirmed a progressive elevation in serum miR-505-5p levels corresponding to the increasing severity of ACI (P < 0.001, Fig. 2B).

Prognostic value of miR-505-5p after endovascular mechanical thrombectomy (EMT) in patients with ACI

No patients experienced dislodgment during the follow-up. The prognostic significance of miR-505-5p in patients with ACI undergoing EMT for one year was assessed using the mRS score. As shown in Fig. 3A, serum miR-505-5p exhibited a significant positive correlation with the mRS score (r = 0.731, P < 0.05). Furthermore, patients were stratified into two prognostic groups based on their mRS score: good (n = 79) and poor (n = 59) prognosis. The clinical characteristics of both groups were analyzed. Patients with an unfavorable prognosis showed elevated platelet counts, fibrinogen, homocysteine, and NIHSS scores, as well as prolonged APTTs compared to those with a favorable prognosis (P < 0.05, Table 2). Furthermore, serum miR-505-5p levels were also higher in ACI patients with poor prognosis (P < 0.001, Fig. 3B). Clinical indicators and miR-505-5p, which differed significantly among prognostic groups, were included in the logistic regression analysis (the logistic regression model was validated by the Hosmer-Lemeshow goodness-of-fit statistic p = 0.657). As shown in Table 3, miR-505-5p (OR = 7.346, 95% CI: 2.910-18.544, P < 0.001), along with the NIHSS score (OR = 3.293, 95% CI: 1.334-8.129, P = 0.010), could serve as potential risk factors for poor prognosis in patients with ACI (P < 0.05). In addition, the ROC curve confirmed the sensitivity and specificity of serum miR-505-5p in predicting poor prognosis in ACI patients with 89.83% and 73.42%, respectively (AUC = 0.876, Fig. 3C).

Predictive value of miR-505-5p in survival status of ACI patients

Seventeen patients died during the follow-up period, with a death rate of 12.32%. The miR-505-5p levels were considerably higher in dead patients compared to survivors (P < 0.05, Fig. 4A). ROC analysis for serum miR-505-5p indicated a sensitivity of 91.74% and specificity of 70.59% in predicting patient survival (AUC = 0.880, Fig. 4B).



Fig. 2. miR-505-5p was associated with ACI severity.

A. The correlation between serum miR-505-5p and NIHSS score in patients with ACI. B. Expression levels of serum miR-505-5p in patients with ACI of different severities. One-way ANOVA with Tukey's multiple comparison tests was perform, ****P < 0.0001.



Fig. 3. The prognostic of serum miR-505-5p in patients with ACI. A. Correlation between serum miR-505-5p and mRS score. B. The serum miR-505-5p levels were in the good prognosis groups and poor prognosis group. C. The ROC curve is based on serum miR-505-5p levels in ACI patients with different prognoses. Comparisons were performed using unpaired student's t-test, ****P < 0.0001.</p>

Discussion

miRNAs as circulating biomarkers have gained substantial attention in clinical research. For instance, miR-133 has application in diagnosing ACI patients (Xu et al. 2020), whereas elevated levels of miR-497 indicate a poor patient prognosis (Wang et al. 2019). Previous studies have highlighted miR-505-5p's potential as a clinical biomarker. MiR-505-5p can function as a biomarker for imatinib response in chronic myeloid leukemia patients and serves as a diagnostic biomarker for early-stage lung adenocarcinoma (Ramachandran et al. 2017). Furthermore, it stands as a prognostic biomarker for hypertension-associated endothelial dysfunction, including its clinical utility (Fang et al. 2019). MiR-505-5p exhibits ties to prognosis biomarkers associated with hypertension-related endothelial dysfunction (Yang et al. 2022). The context reinforces the potential of miR-505-5p as a valuable clinical biomarker.

We have a keen interest in miR-505, particularly its presence in exosomes of Ox-LDL-treated vascular endothelial cells worsens the advancement of atherosclerosis (Chen et al. 2019). Additionally, miR-505-5p is notably increased in individuals with aortic stenosis (Zhang et al. 2023). Atherosclerotic plaques form the basis for cerebral infarction and peripheral vascular lesions (Tian et al. 2023). Moreover, ACI is recognized as a condition that adversely affects neurological functions, where miR-505-5p has been indicated to cause neurological impairment and cognitive dysfunction. miR-505-5p is notably higher in the cerebrospinal fluid of patients with Alzheimer's disease (Denk et al. 2015). Furthermore, in models of Parkinson's disease induced by MPP+, we notice increased miR-505-5p concentration (Zhu et al. 2018). The Borna disease virus can induce significant neurobehavioral disorders in animals through dysregulation of miR-505-5p expression (Zhao et al. 2015). Interstingly, Abe et al. (2020) analyzed the differential expression of miRNA in healthy individuals and patients with ACI as well as in patients before and after treatment by microarray, in which the overlapping miRNA mainly consisted of five miRNA, including miR-505-5p. Since previous studies have found that the concentration of miRNA in serum may be higher than that in blood, and thus

J. Ruan et al.

Table 2. Clinical data of ACI patients in two groups with different prognoses.

Parameters	Good prognosis $(n = 79)$	Poor prognosis $(n = 59)$	P values
Age, years	61.47 ± 6.78	59.68 ± 7.23	0.138
Gender, male, n (%)	40 (50.63)	31 (52.54)	0.864
BMI, kg/m ²	24.59 ± 3.44	25.11 ± 2.65	0.335
History			
Drinking, n (%)	38 (48.10)	34 (57.63)	0.304
Smoking, n (%)	39 (49.37)	34 (57.63)	0.390
Hypertension, n (%)	44 (55.70)	39 (66.10)	0.225
Diabetes Mellitus, n (%)	34 (43.04)	34 (57.63)	0.121
Hypercholesterolemia, n (%)	42 (53.16)	36 (61.02)	0.037
Biochemical indexes			
Platelet count, \times 10 ⁹ /L	167.67 ± 21.66	186.61 ± 30.56	0.000
Fibrinogen, g/L	3.64 ± 0.96	4.17 ± 1.35	0.007
APTT, s	34.89 ± 5.00	38.35 ± 6.98	0.001
Homocysteine, µmol/L	11.98 ± 2.54	9.89 ± 3.00	0.000
Onset to blood sampling time, h	13.0 (8.5, 17.0)	13.0 (9.0, 18.0)	0.698
Location of the stroke, right, n (%)	51 (64.56)	40 (67.50)	0.720
NIHSS score	9 (5, 13)	15 (10, 21)	0.000

APTT, activated partial thromboplastin time; NIHSS, National Institutes of Health Stroke Scale. Date was presented as mean \pm SD, median and interquartile range (IQR), or N (%).

Table 3. Logistic regression analysis of risk factors influencing poor prognosis in ACI patients.

Variables	OR	95% CI	P value
Hypercholesterolemia	2.116	0.841-5.325	0.111
Platelet count, \times 10 ⁹ /L	2.051	0.811-5.187	0.129
Fibrinogen, g/L	2.078	0.842-5.128	0.112
APTT, s	1.769	0.726-4.309	0.210
Homocysteine, µmol/L	2.352	0.948-5.834	0.065
NIHSS score	3.293	1.334-8.129	0.010
miR-505-5p	7.346	2.910-18.544	0.000

miRNAs in serum are easier to detect (Thakur et al. 2016), and the plasma contains anticoagulants that may affect the release and stability of miRNAs, we focused on miR-505-5p in serum besides CSF. In this research, we noted markedly increased levels of miR-505-5p in the blood serum and CSF of patients with ACI in comparison to control. The findings suggest that dysregulated miR-505-5p may contribute to the initiation and progression of ACI.

Clinically, the optimal timeframe for ACI resuscitation is within 3-4.5 h, with a critical timeframe of 0-3 h (Yuan et al. 2020). Implementing the pre-hospital emergency protocols and efficient pathways ensures that the patient reaches the hospital treatment within a 3-h window. Failure to provide timely diagnosis and intervention may lead to irreversible brain tissue damage, necrosis, or softening, and some patients may suffer from cerebral hemorrhage, further complicating their conditions. Thus, timely diagnosis is particularly important for patient management. However, it is crucial to note that the diagnosis of ACI heavily depends on sophisticated and costly equipment. The current gold standard for diagnosing ACI is CT scans; however, their ability to detect lesions within 24 hours is limited. Cerebral angiography, while capable of identifying narrowed and occluded blood vessels, is an invasive procedure associated with potential complications. Moreover, certain individuals may face challenges in undergoing the assessment due to either physical discomfort or the presence of metal implants within their bodies. Therefore, there is a need to identify a rapid and convenient blood serum marker that can accurately diagnose the severity of ACI and facilitate timely intervention to improve patient prognosis. Previous studies have shown that blood-based biodiagnostic markers can be used for diagnosing and predicting the course of ACI and aiding in the early detection of neurological decline. In our ongoing initial study, elevated miR-505-5p has demonstrated certain sensitivity and specificity in distinguishing



Fig. 4. Predictive value of miR-505-5p in survival status of patients with ACI. A. The serum levels of miR-505-5p in survival status and dead status of patients with ACI. B. The ROC curve is based on serum miR-505-5p in the patients with different survival statuses. Comparisons were performed using unpaired student's t-test, ****P < 0.0001.

patients with ACI from those who are healthy. The NIHSS score effectively indicates the severity of ACI, with higher scores indicating more severe ischemic strokes that lead to greater disability and functional decline (Niu et al. 2023). Our research revealed a correlation between miR-505-5p levels and the NIHSS score, with miR-505-5p levels rising alongside ACI severity.

The primary goal of ACI treatment is to rapidly remove vascular embolisms and restore blood flow to the intracranial ischemic region, thus enhancing neurological recovery and cerebral function. Although arterial thrombolysis and intravenous thrombolysis are commonly used in patients with ACI, they exhibit limitations, such as the slow onset of action, narrow time window, susceptibility to intracranial hemorrhage, high rate of postoperative occlusion, poor prognosis, and many contraindications to thrombolysis. With advancements in minimally invasive techniques, endovascular mechanical thrombectomy offers a high rate of vascular reopening, short recovery times, minimal patient trauma, and reduced damage to brain tissue and neurological functions. Therefore, patients who underwent endovascular mechanical thrombectomy were included in this study.

The mRS score is a widely used assessment tool for the prognosis of patients with ACI (Wu et al. 2022). It evaluates the degree of neurological impairment, assisting physicians in gauging patient recovery post-treatment and forming treatment strategies. The score's objectivity, reproducibility, and simplicity, along with its thorough reflection of neurological deficits in these patients make it valuable for assessing therapeutic effectiveness (Han et al. 2022). In the current research, we discovered a strong positive correlation between miR-505-5p levels and mRS scores. Moreover, serum miR-505-5p levels were heightened in ACI patients with poor outcomes. Both NIHSS score and miR-505-5p levels emerged as risk factors for unfavorable prognosis in ACI. Moreover, the miR-505-5p level may serve as a predictors of adverse outcomes following endovascular mechanical thrombectomy in ACI patients.

Some limitations may apply to our study. Firstly, there is a lack of results from animal and cellular experiments, and combining both of them will help to further elucidate the molecular mechanisms by which miR-505-5p is involved in the progression of ACI. Secondly, the sample size was limited and lacked independent validation samples, and large-scale multicenter sample validation is still needed. In addition, the risk of confounding bias due to systemic comorbidities could not be completely excluded, although there was no significant difference in comorbidities between the two groups of patients and more stringent exclusion criteria were implemented to rule out the effect of comorbidities. In addition, this study preliminarily confirmed that serum and CSF miR-505-5p were significantly positively correlated with the patient's condition and predicted the poor prognosis of the patients after biomechanical thrombectomy; however, it is undeniable that the detection of the level of miR-505-5p may need to be carried out again in the well-equipped hospitals in the clinical practice, and therefore, its generalization and application in clinical practice that needs to be further explored. Also, whether combining miR-505-5p with imaging to have higher clinical value needs to be further explored. Nevertheless, our study opens up new perspectives for clinical prognostic monitoring of ACI patients after vascular mechanical thrombectomy. However, further exploration of biomarkers that simplify testing procedures and are cost-effective in clinical practice is needed.

To sum up, elevated serum miR-505-5p can serve as a biomarker for diagnosing ACI patients and is associated with poor prognosis in patients undergoing endovascular mechanical thrombectomy. Our study may offer a new perspective on the diagnosis and prognosis of ACI patients.

Conflict of Interest

The authors declare no conflict of interest.

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