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Correlation of miR-155-5p and BDNF with Prognosis of Patients with Intracerebral Hemorrhage Undergoing CT-guided Minimally Invasive Surgery

Qihan Chen[1], Dan Lin[2], Zepeng Jiang[1], Hui Yan[1], Liang Wen[3*]

[1]Department of Neurosurgery, The First People's Hospital of Yuhang District, Hangzhou, Zhejiang 311113, China
[2]Department of Neurology, The First People's Hospital of Yuhang District, Hangzhou, Zhejiang 311113, China
[3]Department of Neurosurgery, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang 311121, China

*** *Corresponding author:*** Liang Wen, Department of Neurosurgery, The First Affiliated Hospital, Zhejiang University School of Medicine, No.1282 Wenyi Road, Yuhang District, Hangzhou, Zhejiang Province, 311121, China. Email: Wenliang8207@163.com

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Abstract

Background: Hypertensive intracerebral hemorrhage (HICH) is a spontaneous cerebrovascular disease occuring in the brain parenchyma.
Objectives: To characterize the predictive role of miR-155-5p and BDNF in the prognosis of HICH.
Methods: All patients with HICH who underwent CT-guided minimally invasive surgery were classified into the good and poor prognosis groups using the modified Rankin Scale (mRS). The level of miR-155-5p was determined by qRT-PCR, and the level of brain-derived neurotrophic factor (BDNF) in serum was determined by ELISA. The relationship between miR-155-5p and BDNF was tested by Pearson correlation and luciferase reporter assay. The logistic regression method was used to determine the risk factors. The ROC curve was drawn to explain the predictive role of miR-155-5p, BDNF, or their combination.
Results: A high level of miR-155-5p and a lower level of BDNF were observed in the poor prognosis group. BDNF level was negatively related to the level of miR-155-5p. BDNF is a target of miR-155-5p. BDNF and miR-155-5p were associated with prognosis. BDNF, miR-155-5p or their combination were predictive biomarkers for the prognosis of HICH.
Conclusion: BDNF and miR-155-5p were associated with the outcome of HICH patients.

Keywords: BDNF, HICH, Minimally invasive surgery, MiR-155-5p, Predictive value

1. Background

Hypertensive intracerebral hemorrhage (HICH) is a nontraumatic intracerebral parenchymal hemorrhage with sudden onset, dangerous conditions, high disability rate, and high mortality (1). Only a small proportion of survivors can live independently with mild disability after 3 months (2). Most survivors are left with severe neurologic function and physical and speech impairments (3). Due to the large population and aging trend in China, the number of cerebrovascular disease remains high, which poses a great challenge to the development of society. Although much time and energy have been invested in the treatment of patients with HICH, the overall prognosis of HICH is still poor (4). It has become an important issue for researchers to study the patients and improve their prognosis. D-dimer is an independent indicator to predict the prognosis of HICH patients, indicating that D-dimer is related to HICH (5). The National Institute of Health Stroke Scale (NIHSS) correlate with the one-year mortality of ICH (6). Minimally invasive drainage is one of the currently widely used minimally invasive surgical methods that solves the problems of traditional craniotomy (7). Therefore, in this study, the patients after minimally invasive drainage wre investigated.

MiRNAs are stable markers for predicting the outcome of various diseases. In non-hypertensive ICH, the level of miR-26a is a possible predictor in these patients (8). The level of miR-124 is increased in patients with ICH within 24 hours, and this trend is a promising indicator of the prognosis of patients with ICH (9). Quantification of miR-155-5p is increased in ICH patients compared to patients without ICH, suggesting that miR-155-5p correlates with the occurrence of ICH (10). miRNAs can bind to mRNA targets to form RNA-induced silencing complexes (RISCs), which prevent mRNA from serving as a template for translation and thus regulate gene expression (11). As an extensively studied neurotrophin, the concentration of Brain-Derived Neurotrophic Factor (BDNF) affects the healing of ICH (12). miR-155-5p can bind to the 3'UTR region of BDNF and regulate BDNF expression by forming a RISC (13). However, there are no studies showing the role of miR-155-5p and BDNF in HICH patients with different prognostic outcomes.

In this study, we investigated the value of miR-155-5p and BDNF on the prognosis of HICH patients who underwent CT-guided minimally invasive surgery. We determined the level of miR-155-5p in HICH patients from the good prognosis group and the poor prognosis group. The predictive potential of miR-155-5p or BDNF in the prognosis of HICH patients was revealed.

2. Objectives

To characterize the predictive role of miR-155-5p and BDNF in the prognosis of HICH.

3. Methods

3.1. Recruited patients and sample collection

One hundred and five patients with HICH admitted to First Affiliated Hospital, Zhejiang University School of Medicine from August 2019 to September 2022 were selected as study participants, all of whom underwent CT-guided minimally invasive surgery. Inclusion criteria included: (1) met the diagnostic criteria for the treatment of cerebral hemorrhage (5); (2) had a history of hypertension; were confirmed by CT scan, (3) the amount of intracranial hemorrhage exceeded 30 ml; (4) surgical treatment was performed within 24 h after hemorrhage. Exclusion criteria included: (1) cerebral aneurysm or cerebral cancers, (2) history of traumatic brain injury or head injury, (3) brainstem hemorrhage, (4) accompanied by severe nervous system disease (5) diabetes and hyperlipidemia, and (5) anti-inflammatory drugs or immunosuppressive medications within the previous three months. The study met the requirements of medical ethics of First Affiliated Hospital, Zhejiang University School of Medicine, and all patients signed the written informed consent. Peripheral venous blood was collected from the two groups, centrifuged at 3000 rpm for 15 min, and the supernatant was collected and stored at -80°C for examination.

3.2. Minimally invasive surgery

All patients underwent minimally invasive surgery under the guidance of Definition Flash dual-source 64- -slice CT with 128 slices (Siemens AG, Erlangen, Germany), and the hemorrhage site and hematoma volume were determined by CT scanner. Three-dimensional data were obtained from cranial CT images to locate puncture sites and puncture lines. After local anesthesia, the patient was punctured under the guidance of CT, and the puncture bypassed the functional area and vascular area to reach the predetermined hematoma center. The outflow of the bloody fluid showed that the puncture was successful. The first aspiration amount is less than 50% of the total amount. Urokinase (National drug code H42021792, Wuhan Renfu Pharmaceutical Co. LTD., Wuhan, China) was injected into the hematoma cavity to promote drainage of the hematoma to the outside. The drainage tube was clamped for 4 hours to open the drainage, and the effect of hematoma removal was checked by CT.

3.3. Grouping of patients

At 90 days after surgery, the prognosis of all patients was assessed using the modified Rankin Scale (mRS) (14). Scores of 0-2 meant a good prognosis and scores of 3-6 meant a poor prognosis. Based on this result, all patients were divided into different groups.

3.4. Parameter estimation

Serum D-dimer and BDNF concentrations were determined using ELISA kits (Elabscience, Wuhan, China), and the determination was made in strict accordance with the instrument procedure.

The National Institute of Glasgow Coma Scalec (GCS) and NIHSS were estimated before surgical intervention.

3.5. Ralative miR-155-5p concentration

Total RNA samples were isolated from serum using Trizol LS reagent. The sample was transcribed into cDNA using the PrimeScript RT kit (Thermo Scientific, America). The detection of relative miR-155-5p concentrations was performed using ABI 7500 system and SYBR Premix Ex Taq ll kit (TAKARA, Japan). The reference gene of miR-155-5p was U6 and $2^{-\Delta\Delta CT}$ was used for calculation.

3.6. Detection of the targeted relationship between miR-155-5p and BDNF

The target relationship between miR-155-5p and BDNF was predicted using bioinformatics software. Reporter pmiR-RB-Report™ vectors carrying the sequences of BDNF widetype (BDNF-WT) or mutant BDNF (BDNF-MUT) were synthesized by RIBOBIO (Guangzhou, China). The miR-155-5p mimics, inhibitors, and their controls were purchased from RIBOBIO (Guangzhou, China). The different carriers were transfected into 293T cells (ATCC, Americа) with miR-155-5p mimics, inhibitorsor their controls, respectively. After 48 hours, luciferase activities were detected using the dual-luciferase reporter kit (Yeason, Shanghai, China).

3.7. Statistical analysis

Data were analyzed by one-way ANOVA and Student t-test using SPSS 19.0. Prism 8.0 was used to draw the graphs. Pearson analysis was applied to analyze the association between BDNF and miR-155-5p. Univariate and multivariate logistic regression analyses were used to show the relationship between factors and prognosis. The ability of miR-155-5p to discriminate patients with poor prognosis was shown by the ROC curve. $P < 0.05$ signified a significant difference.

4. Results

4.1. Comparison of clinicopathological characteristics

According to the prognosis of each patient, 56 patients were classified into the group with good prognosis, and the other 49 patients were classified into the group with poor prognosis. No differences

were found between the good prognosis group and the poor prognosis group with respect to sex, age, degree of hypertension, duration, and location (P > 0.05, Table 1). Intracranial hemorrhage volume was increased in the poor prognosis group, suggesting that the increased volume might affect prognosis (P < 0.001, Table 1). D-dimer levels in the poor prognosis group were elevated compared with the good prognosis group (P < 0.05, Table 1). In addition, GSC score was decreased and NIHSS scores were increased in the poor prognosis group, indicating the more severe situation of patients in the poor prognosis group (P < 0.05, Table 1).

4.2. Concentration of miR-155-5p and BDNF

The concentration of the miR-155-5p was increased in patients in the poor prognosis group compared with the good prognosis group, indicating that the patients with a poor prognosis had a high concentration of miR-155-5p (P < 0.001, Figure 1A). BDNF concentration was decreased in the patients with poor prognosis compared with the group with good prognosis (P < 0.001, Figure 1B), resulting in an inverse trend of miR-155-5p. The concentration of miR-155-5p was inversely correlated with BDNF levels in all patients with HICH (r = -0.822, P < 0.001, Figure 1C).

4.3. MiR-155-5p and its target BDNF

Three bioinformatics websites, including TargetScan, miRDB, and miRWalk, documented that BDNF could be a target of miR-155-5p (Figure 2A). The sequences in Figure 2B documented the putative

Table 1. Discrepancy of clinical characteristics between the good prognosis group and the poor prognosis group

Parameter	Good prognosis group (N = 56)	Poor prognosis group (N = 49)	P value
Gender			0.693
Male (N, %)	33, 58.9%	27, 55.1%	
Female (N, %)	23, 41.1%	22, 44.9%	
Age			0.369
Mean (year)	55.48 ± 8.30	56.88 ± 7.41	
Range (year)	39.0-75.0	38.0-75.0	
Hypertension grade			0.169
Grade I (N, %)	36, 64.3%	25, 51.0%	
Grade Ⅱ (N, %)	20, 35.7%	24, 49.0%	
Duration time			0.104
Mean (hour)	15.77 ± 5.22	17.33 ± 4.40	
Range (hour)	3.0-24.0	5.0-24.0	
Intracranial hemorrhage volume			< 0.001
Mean (ml)	37.75 ± 5.08	51.35 ± 5.43	
Range (ml)	30.0-50.0	38.0-66.0	
Location			0.694
Basal ganlia region (N, %)	32, 57.1%	25, 51.0%	
Thalamus (N, %)	14, 25.0%	12, 24.5%	
Lobe (N, %)	10, 17.9%	12, 24.5%	
D-dimer			0.021
Mean (mg/l)	1.42 ± 0.49	1.66 ± 0.47	
Range (mg/l)	0.38-3.88	1.06-3.80	
GSC score			< 0.001
Mean	9.16 ± 2.95	7.08 ± 2.40	
Range	4.0-15.0	2.0-12.0	
NIHSS score			0.035
Mean	18.30 ± 6.70	20.92 ± 5.74	
Range	5.0-33.0	6.0-36.0	

Abbreviations: GCS, Glasgow coma scale; NIHSS, National Institute of Health Stroke Scale.

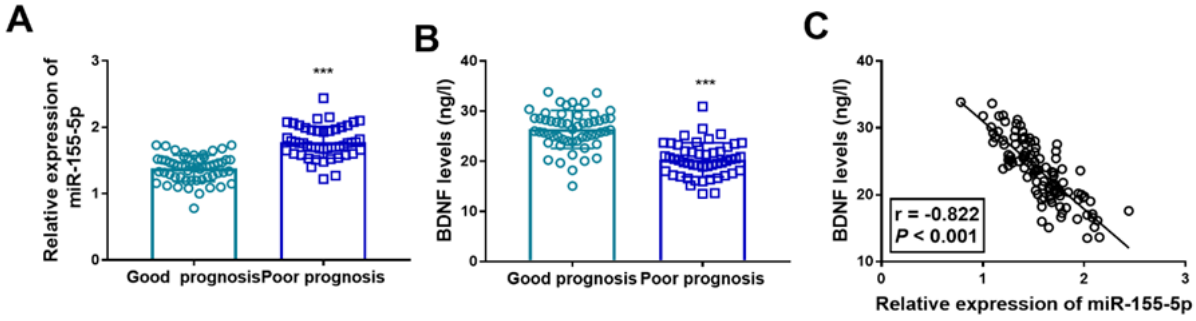

Figure 1. The levels of miR-155-5p and BDNF in HICH. (A) The concentration of miR-155-5p was elevated in the poor prognosis group. (B)

The BDNF levels declined in the poor prognosis group. (C) The reverse correlation between BDNF and miR-155-5p. ***P < 0.001

sequence between this miRNA and BDNF. Moreover, the relative luciferase activity of the cotransfected miR-155-5p mimics and BDNF-WT group was decreased and that of the cotransfected miR-155-5p inhibitors and BDNF-MUT group was increased, indicating that the change in miR-155-5p could alter the relative luciferase activity of the BDNF-WT group ($P < 0.001$, Figure 2C).

4.4. Correlations between prognosis and miR-155-5p or BDNF

Considering the interaction between this miRNA and BDNF, the logistic regression method was performed to predict the correlations between these two markers and the prognosis of patients with HICH. As shown in Table 2, single-factor logistic analysis revealed that intracranial hemorrhage volume was (OR = 2.222, 95% CI = 1.016-4.861, P = 0.046), D-dimer (OR = 2.390, 95% CI = 1.085-5.262, P = 0.030), GSC score (OR = 0.386, 95% CI = 0.174-0.854, P = 0.019), NIHSS (OR = 2.296, 95% CI = 1.047-5.038, P = 0.038), BDNF (OR = 0.227, 95% CI = 0.100-0.515, $P < 0.001$), and miR-155-5p (OR = 3.963, 95% CI = 1.744-9.009, P = 0.001) could predict the prognostic outcome of HICH patients. In addition, the multifactor logistic analysis showed that intracranial hemorrhage volume (OR = 2.979, 95% CI = 1.056-8.401, P = 0.039), BDNF (OR = 0.357, 95% CI = 0.137-0.933, P = 0.036), and miR-155-5p (OR = 3.480, 95% CI = 1.273-9.513, P = 0.015) were independent prognostic risks for poor outcome (Table 3).

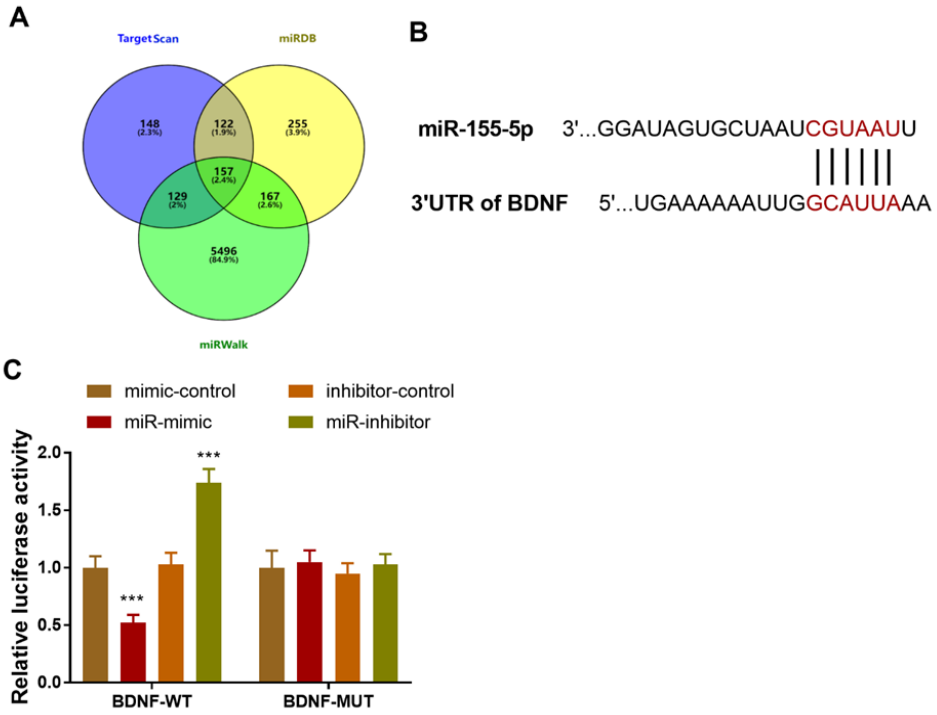

Figure 2. The putative target of miR-155-5p. (A) The Venn diagram of targets of miR-155-5p. (B) The predictive targeted oligonucleotides between BDNF and miR-155-5p. (C) The luciferase activities of the BDNF-WT group were regulated by the change of miR-155-5p levels. ***P < 0.001

Table 2. Single-factor logistic regression analysis of prognostic risks

Indicators	OR	95% CI	P value
Gender	0.855	0.394-1.856	0.693
Age (year)	1.064	0.493-2.297	0.875
Hypertension grade	0.579	0.265-1.266	0.171
Duration time (hour)	0.605	0.279-1.310	0.202
Intracranial hemorrhage volume (ml)	2.222	1.016-4.861	0.046
Location	0.651	0.242-1.750	0.395
D-dimer (mg/l)	2.390	1.085-5.262	0.030
GSC score	0.386	0.174-0.854	0.019
NIHSS score	2.296	1.047-5.038	0.038
BDNF (ng/l)	0.227	0.100-0.515	< 0.001
miR-155-5p	3.963	1.744-9.009	0.001

Abbreviations: OR, odds ratio; CI, confidence interval; GSC, Glasgow Coma Scale; NIHSS, National Institute of Health Stroke Scale; BDNF,

brain-derived neurotrophic factor.

4.5. *The predictive role of miR-155-5p and BDNF*

The ROC curve yielded an area of 0.908, a sensitivity of 0.837, and a specificity of 0.839, indicating that miR-155-5p could distinguish patients with poor prognosis from patients with good prognosis (Figure 3). As for the ROC result of BDNF, the area of 0.885, sensitivity of 0.898, and specificity of 0.804 indicated that BDNF had some value in predicting the prognosis of HICH patients (Figure 3). Moreover, the combination of miR-155-5p and BDNF had a higher AUC value (0.918) than miR-155-5p or BDNF alone (Figure 3), indicating that the combination of miR-155-5p and BDNF had high accuracy. The specificity of the combined prediction was 0.929 and the sensitivity was 0.796 (Figure 3). The results demonstrate that the combination of miR-155-5p and BDNF has relatively high specificity but relatively low sensitivity.

Table 3. Multi-factor logistic regression analysis of prognostic risks

Indicators	OR	95% CI	P value
Gender	1.124	0.414-3.049	0.819
Age (year)	0.999	0.368-2.712	0.998
Hypertension grade	0.452	0.168-1.213	0.115
Duration time (hour)	0.681	0.250-1.856	0.452
Intracranial hemorrhage volume (ml)	2.979	1.056-8.401	0.039
Location	0.391	0.114-1.342	0.136
D-dimer (mg/l)	0.384	0.141-1.045	0.061
GSC score	0.521	0.201-1.355	0.181
NIHSS score	0.495	0.172 -1.421	0.191
BDNF (ng/l)	0.357	0.137-0.933	0.036
miR-155-5p	3.480	1.273-9.513	0.015

Abbreviation Abbreviations OR, odds ratio; CI, confidence interval; GSC, Glasgow Coma Scale; NIHSS, National Institute of Health Stroke Scale; BDNF, brain-derived neurotrophic factor.

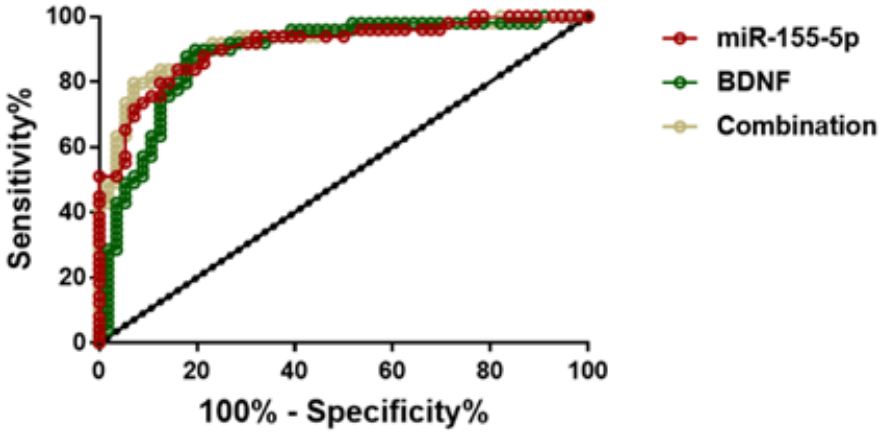

Figure 3. The findings of the ROC curve showed the predictive roles of miR-155-5p, BDNF, or their combination.

5. Discussion

HICH is essentially a spontaneous hemorrhage of blood vessels in the brain parenchyma caused by hypertension (15). The high-risk population for HICH is middle-aged and elderly people. The occurrence of HICH can lead to acute disorder of consciousness and focal neurological deficits (16). Because of the poor prognosis, high disability rate, and mortality rate, timely treatment and scientific prediction seem to be crucial. Surgical treatment of ICH at home and abroad includes large bone flap craniotomy, small bone flap craniotomy and endoscopic surgery, and minimally invasive puncture and drainage of the hematoma (17). The main advantages of minimally invasive puncture and hematoma drainage are low surgical traumaand less damage to brain tissue, can be performed under local anesthesia, relatively short operation time, and commonly performed in hospitals (18). In the present study, we selected patients with HICH who underwent minimally invasive puncture. Considering the importance of the clinical outcome of HICH, we categorized patients with HICH according to their prognosis. Intracranial hemorrhage volume, D-dimer, and NIHSS score were increased in the poor prognosis group, suggesting that the increase in these indicators suggested the risks of poor prognosis. In addition, the GSC score

was lower in the poor prognosis group, demonstrating that the patients with a good prognosis had a lower degree of coma.

MiRNAs are widely explored for their predictive capabilities in clinical applications in ICH. Several studies have confirmed that the level of miR-155-5p is altered in ICH, suggesting that miR-155-5p is involved in the occurrence of ICH (19,20). ICH induces the overexpression of miR-155-5p and the aberrant level of miR-155-5p is involved in the biological damage of the nerve during ICH (21). Gareev et al. reported that miR-155-5p is increased during spontaneous ICH (10). In the present study, the level of miR-155-5p was increased in patients with poor prognosis, suggesting that poor outcome seems to contribute to the increase of miR-155-5p. As for BDNF, the increased levels of this gene in patients with HICH who undrewent minimally invasive drainage predicted the partial recovery of neurological abilities (22). Inthe acupuncture group, BDNF levels are increased, indicating improved neurological function in ICH (23). In chronic colitis caused by dextran sodium sulfate, overexpression of miR-155-5p may inhibit BDNF levels, indicating an opposite trend between them (24). We found that the level of the targeted gene was decreased in the poor prognosis group, demonstrating that the decrease of BDNF is a risk indicator of poor prognosis in patients with HICH. Moreover, the concentration of miR-155-5p was inversely related to the quantification of BDNF, suggesting that miR-155 may affect the concentration of BDNF.

Targeted genes are crucial elements on the regulatory website of miRNAs (25). Gao et al. confirmed that miR-155-5p targets BDNF in diabetic nephropathy (13). MiR-155-5p is identified as involved in the regulation of BDNF level, suggesting a targeted relationship between them (26). In this study, miR-155-5p had a putative sequence of BDNF. Luciferase report assay showed that the relative activity of BDNF WT group was decreased by overexpression of miR-155-5p and increased by knockdown of miR-155-5p. This result suggests that miR-155-5p may exert functions by binding BDNF.

Previously published articles have investigated the role of miRNAs in studying the prognosis of ICH. Incidentally, miR-126 and miR-182 are abnormally expressed in patients with good prognosis compared with patients with poor prognosis, suggesting that the levels of miR-126 and miR-182 are related to prognosis (27). The serum concentration of miR-130a is closely related to the unfavorable prognosis of patients with acute ICH (28). Importantly, the expression of miR-155-5p in patients can serve as an alternative tool to detect ICH patients (10). Low BDNF concentration predicts poor outcome in patients with ischemic stroke, suggesting that BDNF is related to the prognosis of brain injury (29). Considering the abnormal concentration of miR-155-5p and BDNF, their predictive significance was estimated. The univariate logistic method showed that both miR-155-5p and BDNF were related to patinets' prognosis with HICH. The multivariate logistic regression method also showed that miR-155-5p and BDNF were independent biomarkers for the prognosis of patients with HICH. In addition, the ROC curve showed that detection of miR-155-5p, BDNF, or their combination could distinguish patients with poor prognosis from patients with good prognosis, suggesting that miR-155-5p, BDNF, or their combination could be considered as an alternative biomarker for HICH patients who underwent CT-guided minimally invasive surgery.

6. Conclusion

Overall miR-155-5p levels were increased and BDNF levels were decreased in patients with poor prognosis. BDNF was a target of miR-155-5p, and its level inversely correlated with miR-155-5p concentration. The combination of miR-155-5p and BDNF could serve as a biomarker for the prognosis of HICH with a specificity of 0.929 and sensitivity of 0.796.

Acknowledgments

Not applicable.

Footnotes

Conflicts of Interest: None to declare.
Author Contribution: Conceptualization: Qihan Chen; Liang Wen; Data curation: Dan Lin, Zepeng Jiang, Hui Yan; Formal analysis: Dan Lin; Zepeng Jiang; Investigation: Dan Lin; Hui Yan; Methodology: Qihan Chen; Dan Lin; Project administration: Liang Wen; Supervision: Liang Wen; Validation: Zepeng Jiang; Roles/Writing - original draft: Qihan Chen; Writing - review & editing: Liang Wen.
Funding: None.
Ethical Statements: The study met the requirements of medical ethics of First Affiliated Hospital, Zhejiang University School of Medicine, and all patients signed the written informed consent.

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