Clinical Neuroscience Research

Editors-in-Chief

J.B.M. Kuks

University Medical Center Groningen, The Netherlands

Deqin Geng

Affiliated Hospital of Xuzhou Medical University, China

BIO-BYWORD SCIENTIFIC PUBLISHING PTY LTD
(619 649 400)
Level 10
50 Clarence Street
SYDNEY NSW 2000

Clinical Neuroscience Research

Focus and Scope

Clinical Neuroscience Research is a peer-reviewed articles across a wide spectrum of basic, translational, and clinical research that help improve patient care. The journal publishes original articles, editorials and reviews to educate its readers, and to better understand, treat, and prevent neurological disorders. Published papers describing the results of original research on any aspect of the scientific study of the nervous system. Any paper, however short, will be considered for publication provided that it reports significant, new and carefully confirmed findings with full experimental details.

The journal provides a platform for studies that explores the diagnosis, nature, causes, treatment, and public health aspects of neurological illnesses.

About Publisher

Bio-Byword Scientific Publishing is a fast-growing, peer-reviewed and open access journal publisher, which is located in Sydney, Australia. As a dependable and credible corporation, it promotes and serves a broad range of subject areas for the benefit of humanity. By informing and educating a global community of scholars, practitioners, researchers and students, it endeavors to be the world's leading independent academic and professional publisher. To realize it, it keeps creative and innovative to meet the range of the authors' needs and publish the best of their work.

By cooperating with University of Sydney, University of New South Wales and other world-famous universities, Bio-Byword Scientific Publishing has established a huge publishing system based on hundreds of academic programs, and with a variety of journals in the subjects of medicine, construction, education and electronics.

Publisher Headquarter

BIO-BYWORD SCIENTIFIC PUBLISHING PTY LTD
Level 10
50 Clarence Street
Sydney NSW 2000
Website: www.bbwpublisher.com
Email: info@bbwpublisher.com

2024, Volume 2, Issue 1

Table of Contents

Clinical Neuroscience Research, 2024, Volume 2, Issue 1
http://ojs.bbwpublisher.com/index.php/CNR

Application of Neural Rehabilitation Manipulator Training in Upper Limb Rehabilitation of Stroke Patients with Hemiplegia

Shan Xiang[1], Qingze Lu[2*], Pei Liu[3]

[1]The Thirteenth People's Hospital of Chongqing, Chongqing 400000, China
[2]Chongqing Orthopedic Hospital of Traditional Chinese Medicine, Chongqing 400000, China
[3]Chongqing Traditional Chinese Medicine Hospital, Chongqing 400000, China

***Corresponding author:** Qingze Lu, yy77443211@163.com

Abstract: *Objective:* To analyze the application of neural rehabilitation manipulator training in upper limb rehabilitation of stroke patients with hemiplegia. *Methods:* 94 patients with hemiplegia after stroke were selected from January 2021 to January 2023. The patients were randomly divided into a control group and an observation group, with 47 cases in each group. The control group received routine rehabilitation training while the observation group received neural rehabilitation manipulator training. The upper limb and nerve function, daily task performance ability, quality of life, and rehabilitation training satisfaction were compared between the two groups. *Results:* There was no significant difference in upper limb and nerve function between the two groups before training, $P > 0.05$. After training, the observation group had 51.45 ± 8.75 points in ARAT and 52.59 ± 8.48 points in FMA-UE, which were higher than those in the control group with 43.81 ± 6.67 points and 45.51 ± 7.31 points respectively, $P < 0.05$. The observation group had 5.71 ± 1.53 points in NIHSS, which was lower than those in the control group with 8.04 ± 2.39 points, $P < 0.05$. In terms of daily task performance ability and quality of life, there was no significant difference between the two groups before training, $P > 0.05$. After training, the observation group had 78.54 ± 10.63 scores in MBI and 171.93 ± 19.12 scores in SS-QOL, which were higher than those in the control group with 70.51 ± 9.25 scores and 160.13 ± 18.42 scores respectively, $P < 0.05$. In terms of satisfaction, the total satisfaction rate of the observation group was 93.62%, which was higher than that of the control group with 74.47%, $P < 0.05$. *Conclusion:* The application of neural rehabilitation manipulator training in the upper limb rehabilitation of stroke patients with hemiplegia can significantly improve the upper limb function of patients, relieve nerve defects, improve daily task performance ability and quality of life, and increase patient satisfaction with rehabilitation training.

Keywords: Neural rehabilitation manipulator training; Hemiplegia after stroke; Upper limb rehabilitation; Application effect

Online publication: April 9, 2024

1. Introduction

Stroke is a cerebrovascular disease with the highest incidence rate in China. Stroke causes disability and

mortality, which greatly impact the quality of life of patients. Most stroke patients have symptoms of hemiplegia that result in limb impartment and partial or complete loss of the ability to perform daily tasks [1]. Rehabilitation exercises in the past mostly focused on lower limb function and neglected upper limb function rehabilitation due to its difficulty, so this hindered the overall rehabilitation of patients. With the improvement of rehabilitation technology in recent years, various advanced equipment and means have been gradually developed for the upper limb rehabilitation of stroke patients with hemiplegia [2]. For example, the neural rehabilitation manipulator is a kind of instrument specially used for limb rehabilitation. The use of advanced technology to help patients carry out training is conducive to improving the rehabilitation effect [3]. Based on this, 94 patients with stroke hemiplegia from January 2021 to January 2023 were selected in this paper, and the application of neural rehabilitation manipulator training in upper limb rehabilitation of these stroke hemiplegia patients was analyzed.

2. Data and methods

2.1. General information

A total of 94 stroke patients with hemiplegia were selected from January 2021 to January 2023. The patients were randomly divided into the control group and the observation group, with 47 cases in each group. There were 25 male and 22 female patients in the control group, with an average age of 68.12 ± 3.43 years, ranging between 52–81 years old. There were 27 male and 20 female patients in the observation group, with an average age of 68.20 ± 3.35 years, ranging between 53–82 years old. There was no significant difference in the above indexes between the two groups ($P > 0.05$). The study was approved by a medical ethics committee [4].

Inclusion criteria: All patients met the diagnostic criteria for stroke hemiplegia, and all had obvious manifestations of upper limb dysfunction. Patients and their families were informed of the study content and agreed to participate.

Exclusion criteria: Patients with audio-visual impairment, unconsciousness, coma, etc., patients with upper limb dysfunction due to peripheral nerve injury and other reasons.

2.2. Methods

2.2.1. Control group

The control group received routine rehabilitation training. Specific methods were used to induce the loosening of the finger joints of the limbs and effective passive activities of the patients. The muscle strength training of the wrist extensor muscle group and the stretching training of the wrist flexor finger muscle group were gradually increased for the patients. At the same time, the patients were guided to perform trunk control exercises, active and passive limb movements, gravity adjustment training, and the training of daily activities. The training lasted for one month [5,6].

2.2.2. Observation group

The observation group received neural rehabilitation manipulator training by using the upper limb intelligent rehabilitation training system manufactured by Yikang Medical Equipment Company, Guangzhou. The electrodes were attached to the flexor and extensor muscles of the forearm of the patient with the active and passive training modes set. In the active training mode, the rehabilitation doctor guides the patients to complete specific actions by themselves while adjusting the threshold according to the EMG signal to complete the subsequent training content. When the EMG signal is higher than the threshold level, the manipulator can be driven to complete the corresponding specific training action. In the passive training mode, the robot guides

the finger on the affected side of the patient to complete the corresponding training action. This training is conducted for one hour per day, five times per week with two resting days. Regular rehabilitation training is conducted during the two resting days. This training lasted for one month [7–9].

2.3. Evaluation index

The upper limb and nerve function, daily task performance ability, quality of life, and rehabilitation training satisfaction were compared between the two groups. The upper limb function was evaluated by the ARAT scale and FMA-UE scale respectively. The higher the score, the better the upper limb function was. Nerve function was evaluated by the NIHSS scale. The lower the score, the better the nerve function was. Daily task performance ability and quality of life quality were evaluated by the MBI scale and SS-QOL scale respectively. The higher the score, the better the daily task performance ability and quality of life. Satisfaction was evaluated by a self-made questionnaire. The total score of the questionnaire was 100, 80–100 points represented very satisfied, 60–79 points represented satisfied, and less than 60 points represented dissatisfied [10–12].

2.4. Statistical Processing

SPSS 20.0 software was used to process the data obtained from the study. The data was expressed in number or rate with χ^2 test. The measurement data were expressed by mean ± standard deviation (SD) and *t*-test was used. If $P < 0.05$, there is a significant difference.

3. Results

3.1. Results of upper limb function and nerve function were compared between the two groups

In terms of upper limb and nerve function, there was no significant difference between the two groups before training as shown in **Table 1**, $P > 0.05$. After training, the observation group had 51.45 ± 8.75 points in ARAT and 52.59 ± 8.48 points in FMA-UE, which were higher than those in the control group with 43.81 ± 6.67 points and 45.51 ± 7.31 points respectively, $P < 0.05$. The observation group had 5.71 ± 1.53 points in NIHSS, which was lower than those in the control group with 8.04 ± 2.39 points, showing $P < 0.05$.

Table 1. Comparison of upper limb and nerve function between the two groups (mean ± SD）

Group	Number of cases	ARAT (Points)		FMA-UE (Points)		NIHSS (Points)	
		Before training	After training	Before training	After training	Before training	After training
Observation group	47	36.44 ± 5.28	51.45 ± 8.75	36.13 ± 6.82	52.59 ± 8.48	13.03 ± 3.39	5.71 ± 1.53
Control group	47	37.17 ± 5.97	43.81 ± 6.67	35.37 ± 5.35	45.51 ± 7.31	13.26 ± 3.88	8.04 ± 2.39
t		0.628	4.761	0.601	4.335	0.306	5.629
P		0.532	0.000	0.549	0.000	0.760	0.000

3.2. Results of daily task performance ability and quality of life compared between the groups

In terms of daily task performance ability and quality of life, there was no significant difference between the two groups before training as shown in **Table 2**, $P > 0.05$. After training, the observation group had 8.54 ± 10.63 scores in MBI and 171.93 ± 19.12 scores in SS-QOL, which were higher than those in the control group

with 70.51 ± 9.25 scores and 160.13 ± 18.42 scores respectively, $P < 0.05$.

Table 2. Results comparing daily task performance ability and quality of life between the two groups (mean ± SD)

Group	Number of cases	MBI (Score)		SS-QOL (Score)	
		Pre-training	Post-training	Pre-training	Post-training
Observation group	47	62.71 ± 9.87	78.54 ± 10.63	140.20 ± 15.42	171.93 ± 19.12
Control group	47	61.27 ± 8.38	70.51 ± 9.25	142.72 ± 16.31	160.13 ± 18.42
t		0.762	3.907	0.770	3.047
P		0.448	0.000	0.443	0.003

3.3. Comparison of satisfaction results between the two groups

In terms of satisfaction, the total satisfaction rate of the observation group was 93.62%, which is higher than that of the control group with 74.47% as shown in **Table 3**, $P < 0.05$.

Table 3. Results of comparing satisfaction between the two groups [*n* (%)]

Group	Number of cases	Very satisfied	Satisfied	Dissatisfied	Overall satisfaction rate
Observation group	47	20 (42.55)	24 (51.06)	3 (6.38)	44 (93.62)
Control group	47	15 (31.91)	20 (42.55)	12 (25.53)	35 (74.47)
χ^2		0.728	0.385	5.077	5.077
P		0.393	0.535	0.024	0.024

4. Discussion

Stroke is a common cerebrovascular disease. Stroke patients generally show disability and neurological impairment due to its sudden onset and delayed treatment [13]. The patient still has a high probability of sequelae even if emergency care has been provided. Hemiplegia is one of the most prevalent complications of stroke, which is manifested as the impartment of limb function, the reduction of daily task performance ability, and the serious decline of quality of life. Although this dysfunction is irreversible, it can be alleviated through active rehabilitation training to improve the limb function of patients to a certain extent [14]. Effective rehabilitation training can stimulate the damaged areas of the brain tissue of patients, improve the excitability of the remaining cells, increase the efficiency of synapses, and promote the regeneration of synapses, thus achieving partial recovery of activity and function [15].

Upper limb rehabilitation is an important part of rehabilitation exercise for stroke patients with hemiplegia. However, upper limb function impartment often lasts a long time with a slow and difficult recovery. However, this impairment can still be reduced through rehabilitation training [16]. Conventional rehabilitation techniques mainly include electromechanical biofeedback, acupuncture, massage, occupational therapy, exercise therapy, and so on, but the overall effect of these techniques is not optimal. The recent development of robotic rehabilitation technology has also played a positive role in the upper limb rehabilitation of stroke patients with hemiplegia. One of the technologies is the professional neural rehabilitation manipulator with active and passive motion function modes which can be used according to the rehabilitation procedure of the patient and has intelligent speech function [17]. The device can collect and analyze the EMG feedback of the patient and convert it into audiovisual signals that can be recognized by the patient. The device can provide strong support

for the upper limb function exercise of patients by adjusting the relevant threshold level. This method can increase the sensory input of patients, reshape the damaged tissues of the upper limb, and promote the axonal synaptic connection and the regeneration of nerve collateral with good repeatability and consistent results for the recovery of limb function of patients [18–20].

In summary, the application of neural rehabilitation manipulator training in the upper limb rehabilitation of stroke patients with hemiplegia can significantly improve the upper limb function of patients, alleviate nerve defects, improve life task performance ability and quality of life, and increase patient satisfaction with rehabilitation training.

Disclosure statement

The authors declare no conflict of interest.

References

[1] Wang MM, Er ZJ, Xiao ZX, 2019, Clinical Effect Analysis of Mandatory Exercise Therapy Combined with Neuromuscular Electrical Stimulation in Upper Limb Functional Rehabilitation of Stroke Patients with Hemiplegia. Journal of Rare Diseases, 46(33): 178–180.

[2] Zhang SX, Zheng YD, Li X, et al., 2019, Application of Intelligent Motor Feedback Training in Hand and Upper Limb Function Rehabilitation of Hemiplegia Patients in Convalescent Period of Stroke. Chinese Journal of Rehabilitation Medicine, 34(10): 164–166.

[3] Yuan GQ, Zhao Y, 2020, Effect of Intensive Training of Neurorehabilitation Manipulator on Upper Limb Motor Function Recovery of Stroke Patients with Hemiplegia. Chinese Community Physician, 36(33): 152–154.

[4] Lu YX, Yao HY, Wang L, et al., 2019, Effect of Neuro-loosening Combined with Upper Limb Robot on Upper Limb Functional Rehabilitation of Stroke Patients with Hemiplegia. Chinese and Foreign Medical Research, 17(21): 77–78.

[5] Wu QY, Ye JP, Li Y, et al., 2013, Cost-Effectiveness Analysis of Upper Limb Motor Function Rehabilitation for Stroke Patients with Hemiplegia Treated with MOTOmed Gracile. Chinese Journal of Rehabilitation Theory and Practice, 19(2): 154–157.

[6] Yang, Liu WH, Wang CX, et al., 2019, Application of Robot-Assisted Upper Limb Rehabilitation in Upper Limb Functional Rehabilitation of Stroke Patients with Hemiplegia. Nerve injury and functional Reconstruction, 14(9): 133–135.

[7] Zhang FF, Zhou L, Zhu HS, 2021, Application Effect of Motor Imagination Combined Rehabilitation Robot in Upper Limb Motor Function Recovery after Stroke with Hemiplegia. Beijing Medical Journal, 48(37): 126–128.

[8] Wang M, 2020, Evaluation of Application Effect of Upper Limb Intelligent Rehabilitation Training System in Rehabilitation Treatment of Stroke Patients with Hemiplegia. Journal of Shanxi Health Vocational College, 30(5): 9–11.

[9] Ren H, Xie ZM, 2019, Effect of Brain-Computer Interface Technology on Upper Limb Motor Function Rehabilitation of Stroke Patients with Hemiplegia. Chinese Journal of Practical Medicine, 15(10): 113–115.

[10] Gao TT, Liu Q, 2023, To Evaluate the Clinical Value of Forced Motor Therapy (CIMT) + Neuromuscular Electrical Stimulation (NMES) in Upper Limb Functional Rehabilitation of Stroke Patients with Hemiplegia. Life Science Instruments, 2023(0z1): 21.

[11] Huang CF, Ou JY, Zhang RB, 2017, Effect of Closed Chain Exercise Training on Upper Limb Motor Function and Functional Ability Recovery in Stroke Patients with Hemiplegia. Medical Theory and Practice, 30(14): *2165–2167.*

[12] Liu FJ, Zhou DA, Gao RP, et al., 2013, Effect of Hand Intensive Training on Upper Limb Function Recovery in

Patients with Hemiplegia after Stroke. Chinese Journal of Physical Medicine and Rehabilitation, 2013(35): 557–558.

[13] Wang YJ, Wang SY, Zhao DX, et al., 2021, Application of Multi-Functional Wheelchair Support Panel in Upper Limb Rehabilitation Training of Stroke Patients with Hemiplegia. Journal of China Medical University, 50(4): 366–370.

[14] Gong Y, Zhang Y, Wang R, et al., 2021, Effect of Upper Limb Rehabilitation System on Upper Limb Motor Function Rehabilitation of Patients with Hemiplegia after Stroke. Nerve Injury and Functional Reconstruction, 16(12): 769–771.

[15] Zou Q, Cao SE, Yuan C, et al., 2015, The Value of 99mTc-ECD Cerebral Blood Flow Perfusion Imaging in the Evaluation of the Efficacy of Upper Limb Functional Training in Stroke Patients. Journal of Sun Yat-sen University (Medicine Science Edition), 36(6): 932–935 + 954.

[16] Kuang JL, 2021, Effect of Upper Limb Rehabilitation Robot Training Combined with Rehabilitation Nursing on Upper Limb Function of Stroke Patients with Hemiplegia. Chinese Medicine for Disability, 29(12): 77–78.

[17] Jing Y, Liu PP, Xie J, et al., 2021, Application of Rehabilitation Apparatus in Rehabilitation of Stroke Patients with Upper Limb Paralysis. Journal of Advanced Nursing, 36(1): 90–93.

[18] Jiang WL, Zhou Q, 2023, Effect of Acupuncture Combined with Rehabilitation Therapy on Walking Function of Stroke Patients with Hemiplegia. Chinese Modern Education of Traditional Chinese Medicine, 21(20): 130–132.

[19] Fu LL, Su BR, 2019, Effect of Neuro-loosening Combined with Routine Rehabilitation Training on Hand Function Recovery of Hemiplegia Patients at Different Stages after Stroke. Nerve Injury and Functional Reconstruction, 14(6): 314–315.

[20] Zhang CB, Li LL, 2017, Effect of MOTOmed Intelligent Motor Training System on Upper Limb Function and Activity of Daily Living in Stroke Patients with Hemiplegia. Chinese Journal of Metallurgical Industry Medicine, 34(2): 225–226.

Clinical Neuroscience Research, 2024, Volume 2, Issue 1
http://ojs.bbwpublisher.com/index.php/CNR

Relationship between Cognitive Impairment and Serum ALP after Light Acute Ischemic Stroke in the Elderly

Xi Chen[1], Xiaojun Hou[2], Hongjuan Fu[2], Peng Zhang[2], Yueping Huang[2], Ying Shi[2], Jujun Xue[2]*

[1]Department of Laboratory, Heilongjiang Provincial Hospital, Harbin 150036, Heilongjiang Province, China.
[2]Department of Geriatric Neurology, Heilongjiang Provincial Hospital, Harbin 150036, Heilongjiang Province, China.

***Corresponding author:** Jujun Xue, xxuejjun@163.com

Abstract: *Objective:* To analyze the association between cognitive impairment and serum ALP levels in elderly patients who developed light acute ischemic stroke. *Methods:* 100 cases of elderly patients with mild acute ischemic stroke admitted from January 2022 to June 2023 were selected as the study subjects, and were divided into two groups according to whether or not they developed cognitive impairment within six months; those who did not develop cognitive impairment were classified into the control group, with a total of 62 cases, while those who developed cognitive impairment were classified into the case group, with a total of 38 cases. The general data and serum ALP levels of the two groups were compared, and the correlation between serum ALP levels and MoCA scores was analyzed. *Results:* There was no significant difference between the general information of the two groups of patients in the control group and the case group ($P > 0.05$). The serum ALP level of the patients in the case group was higher than that of the control group ($P < 0.05$), and there was a negative correlation between the serum ALP level and the total score of MoCA, the visuospatial and executive scores, and the memory score ($P < 0.05$). *Conclusion:* The serum ALP levels of elderly patients with cognitive impairment after mild acute ischemic stroke were higher than those of elderly patients without cognitive impairment after mild acute ischemic stroke, so the risk of cognitive impairment can be predicted in advance by detecting serum ALP levels.

Keywords: Elderly mild acute ischemic stroke; Cognitive impairment; Serum ALP level

Online publication: March 29, 2024

1. Introduction

Stroke is a very highly prevalent cerebrovascular disease in China, which can be divided into two types, ischemic stroke and hemorrhagic stroke. Statistics show that China has become the country with the highest lifelong risk of stroke. Stroke can cause a variety of functional disorders, such as cognitive impairment, which is experienced by about one-third of all stroke patients and seriously affects the quality of life and even shortens lifespan [1,2]. Post-stroke cognitive impairment is a clinical syndrome that occurs after a stroke event and lasts for six months or more. The increase in the median age at stroke onset and the decrease in stroke mortality rate

in recent years has led to a gradual increase in the prevalence of post-stroke cognitive impairment. So early detection and diagnosis is the key to improving the prognosis, as the burden of cerebrovascular disease and dementia in China is very heavy. Biomarkers with high sensitivity and accuracy should be introduced to predict patients with high risk of post-stroke cognitive impairment in advance to reduce its impact on individuals, families, and even society. ALP (alkaline phosphatase) is a metalloenzyme encoded by a multigene family that dephosphorylates its corresponding substrate and it is commonly used in the diagnosis of liver disease and bone disease. ALP is associated with the prognosis of cardiovascular and peripheral arterial diseases [3]. This study aims to analyze the relationship between cognitive impairment and serum ALP levels in elderly patients with mild acute ischemic stroke. A total of 100 patient cases admitted from January 2022 to June 2023 were included in this study. The details of this study are described in the following section.

2. Information and methods

2.1. Data

One hundred elderly patients with mild acute ischemic stroke were selected as study subjects (admission time: January 2022 to June 2023) based on the criteria and were divided into 62 cases in the control group (no cognitive impairment) and 38 cases in the case group (with cognitive impairment) according to whether or not cognitive impairment had occurred within six months.

The control group consists of 38 men and 24 women with age between 65–79 (70.56 ± 3.35) years. The case group consists of 23 males and 15 females with age between 65–80 (70.32 ± 3.12) years. The gender and age of the two groups were statistically analyzed, yielding a P value > 0.05.

Inclusion criteria:

(1) Meeting the diagnostic criteria of acute ischemic stroke, NIHSS score of 3 or less, and has a new infarct lesion.
(2) Age of 65 years and above.
(3) Normal cognitive function before stroke, good social adaptability, and no history of schizophrenia, depression, anxiety, etc.
(4) Patients or their family members were informed of and agreed to this study.
(5) Complete clinical data.

Exclusion criteria:

(1) Unable to cooperate with the completion of cognitive function assessment.
(2) Accompanied by other neurological diseases, such as epilepsy, etc.
(3) Accompanied by hematologic diseases, severe cardiopulmonary and renal insufficiency, and malignant tumors.

Diagnostic criteria for acute ischemic stroke [4]:

(1) The results showed acute onset after examination
(2) Symptoms of focal or comprehensive neurological deficits, such as limb weakness, facial numbness, etc.
(3) The presence of signs or symptoms, with the duration of the condition >24 hours
(4) Exclusion of non-vascular causes and cerebral hemorrhage.

Diagnostic criteria for post-stroke cognitive impairment [5]:

(1) Cognitive impairment within six months after stroke.
(2) Emphasizing the causal relationship between stroke and cognitive impairment.
(3) Having the relevance of clinical management, including cognitive impairment due to multiple stroke events.

2.2. Methods

Serum ALP levels of the subjects were tested within two days, at three months, and at six months after the onset of the disease. 5 ml of venous blood was collected from the fasting subjects and centrifuged, then the upper serum layer was analyzed with a fully automated biochemical analyzer.

Cognitive function was assessed within seven days, at three months, and at six months after the onset of the disease. The assessment scales included the mini-mental state examination (MMSE) and the Montreal Cognitive Assessment (MoCA), both of which were in Chinese [6,7]. The critical value of the MMSE scale was set according to the level of literacy, which was illiterate (≤17 points), elementary school (≤20 points), secondary school, and higher education (≤24 points), while the critical value of the MoCA scale was 22 points. The MMSE or MoCA score lower than the critical value indicated the presence of cognitive impairment, whereas a score higher than the critical value indicated the absence of cognitive impairment.

2.3. Observation indexes

(1) Compare the general information of the two groups of patients.
(2) Compare the serum ALP levels of the two groups.
(3) Analyze the correlation between serum ALP levels and cognitive impairment after mild acute ischemic stroke in the elderly.

2.4. Statistical methods

SPSS 25.0 version of the statistical software was used to analyze the data in the text. The count data and the measurement data were expressed by mean ± standard deviation (SD) and [*n* (%)] respectively, in which the former was tested by χ^2 test and the latter was tested by *t*-test. The *P* value < 0.05 indicated that the comparison data were statistically significant.

3. Results

3.1. General information

As shown in **Table 1**, the difference between the general information of the two groups was not obvious when compared, $P > 0.05$.

Table 1. General information of subject groups (mean ± SD)

	Control group	Case group	χ^2/t	*P*
Male/female	38/24	23/15	0.006	0.939
Age (years)	70.56 ± 3.35	70.32 ± 3.12	0.371	0.712
BMI (kg/m^2)	23.25 ± 2.16	23.10 ± 2.21	0.343	0.732
History of hyperlipidemia	11	6	0.064	0.801
History of diabetes	9	4	0.332	0.565
History of hypertension	36	20	0.282	0.595
History of smoking	23	10	1.239	0.266
TG (mmol/L)	1.32 ± 0.26	1.35 ± 0.23	0.611	0.543
TC (mmol/L)	4.51 ± 1.15	4.52 ± 1.20	0.043	0.966
HDL-C (mmol/L)	1.20 ± 0.25	1.18 ± 0.31	0.355	0.723
LDL-C (mmol/L)	3.53 ± 0.75	3.58 ± 0.69	0.347	0.729

3.2. Serum ALP level

As shown in **Table 2**, the serum ALP level of the case group was higher than that of the control group, $P < 0.05$.

Table 2. Serum ALP levels (mean ± SD, U/L)

Group	Case (*n*)	ALP level
Control group	62	76.25 ± 12.31
Case group	38	82.25 ± 10.18
t	-	2.521
P	-	0.013

3.3. Correlation analysis

As shown in **Table 3**, serum ALP level is negatively correlated with the total MoCA score, visuospatial and executive ability scores, and memory scores respectively, $P < 0.05$.

Table 3. Correlation analysis of serum ALP level and MoCA score

MoCA variable	R	*P*
Total score	-0.359	0.011
Visuospatial and executive ability	-0.380	0.006
Memory	-0.329	0.023
Naming	-0.158	0.291
Language	-0.225	0.123
Attention	-0.185	0.201
Orientation	-0.045	0.749
Abstraction	-0.116	0.425

4. Discussion

Stroke is a very typical cerebrovascular disease with a high prevalence in the elderly that can lead to balance disorders, cognitive disorders, vascular dementia, and other adverse manifestations. The etiology of the disease is unknown but studies have suggested that it is related to structural changes in small blood vessels, microembolism, hypoperfusion, or metabolic disorders [8]. Stroke lesions can cause cognitive disorders such as ischemic alterations in both deep gray matter and subcortical white matter. The ischemic alterations cut off the frontal-subcortical circuit, which causes a decrease in the normal speed of information processing, frontal lobe attention, and executive function. This will lead to dementia and vascular cognitive impairment if the disease continues to progress, affecting the subsequent quality of life. Previous studies have suggested that vascular calcification is prevalent in all stages of human pathology and physiology and that it is an uncontrollable and passive process. However, recent studies have found that the pathological basis of vascular calcification is a transitional stage that triggers atherosclerosis, which is a common pathological manifestation of chronic kidney disease and cardiovascular disease that can be regulated and controlled [9]. Moreover, vascular calcification decreases vascular elasticity and increases vascular stiffness and the risk of atherosclerosis and vascular rupture. So the degree and location of vascular calcification can serve as an early warning for stroke and cardiovascular disease. Post-stroke cognitive impairment has its characteristics, such as fluctuating course, patchy cognitive

deficits, and so on, which can be prevented and cured. Currently, cognitive function is often used in clinical screening and assessment, while the diagnosis is mainly based on clinical manifestations, neuroimaging, and neuropsychological assessment. Sensitive, accurate, and reliable biomarkers should be introduced to identify patients at high risk of developing post-stroke cognitive impairment to reduce its negative impact [10].

ALP is a metalloenzyme encoded by a multigene family that is mainly found in bone, liver, and kidney. ALP increases the incidence of cardiovascular and cerebrovascular diseases through vascular calcification and vascular endothelial dysfunction in response to inflammatory factors. ALP is divided into two types according to tissue expression, the first is tissue-specific alkaline phosphatases (ALPs) expressed in the intestine, placenta, and germ cells, while the other is tissue-nonspecific alkaline phosphatases (TNAPs), which are expressed in tissues such as the liver, kidneys, and bones. TNAPs account for more than 90% of the total circulating ALP, which is expressed in neuronal cells, endothelial cells, and neuronal synapses of the brain [11,12]. Relevant studies have indicated that circulating ALP levels can predict the prognosis of cerebral infarction [12]. So in this study, 100 elderly patients with mild acute ischemic stroke were selected as research subjects and divided according to the occurrence of cognitive impairment into the control group (without cognitive impairment) and the case group (with cognitive impairment). The data showed that the differences in the general conditions of the two groups were not obvious, but the serum ALP levels of patients in the case group were higher than those of the patients in the control group. There was a negative correlation between the ALP level of the patients in the case group and their MoCA total score, visuospatial and executive scores, and memory scores. This suggests that there is a correlation between serum ALP level and cognitive deficits in the post-stroke period which can be used as a biomarker for early identification of high-risk cases of cognitive deficits in post-stroke periods.

As for the mechanism of vascular calcification, it works by promoting calcification in vivo and inhibiting calcification at the same time [13]. These two systems interact with each other, so when ALP is elevated, the balance between these two systems is disrupted. When ALP is overexpressed, it increases the rate of hardening of the blood vessels, which causes atherosclerosis and cerebral ischemic changes. These changes can lead to mild manifestations of vascular cognitive impairment and dementia.

As for the inflammatory mechanism, serum ALP levels will be raised similar to C-reactive protein when the body is subjected to inflammatory infections, thus triggering endothelial dysfunction and vascular damage. Cerebrovascular pathological changes of the collagen deposition mechanism have many types. Such as in periventricular venous collagenous disease, ALP will induce collagen deposition that increases the thickness of the venous and microvascular wall, triggering chronic ischemia of brain tissue [14].

In summary, it is shown that cognitive impairment is a common manifestation after a stroke. Hence assessing the risk coefficient of cognitive impairment in advance and adopting certain interventions can actively reduce its incidence and impact. The present study found that there is a correlation between the level of ALP and cognitive impairment after mild acute ischemic stroke in the elderly. The level of ALP in patients with cognitive impairment is significantly elevated, which suggests that it is possible to predict the incidence and severity of cognitive impairment through the detection of the serum ALP level in advance. Thus, a targeted therapeutic plan can be formulated in advance to improve the clinical prognosis positively.

Funding

Scientific Research Project of Heilongjiang Provincial Health Commission Project (No. 20210303070132)

Disclosure statement

The authors declare no conflict of interest.

References

[1] Lin YF, Wei TY, Zhang XY, et al., 2023, Effectiveness of Music Therapy on Cognitive Impairment after Stroke. Chinese Rehabilitation Theory and Practice, 29(6): 714–719.

[2] Li WY, Jiang JW, Wang LL, et al., 2023, Factors Affecting Post-Stroke Cognitive Impairment and its Correlation with Cognitive Scores in Acute Ischemic Stroke Patients. Chinese Journal of Health Management, 17(1): 7–12.

[3] Xiao T, Tang ZY, Huang XH, 2020, Relationship between Blood Alkaline Phosphatase Level and Vascular Mild Cognitive Impairment in Patients with Cerebral Small Vessel Disease. Medical Equipment, 33(13): 95–97.

[4] Tan ZF, Liu LP, Xu AD, et al., 2023, Guidelines for the Clinical Management of Cerebrovascular Disease in China: Chapter 1 Overview. Chinese Journal of Stroke 2nd edition, 18(7): 817–821.

[5] Cui Q, Li RL, Li WJ, et al., 2022, Interpretation of the Guideline "Cognitive Impairment after Stroke". Nursing Research, 36(22): 3949–3952.

[6] Liu ZJ, Yang FS, Zhao LL, 2022, Study on the Efficacy of Olanzapine Combined with Cognitive Training in Treating Patients with Post-Stroke Cognitive Dysfunction and the Effect on MMSE Score. Intelligent Health, 8(27): 49–52.

[7] Wu X, Gou X, Ba XT, 2021, Effect of Cilostazol Combined with Aspirin on MoCA Score, Serum GSHPx Level and FMA Score in Interventional Acute Ischemic Stroke Patients. Journal of Clinical and Experimental Medicine, 20(21): 2270–2273.

[8] Sensenbrenner B, Rouaud O, Graule-Petot A, et al., 2020, High Prevalence of Social Cognition Disorders and Mild Cognitive Impairment Long Term After Stroke. Alzheimer Disease and Associated Disorders, 34(1): 72–78.

[9] Geng MH, Lai YY, Tao M, et al., 2022, Relationship Between Calcium and Phosphorus Metabolism Disorders and Cognitive Impairment in Maintenance Hemodialysis Patients. Journal of Clinical Nephrology, 22(9): 730–736.

[10] Zhang Q, Yuan J, Dong XY, et al., 2023, Application of Magnetic Resonance Diffusion Tensor Imaging in Cognitive Impairment in Patients with Asymptomatic Lacunar Cerebral Infarction. Shaanxi Medical Journal, 52(1): 57–61.

[11] Li HJ, Tian HJ, Liu XY, et al., 2020, Correlation between Cognitive Dysfunction and Blood Alkaline Phosphatase Level in Patients with Cerebral Small Vessel Disease. Shanxi Medical Journal, 49(7): 837–839.

[12] Xiao T, Gan Q, Tang ZY, et al., 2022, Correlation between Alkaline Phosphatase and Cognitive Function in Patients with Cerebral Small Vessel Disease. Jiangxi Medicine, 57(8): 907–911.

[13] Shin M, Sohn MK, Lee J, et al., 2020, Effect of Cognitive Reserve on Risk of Cognitive Impairment and Recovery After Stroke: The KOSCO Study. Stroke, 51(1): 99–107.

[14] Wei QL, 2021, Correlation between Serum ALP and hs-CRP Levels and Cognitive Dysfunction after Intravenous Thrombolytic Therapy in Ischemic Stroke Patients. Heilongjiang Traditional Chinese Medicine, 50(6):14–15.

Clinical Neuroscience Research, 2024, Volume 2, Issue 1
http://ojs.bbwpublisher.com/index.php/CNR

Application of Network Pharmacology to Explore the Anti-Aging Molecular Mechanism of *Radix notoginseng*

Junyang Zhang†, Qinglin Yu†, Tong Zhao, Xueru Ding, Na Li*

Kunming Medical University, Kunming 650500, Yunnan Province, China
†These authors contributed equally to this work

***Corresponding author:** Na Li, 1398932495@qq.com

Abstract: *Objective:* To study the anti-aging effects of *Radix Notoginseng* and to explore its molecular network mechanism. *Methods:* Aging and *Radix notoginseng* gene targets were searched and downloaded from the Genecards website, then Venn intersection analysis was performed to find common genes for diseases and drugs to explore candidate targets for *Radix notoginseng* in the treatment of aging. Bioinformatics was then used to analyze the biological processes, cellular components, molecular functions, and KEGG signaling pathways of the shared target network. Protein molecular network construction was carried out to find the core molecular network genes of the drug *Radix notoginseng* for the treatment of aging. A final PubMed literature comparison was performed to assess the value of the potential role of core network genes. *Results:* The keywords "Aging" and "*Radix notoginseng*" were queried in Genecards and 25,000 aging-related targets were obtained, 17 for *Radix notoginseng*. GO and KEGG analysis of the intersecting genes obtained from the Venn intersection analysis then showed that the BP with the highest potential to be associated with disease and drugs is positive regulation of protein phosphorylation, CC is macromolecular complex and MF is identical protein binding. The KEGG with the higher correlation is lipid and atherosclerosis, AGE-RAGE signaling pathway in diabetic complications, and proteoglycans in cancer. A total of 10 hub genes were identified in the PPI network construction, including EGFR, MMP9, TNF, VEGFA, RHOA, CDKN1A, CASP3, CCND1, AKT1, and IL1B. Among these, it found that a large number of MMP9 and TNF genes were reported in the literature, with the remaining hub genes less frequently reported in the literature. *Conclusion:* This study uses bioinformatics and network pharmacology to explain the core network mechanisms of the drug *Radix notoginseng* in the treatment of aging using the latest databases. The results show that hub genes such as CDKN1A, EGFR, and AKT1 are involved in the core biological processes of aging. The results of the study provide an important reference for resolving the core molecular network mechanism of anti-aging properties and provide a validation basis for future experimental validation.

Keywords: Aging; *Radix notoginseng*; Network pharmacology; Core network; Network factors

Online publication: March 29, 2024

1. Introduction

Aging, a complex network characterized by multiple changes occurring at different biological levels, is a pathological process that leads to the deterioration of cellular, tissue, and organismal functions [1–2]. Aging needs to meet ICD-11 criteria to be considered a disease [3]. Mammalian aging is often attributed to molecular cross-linking, free radical-induced damage, telomere shortening, and methylation of DNA [4–7]. Aging is a major risk factor for most late-onset diseases, such as cancer, cardiovascular disease, diabetes, neurodegenerative diseases, and so on [8]. The accumulation of senescent cells in the nervous system increases the probability of Alzheimer's disease (AD) and Parkinson's disease (PD), and aging is the greatest risk factor for late-onset Alzheimer's disease (LOAD) [8–10]. In addition, aging can indirectly lead to obesity, diabetes, and insulin resistance by altering lipid metabolic pathways and inducing adverse metabolic conditions. Targeting anti-aging mechanisms may contribute to the progression of diabetes and the development of diabetic complications [11]. Senescent cells are often carcinogenic and are also closely associated with the development of premature cardiovascular failure [12–13]. Although very little is known about aging, it is unlikely that a panacea for it will be discovered. However, there may be new drugs available to intervene in the development of aging [14]. Vitorino et al. argue that aging is not an inevitable fate for all organisms and that it can be delayed [1]. As the world ages and the economic burden of aging-related diseases continues to increase for society and individuals, there is an urgent need for effective ways to prevent and treat aging.

The Chinese herb *Radix notoginseng* (RN), which contains the important bioactive components Radix notoginseng saponin (PNS) and ginsenoside (Rg1), is used as a medicinal and functional herb [15]. Chen et al. showed that Rb1 delays the replicative aging of endothelial progenitor cells, protecting human umbilical vein endothelial cells and human fibroblasts, and counteracts the onset of aging [16]. PNS also exhibits anti-inflammatory, antioxidant, and anti-aging pharmacological properties in some cells [16–19]. Xu et al. reported that RN has been used not only for the treatment of neurological and immune diseases, but also exerts significant pharmacological effects in cardiovascular protection and tumor suppression, and that RN also has important pharmacological effects in a variety of chronic diseases, such as inflammatory bowel disease, arthritis, diabetes, and others [15, 20–21]. In addition, PNS is used clinically to treat diabetes and obesity. *Radix notoginseng* has been shown to have anti-aging effects on the brain and is thought to possibly help prolong life [2]. Such evidence provides a good explanation for the possible use of *Radix notoginseng* as a treatment for aging. However, no studies so far have reported on the molecular network mechanisms by which RN improves the aging process.

Bioinformatics plays an important role in the progress of human aging research. Genes and pathways that control aging may be hidden in human genomic data [14]. Cyber pharmacology offers a new way of explaining diseases, starting from the analysis of the mechanism of action of herbal formulas on diseases and using the relationship between drugs and disease gene networks. Through big data analysis, the core biological mechanism of aging and the interaction of known drug RN targets can be analyzed, which will help to explore the anti-aging network mechanism of *Radix notoginseng* from a holistic and systemic perspective, and this new therapy has the potential to find anti-aging targets [22].

This study combines modern bioinformatics and network pharmacology to shift from a "one target, one drug" model to a "network target, herbal therapy" model [23]. The *Radix notoginseng* aging intersection genes were analyzed and GO and KEGG signaling pathway analysis was used to construct PPI network maps and find hub genes to predict the interaction of aging targets with *Radix notoginseng* drug components. This use of the link between structural formulas of disease molecules and drugs provides direction and reference for the development of drugs for anti-aging and the treatment of aging diseases [8].

2. Methods

2.1. *Radix notoginseng* and aging-related database search

The human aging-related genes were searched on the Genecards database in Baidu (https://www.genecards.org) using the keyword "Aging" and the results were exported to an Excel sheet. Similarly, Genes related to *Radix notoginseng* were searched using the keyword "*Radix notoginseng*", and the obtained gene data was exported to the local Excel result named RN.

2.2. Analysis of the data Venn intersection related to *Radix notoginseng* and aging

The Draw Venn Diagram website in Baidu (https://bioinformatics.psb.ugent.be/webtools/Venn/) was searched and the genes related to aging and Radix notoginseng were pasted into the lists labeled "Aging" and "RN" respectively, which were then submitted for cross-analysis of aging and *Radix notoginseng* genes. The intersection Venn diagram was saved in svg. format.

2.3. Functional enrichment and KEGG signaling pathway analysis of anti-aging targeting *Radix notoginseng*

The David database in Baidu (https://david.ncifcrf.gov) was searched as follows. The functional annotation in the shortcut to DAVID tools was clicked, mapping the intersecting genes of aging and *Radix notoginseng*. Afterward, OFFICIAL_GENE_SYMBOL was clicked and *Homo sapiens* was selected, then the gene list was clicked and submitted. In gene ontology, the chart was downloaded and pasted into an Excel sheet. The results of the GO analysis were obtained for cellular composition (CC), molecular function (MF), and biological processes (BP). The Kyoto Encyclopedia of Genes and Genomes (KEGG) was obtained in pathways and the 10 most significant signaling pathways were selected in ascending order of P-value and visualized using the Microbiology website (https://www.bioinformatics.com.cn) for visual analysis. To generate horizontal bar graphs with color gradients, the data from the GO and KEGG analysis were imported into Micrographics for plotting. Then the width, height, and X-axis maximum of the bar chart were modified with the Times New Roman font style, and Adobe Illustrator 2020 was used to beautify the exported bar chart layout.

2.4. Construction of PPI network map of the common target of aging and *Radix notoginseng* and prediction of hub gene

The string database in Baidu (https://string-db.org/) was searched by selecting multiple proteins, uploading the 17 intersecting genes of aging and *Radix notoginseng*, defining the species as *Homo sapiens*, and clicking on search and continue. This protein-protein-interaction network analysis (PPI) used to predict Hub genes accordingly were exported as svg. and tsv. format files.

The tsv. format file exported in String was then imported into Cytoscape 3.7.2 software (http://www.Cytoscape.org/) and topologized using the cytoHubba plugin to analyze the protein interactions network to obtain degree values. The top 10 most critical genes were filtered in descending order according to degree values, which are EGFR, MMP9, TNF, VEGFA, RHOA, CDKN1A, CASP3, CCND1, AKT1, and IL1B.

2.5. Hub gene search in Pubmed for comparison

The 10 core molecules identified by the PPI were entered into the Pubmed database (https://pubmed.ncbi.nlm.nih.gov/) together with the keyword "Aging", and the literature was queried for comparison to evaluate the investigative activity and novelty of the hub genes.

3. Results

3.1. Query of targets related to aging and *Radix notoginseng*

The Genecards website was searched for human aging-related genes using the keyword "Aging" and 25,000 results were generated as shown in **Table 1**. Similarly, all the genes of *Radix notoginseng* were searched by the keyword "*Radix Notoginseng*" and 17 results were derived as shown in **Table 2**.

Table 1. Selected Aging-related genes

Aging-related genes						
APOE	TRAK2	PTEN	LEP	BRAF	BDNF	BRCA2
PDGFRB	SOD2	IGF1R	TLR4	KRAS	ESR1	VEGFA
TP53	COMT	CST3	TDRD5	C3	LMNA	ARMS2
IGF1	TERT	CFI	MLH1	APP	ACE	ALB
CFH	SERPINE1	ERCC2	MMP9	CDKN2A	HTRA1	MAPT
INS	CFB	NOS3	ERCC6	HMCN1	IL1B	CRP
IL6	MSH2	HIF1A	ADIPOQ	AKT1	FBLN5	MTHFR
ABCA4	SOD1	ATM	MT-TL1	IGF2	PPARG	EGFR
BRCA1	NFKB1	AGER	TGFB1	AR	ERBB2	APOB
TNF	CFHR3	CXCL8	SNCA	VDR	WRN	IL10

Table 2. *Radix notoginseng*-related genes

***Radix Notoginseng*-related genes**			
BAX	TNF	SELP	CDKN1A
BCL2	IL1B	MAPK1	NFE2L2
KDR	EGFR	AKT1	VCAM1
VEGFA	CCND1	MMP9	RHOA
CASP3			

3.2. Venn intersection analysis

To obtain the intersection genes of aging and *Radix notoginseng*, the genes related to aging and Radix notoginseng were crossed and analyzed through the Draw Venn Diagram website, and 17 aging-*Radix notoginseng* intersection genes were obtained, which were BAX, BCL2, KDR, VEGFA, CASP3, CDKN1A, NFE2L2, VCAM1, RHOA, SELP, MAPK1 AKT1, MMP9, TNF, IL1B, EGFR, and CCND1. The Venn diagram plotted is shown in **Figure 1**.

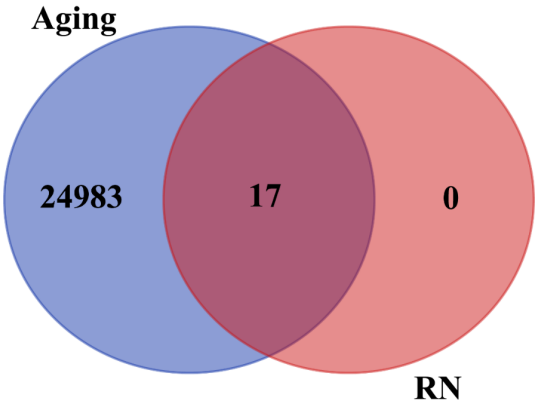


Figure 1. Venn diagram of aging-*Radix notoginseng* crossover genes, with aging-associated genes on the left, *Radix notoginseng*-associated genes on the right, and aging-*Radix notoginseng* intersection genes in the middle

3.3. GO functional enrichment and KEGG signaling pathway analysis of aging-*Radix notoginseng* intersection genes

To further investigate the localization distribution, molecular function, and biological processes of aging-*Radix notoginseng* crossover genes in cells, the GO functional enrichment and KEGG signaling pathway analysis data were downloaded separately using the David database. There are 239 signaling pathways in BP, and the top 10 pathways were screened in ascending order of P value, namely, positive regulation of protein phosphorylation, positive regulation of cell migration, negative regulation of apoptotic process, positive regulation of peptidyl-serine phosphorylation, response to UV-A, cellular response to DNA damage stimulus, cellular response to vascular, endothelial growth factor stimulus, cellular response to reactive oxygen species, negative regulation of extrinsic apoptotic signaling pathway in absence of ligand and lipopolysaccharide-mediated signaling pathway. Similarly, CC has a total of 29 results, with the top 10 results for macromolecular complex, membrane raft, extracellular space, external side of plasma membrane, nucleus, pore complex, cytosol, cell surface, cell junction, and nuclear membrane, in that order. There are a total of 22 signaling pathways in MF, the first 10 being identical protein binding, integrin binding, protein kinase binding, protein binding, BH3 domain binding, BH3 domain binding, nitric-oxide synthase regulator activity, cyclin-dependent protein serine/threonine kinase inhibitor activity, cytokine activity, protein binding, and kinase activity, in that order. KEGG has a total of 120 signaling pathways, the top 10 being lipid and atherosclerosis, AGE-RAGE signaling pathway in diabetic complications, Proteoglycans in cancer, fluid shear stress and atherosclerosis, colorectal cancer, human cytomegalovirus infection, pathways in cancer, endocrine resistance, pancreatic cancer, and EGFR tyrosine kinase inhibitor resistance. The first 10 pathways from the GO and KEGG analysis were then plotted as horizontal bars using the Microbiotics website, and the results are shown in **Figure 2**.

The results show that a variety of CC, BP, and MF are involved, including cellular components such as macromolecular complex, membrane raft, extracellular space, cellular response to DNA damage stimulus, cellular response to reactive oxygen species, response to UV-A, protein kinase binding and other signaling pathways are relevant to the topic of this paper.

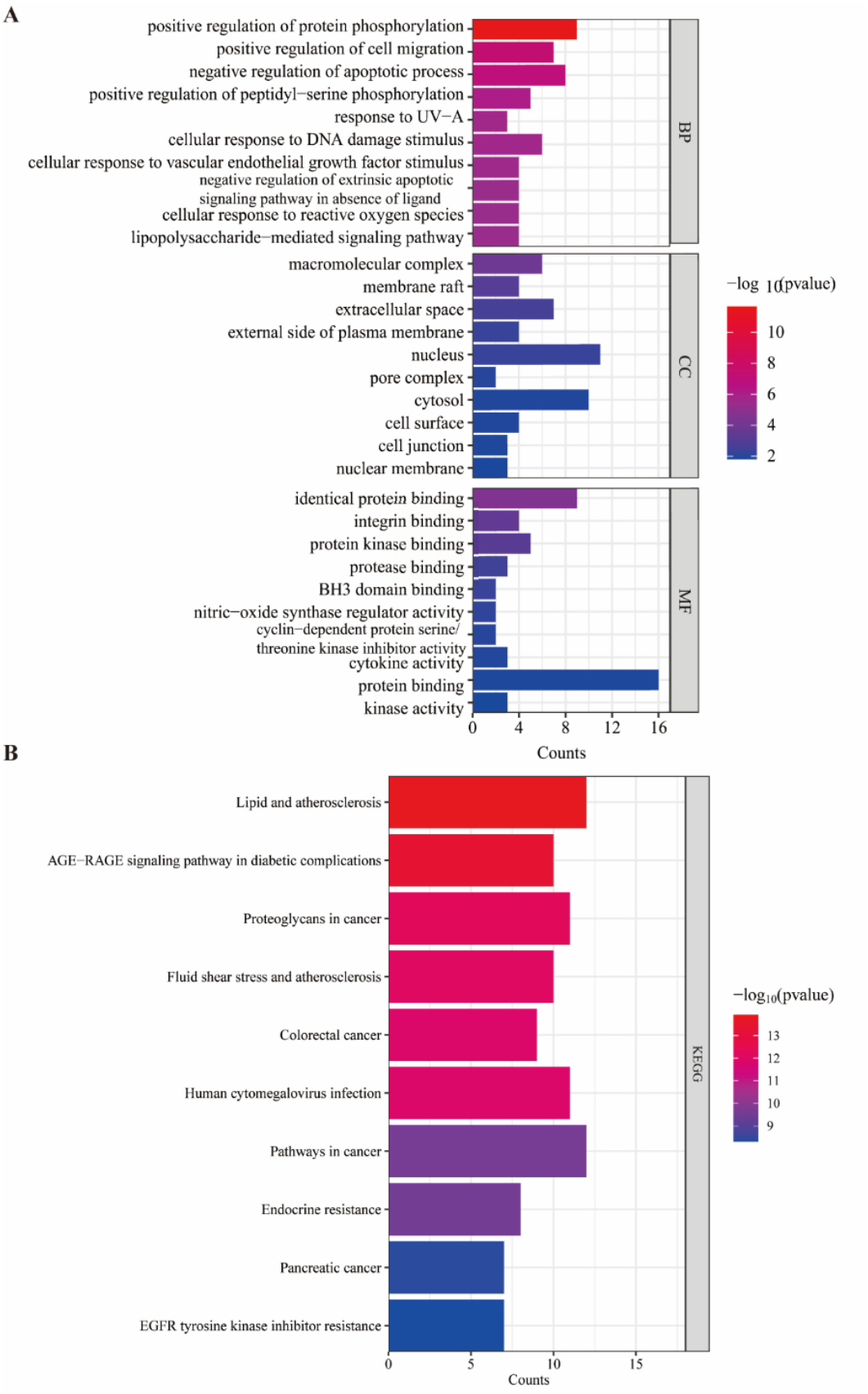


Figure 2. GO functional enrichment and KEGG pathway analysis

Note: A. GO functional enrichment histogram (BP, CC, MF) B. KEGG signaling pathway histogram. The horizontal coordinate is the number of enriched genes (counts), and the vertical coordinate is GO terms/KEGG terms. The gradient of the bars indicates the number of enriched genes, the redder the color indicates the smaller the p-value, the more statistically significant it is.

3.4. Prediction of PPI network and hub gene of the common targets of aging and *Radix notoginseng*

The 17 cross-targets of aging and *Radix notoginseng* were imported into the String website and the protein interaction analysis and protein interaction network (PPI) construction for the aging-*Radix notoginseng* crossover genes were performed as shown in **Figure 3**. The number of edges is 104, the average node degree is 12.2, the average local clustering coefficient is 0.863, the expected number of edges is 35, and the PPI enrichment p-value is 35, $< 1.0e^{-16}$. A total of 104 interactive network edges were obtained, indicating that aging is highly correlated with *Radix notoginseng*. Three panels with high linkage density are present in the figure, and AKT1 is found to be the densest, surrounded by a core network of CDKN1A, CCND1, MAPK1, RHOA, and CASP3, suggesting the possible existence of core proteins in this part. In the PPI network diagram, a strong correlation between aging and *Radix notoginseng* was found in 17 intersecting genes. The top 10 pairs of genes with the strongest linkage strength were taken in descending order according to the combined score values as shown in **Table 3**, in order of CCND1: CDKN1A; KDR: VEGFA; BAX: BCL2; AKT1: RHOA; CASP3: CDKN1A; AKT1: CDKN1A; MMP9: VEGFA; TNF: VCAM1; IL1B: TNF; and EGFR: RHOA. The top 10 hub genes were filtered by degree value in descending order as shown in **Figure 3**, which are EGFR, MMP9, TNF, VEGFA, RHOA, CDKN1A, CASP3, CCND1, AKT1, and IL1B. The hub genes in the KEGG pathway were mapped and 10 hub genes were found distributed in different pathways. Nine of the hub genes were related to proteoglycans in cancer and human cytomegalovirus infection signaling pathways. Among these, lipid and atherosclerosis, AGE-RAGE signaling pathways in diabetic complications, proteoglycans in cancer, and endocrine resistance pathways are relevant to the topic of this paper. AKT1 and EGFR are the most enriched genes, suggesting that *Radix notoginseng* may act on the biological process of aging through a related pathway with AKT1 and EGFR.

Table 3. The connection strength ranked among the top ten pairs of targets.

Node 1	Node 2	Node 1 string ID	Node 2 string ID	Co-expression	Experimentally determined interaction	Database annotated	Automated text mining	Combined score
CCND1	CDKN1A	9606.ENSP00000227507	9606.ENSP00000384849	0.085	0.983	0.9	0.99	0.999
KDR	VEGFA	9606.ENSP00000263923	9606.ENSP00000478570	0.062	0.984	0.9	0.992	0.999
BAX	BCL2	9606.ENSP00000293288	9606.ENSP00000381185	0	0.981	0.9	0.758	0.998
AKT1	RHOA	9606.ENSP00000451828	9606.ENSP00000400175	0.062	0.14	0.9	0.945	0.995
CASP3	CDKN1A	9606.ENSP00000311032	9606.ENSP00000384849	0	0.77	0.8	0.883	0.994
AKT1	CDKN1A	9606.ENSP00000451828	9606.ENSP00000384849	0	0.789	0.9	0.71	0.993
MMP9	VEGFA	9606.ENSP00000361405	9606.ENSP00000478570	0	0	0.9	0.879	0.987
TNF	VCAM1	9606.ENSP00000398698	9606.ENSP00000294728	0	0	0.9	0.884	0.987
IL1B	TNF	9606.ENSP00000263341	9606.ENSP00000398698	0.462	0	0.5	0.942	0.983
EGFR	RHOA	9606.ENSP00000275493	9606.ENSP00000400175	0	0.115	0.9	0.667	0.968

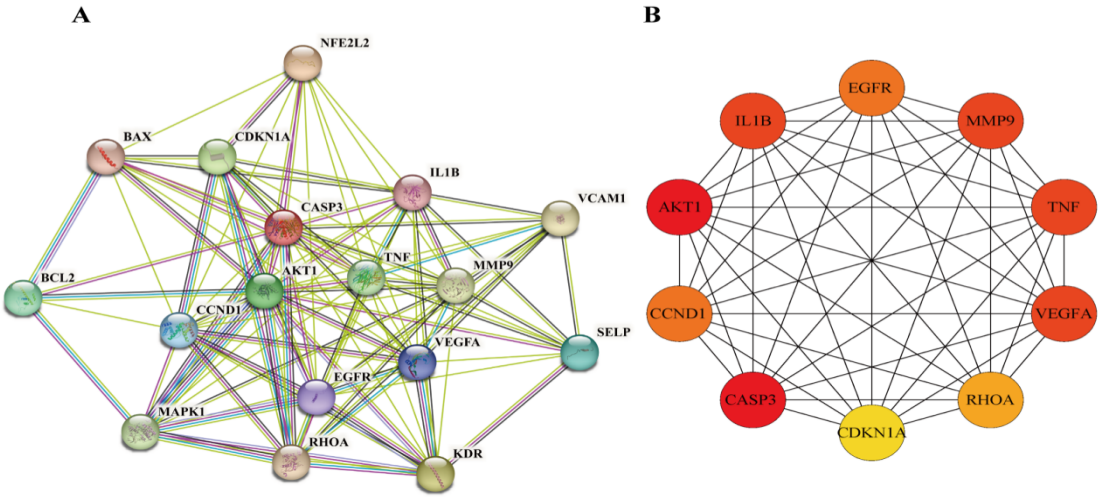


Figure 3. PPI protein interactions (A) and hub gene maps (B)

3.5. Evaluation of the innovation value of hub genes

The 10 hub genes were entered into the Pubmed database simultaneously with the keyword "Aging" to search the literature. There were 1751, 862, 4459, 395, 249, 913, 2005, 135, 311, 296 results found for EGFR, MMP9, TNF, VEGFA, RHOA, CDKN1A, CASP3, CCND1, AKT1, IL1B respectively. Among them, EGFR, MMP9, TNF, CDKN1A, and CASP3 have been extensively reported in the literature, indicating that these genes are hot spots for current research and have greater clinical application prospects. VEGFA, RHOA, CCND1, AKT1, and IL1B have been less reported in the literature, indicating that these genes are highly novel and of greater research value.

3.6. Core genetic relationships between PPI, GO enrichment analysis, and the KEGG pathway

To investigate the relationship between the PPI, GO, and KEGG pathways and the core genes, the positions of the 10 hub genes in the GO and KEGG pathways were compared and the hub gene-enriched pathways were collected as shown in **Table 4**. Results show that all hub genes were involved in the BP and KEGG signaling pathways, with the protein binding pathway in BP enriched for 10 hub genes, suggesting that this pathway may be highly relevant to the theme. AKT1 was enriched in seven BP and ten KEGG pathways, which is the most enriched pathway gene, suggesting that AKT1 may play an important molecular function in biological processes. EGFR enriches 13 pathways of CC and MF, suggesting that EGFR may be expressed in numerous cellular components, thereby regulating biological processes. However, the absence of hub gene enrichment in the BH3 domain binding pathway and pore complex suggests that it may not be related to biological processes. The macromolecular complex is the main result of CC, suggesting its possible thematic relevance. The MMP9 gene appears only in the extracellular space, suggesting that MMP9 may be under- or non-expressed in biological processes. The hub genes are all recurrent in the protein binding pathway, suggesting that the protein binding pathway may be highly thematically relevant. In addition, proteoglycans in cancer and human cytomegalovirus infection pathways were enriched with the most hub genes, and the EGFR tyrosine kinase inhibitor resistance pathway was enriched with the least hub genes. Furthermore, AKT1, EGFR, VEGFA, and CCND1 genes were simultaneously localized in the first 10 KEGG pathways, implying that the above co-expressed genes may interact with each other through different signaling pathways during biological

processes, thus providing a potential molecular explanation for the anti-aging mechanism of *Radix notoginseng*.

Table 4. Core gene relationships between PPI, GO enrichment analysis, and KEGG pathway

	Description	Gene ID							
BP	Positive regulation of protein phosphorylation	EGFR	MMP9	TNF	VEGFA	CDKN1A	CCND1	AKT1	IL1B
BP	Positive regulation of cell migration	EGFR	MMP9	VEGFA	RHOA	IL1B			
BP	Negative regulation of the apoptotic process	EGFR	MMP9	VEGFA	CDKN1A	CASP3	AKT1		
BP	Positive regulation of peptidyl-serine phosphorylation	EGFR	TNF	VEGFA	AKT1				
BP	Response to UV-A	EGFR	CCND1	AKT1					
BP	Cellular response to DNA damage stimulus	CDKN1A	CASP3	CCND1	AKT1				
BP	Cellular response to vascular endothelial growth factor stimulus	VEGFA	AKT1						
BP	Cellular response to reactive oxygen species	EGFR	MMP9	AKT1					
BP	Negative regulation of extrinsic apoptotic signaling pathway in the absence of ligand	TNF	AKT1	IL1B					
BP	Lipopolysaccharide-mediated signaling pathway	TNF	AKT1	IL1B					
CC	Macromolecular complex	EGFR	TNF	CDKN1A	AKT1				
CC	Membrane raft	EGFR	TNF	CASP3					
CC	Extracellular space	EGFR	MMP9	TNF	VEGFA	IL1B			
CC	External side of plasma membrane	TNF							
CC	Nucleus	EGFR	RHOA	CDKN1A	CASP3	CCND1	AKT1		
CC	Pore complex								
CC	Cytosol	RHOA	CDKN1A	CASP3	CCND1	AKT1	IL1B		
CC	Cell surface	EGFR	TNF	VEGFA					
CC	Cell junction	EGFR	RHOA						
CC	Nuclear membrane	EGFR	CCND1						
MF	Identical protein binding	EGFR	MMP9	TNF	VEGFA	AKT1			
MF	Integrin binding	EGFR	IL1B						
MF	protein Kinase binding	EGFR	RHOA	CDKN1A	CCND1	AKT1			
MF	Protease binding	TNF	CASP3						
MF	BH3 domain binding								
MF	Nitric-oxide synthase regulator activity	AKT1	EGFR						
MF	Cyclin-dependent protein serine/threonine kinase inhibitor activity	CDKN1A	CASP3						
MF	Cytokine activity	IL1B	TNF	VEGFA					

Table 4 (Continued)

Description		Gene ID									
MF	Protein binding	EGFR	MMP9	TNF	VEGFA	RHOA	CDKN1A	CASP3	CCND1	AKT1	IL1B
MF	Kinase activity	CDKN1A	AKT1	EGFR							
KEGG	Lipid and atherosclerosis	MMP9	TNF	RHOA	CASP3	AKT1	IL1B				
KEGG	AGE-RAGE signaling pathway in diabetic complications	TNF	VEGFA	CASP3	CCND1	AKT1	IL1B				
KEGG	Proteoglycans in cancer	EGFR	MMP9	TNF	VEGFA	RHOA	CDKN1A	CASP3	CCND1	AKT1	
KEGG	Fluid shear stress and atherosclerosis	MMP9	TNF	VEGFA	RHOA	AKT1	IL1B				
KEGG	Colorectal cancer	EGFR	RHOA	CDKN1A	CASP3	CCND1	AKT1				
KEGG	Human cytomegalovirus infection	EGFR	TNF	VEGFA	RHOA	CDKN1A	CASP3	CCND1	AKT1	IL1B	
KEGG	Pathways in cancer	EGFR	MMP9	VEGFA	RHOA	CDKN1A	CASP3	CCND1	AKT1		
KEGG	Endocrine resistance	EGFR	MMP9	CDKN1A	CCND1	AKT1					
KEGG	Pancreatic cancer	EGFR	VEGFA	CDKN1A	CCND1	AKT1					
KEGG	EGFR tyrosine kinase inhibitor resistance	EGFR	VEGFA	AKT1							

4. Discussion

The genes associated with aging and *Radix notoginseng* in Genecards were screened and the Venn intersection was mapped to show crossover genes, yielding 17 intersecting genes. The GO enrichment and KEGG signaling pathways show that aging development is associated with macromolecular complex, cellular response to DNA damage stimulus, cellular response to reactive oxygen species, response to UV-A, and protein kinase binding signaling pathways, respectively. Then, PPI network analysis reported the possible molecular mechanisms of CDKN1A, EGFR, and AKT1 involved in the treatment of aging by *Radix notoginseng*. The study provides an important reference for resolving the core molecular network mechanism of the drug *Radix notoginseng* in the treatment of aging. Unfortunately, due to the limitations of the timeliness and comprehensiveness of genetic data, the predicted results are biased from the actual situation. Additional experimental methods are needed to further validate the predicted results subsequently, but new clues are provided to explain the mechanism by which *Radix notoginseng* improves aging.

4.1. Gene target database

To obtain the latest genes, a total of 17 related genes for *Radix notoginseng* and 25,000 related genes for aging in the GeneCards database were queried as of March 20, 2023. Unfortunately, using "*Radix Notoginseng*" as a keyword search did not take into account the possible differences in the way the names of Chinese medicines are translated. Furthermore, due to the limitations of the timeliness and comprehensiveness of Genecards data, only the introduction of the most recent valid data in the Genecards is guaranteed and therefore some bias may exist. Admittedly, there are limitations to the data and these should be taken into account when interpreting the results, but at the same time, they open up greater possibilities for subsequent discoveries.

4.2. Intersecting genes

In this paper, the Draw Venn Diagram website was used to perform a cross-tabulation analysis of genes related

to aging and *Radix notoginseng* and obtained a total of 17 aging-*Radix notoginseng* cross-tabulation genes. It is found that all the targets of *Radix notoginseng* were contained in aging-related targets, suggesting that *Radix notoginseng* may be closely related to the development of aging, while this evidence also provides new insights into the promise of *Radix notoginseng* to delay aging.

4.3. GO analysis

To analyze the biological functions of the genes, the David database was used to download BP, CC, and MF data. For GO functional enrichment results, this can be interpreted as targeting the set of genes obtained experimentally, thus finding the enrichment of hub genes in BP, CC, MF, and so on. Specifically, cellular response to DNA damage stimulus, cellular response to reactive oxygen species, and response to UV-A processes in BP are highly relevant to the topic of this paper. According to Wang et al., UV-A irradiation can damage cells, induce cellular aging, and eventually lead to loss of function [24].

In addition, changes in the levels of reactive oxygen species (ROS), one of the most potent biological effectors in cellular metabolism, are a key mechanism contributing to the onset of aging and disease [25]. Excessive changes in intracellular ROS content, known as oxidative damage can lead to telomere shortening. In vitro experiments by Lin et al. found that fibroblasts cultured under enhanced oxidative stress, such as mild hyperoxia (40% normoxia), prematurely shortened telomeres, and correspondingly shortened lifespan [26–27]. DNA damage triggers a signaling cascade effect whereby once DNA damage is identified in the nuclear genome, cells will avoid replicating the damaged gene at all costs, driving apoptosis or irreversible cell cycle arrest in aging to occur. Moreover, the result of DNA damage, whether endogenous or exogenous, is accelerated aging. Mutations in DNA unwinding enzymes are also associated with a variety of diseases that accelerate aging [28]. All of this evidence supports the idea that DNA damage may be the cause and manner in which aging occurs. Furthermore, oxidative damage leads to telomere shortening, causing telomere dysfunction, which indirectly leads to a DNA damage response and ultimately to the loss of cell proliferation and aging [29]. In summary, the cellular response to reactive oxygen species can be intervened to regulate the DNA damage mechanism, providing new ideas and methods for effective anti-aging processes.

At the cellular component (CC) level, the data show that intersecting genes are located in macromolecular complexes, such as mitochondria. Mitochondria are the most important site of endogenous ROS production in the human body [30]. According to Jauhari et al., neuronal mitochondrial DNA (mtDNA) damage is caused by ROS-induced oxidative stress during neurodegeneration [31]. This corroborates both the cellular response to reactive oxygen species in BP and the cellular response pathway to DNA damage stimuli. A great deal of research is currently focused on finding ways to eliminate or counteract mtDNA mutations to extend human lifespan [32].

The most important MF is protein kinase binding. Zhang et al. identified the interferon gene (STING)-PKR endoplasmic reticulum kinase (PERK)-eIF2α pathway. The binding of STING to cyclic GMP-AMP synthase (cGAMP) directly activates the kinase PERK and activates PERK phosphorylates eIF2α, which in turn regulates cellular aging [33]. Data from Lin et al. show that receptor-interacting protein kinase 1 (RIPK1) also delays cellular aging by kinase-dependently regulating cell aging [26]. In summary, it is believed that the conclusions can be subsequently validated by experimentally modulating the above pathways, offering the potential for new therapies against aging.

4.4. KEGG analysis

KEGG signaling pathway analysis of intersecting genes was performed using the String database, where it was

found that lipid and atherosclerosis, AGE-RAGE signaling pathway in diabetic complications, Proteoglycans in cancer, and endocrine resistance pathway may be closely related to the development of aging. The above pathways suggest an increased probability of developing atherosclerosis, diabetes, cancer, and endocrine diseases during the aging process. Perdomo et al. reported that increased production of apolipoprotein D (apoD) in *Drosophila* leads to increased lifespan [34]. Also, they observed significantly elevated apoD in aging brains, suggesting that apoD is an important molecule that affects aging. The receptor for advanced glycosylation end products (RAGE) mediates multiple signaling and plays an important role in diabetic complications and aging-related diseases, making the AGE-RAGE signaling pathway a promising therapeutic target for anti-aging processes and treatment of aging-related diseases [35]. The association of aging with the increased incidence of several cancers, including gastrointestinal malignancies, was reported in a study by Nautiyal et al. [36]. In addition, aging, whether in a healthy or pathological state, leads to corresponding changes in the endocrine system. Chahal et al. found that peripheral levels of estrogen, growth hormone, and testosterone decreased in the elderly, while levels of luteinizing hormone, follicle-stimulating hormone, and sex hormone binding globulin increased [37]. These changes suggest that endocrine defects are also associated with a higher prevalence of aging-related diseases. However, current research has not found a cure for reversing the aging process. The herb *Radix notoginseng* may offer a new reference as a potential youth hormone in the fight against aging.

4.5. PPI analysis

The relationship between hub genes and PPI, GO, and KEGG pathways was analyzed and it was found that AKT1 was distributed in 9 BPs and 10 signaling pathways, and EGFR, VEGFA, and CCND1 were distributed in 7 signaling pathways. These hub genes were distributed in different pathways, suggesting that they may be highly associated with biological processes.

Numerous studies have shown that CDKN1A (p21) is closely associated with the development of aging. Stein et al. found that the CDK inhibitor p21 can accumulate in senescent cells and bind to the cell cycle protein E-Cdk2 complex to inactivate it, leading to the onset of cell cycle arrest or aging [38]. Prolonged activation of CDKN1A (p21) induces mitochondrial dysfunction and reactive oxygen species production, as reported by Passos et al. [39]. On the one hand, this corroborates the previous discussion of the possible contribution of cellular response to reactive oxygen species in BP and mitochondrial dysfunction in CC to the development of aging. On the other hand, it also suggests that CDKN1A (p21) is closely associated with the development of cellular aging. The EGFR receptor family plays an important regulatory role in senescent cells as Majumdar et al. reported that aging is associated with increased activation of downstream PI3K/Akt signaling regulated by EGFR signaling [40]. Meanwhile, Schmelz et al. observed a 30-35% increase in tyrosine phosphorylated EGFR levels in the colon of 30-35 month-old rats compared to 4-6 month-old rats in their experiments, suggesting that aging may be associated with an increase in EGFR expression and activation [41]. These results suggest a potential role for EGFR in the development of the aging process.

After APOE and FOXO3, AKT1 is thought to be the third longevity gene [42]. The study by Bao et al. found that the gene encoding the nematode insulin-like tyrosine kinase receptor (daf-2) inhibited Akt1 activity through inactivation, thereby increasing the lifespan of *Cryptobacterium hidradenum* [43]. This suggests to us that Akt1 is closely linked to the aging process. In addition, Zhao et al. also reported that AKT1 overexpression promotes cellular aging [44]. Several studies have shown that many intron single nucleotide polymorphisms (SNP) in the insulin/IGF-1 signaling pathway are significantly associated with human lifespan, including AKT1 [44–45]. However, Nygaard et al. showed in 2996 long-lived individuals who are non-elderly and centenarians, and 1840 young controls from Denmark and Germany that AKT1 was unlikely to be associated with human

longevity [42]. Li et al. similarly found no association between the AKT1 gene and human lifespan in a Chinese Han population [46]. Therefore, further studies are needed to confirm whether AKT1 is associated with human lifespan.

5. Conclusion

In summary, this paper explains the network mechanism of *Radix notoginseng* for the treatment of aging by screening targets through disease gene network-drug mechanism of action and evaluating the innovation and translational value in Pubmed. The results show that hub genes such as CDKN1A, EGFR, and AKT1 are involved in the core biological processes and signaling of aging. The factors that cause aging are numerous and complex, and this study provides important evidence for understanding the molecular events of aging in *Radix notoginseng* treatment, providing clues and a basis for future experimental validation.

Disclosure statement

The authors declare no conflict of interest.

References

[1] da Costa JP, Vitorino R, Silva GM, et al., 2016, A Synopsis on Aging: Theories, Mechanisms, and Future Prospects. Ageing Research Reviews, 2016(29): 90–112.

[2] Zhao H, Han Z, Li G, et al., 2017, Therapeutic Potential and Cellular Mechanisms of *Panax Notoginseng* on Prevention of Aging and Cell Senescence-Associated Diseases. Aging and Disease, 8(6): 721–739.

[3] Khaltourina D, Matveyev Y, Alekseev A, et al., 2020, Aging Fits the Disease Criteria of the International Classification of Diseases. Mechanisms of Ageing and Development, 2020(189): 111230.

[4] Wang Z, Lyons B, Truscott RJ, et al., 2014, Human Protein Aging: Modification and Crosslinking through Dehydroalanine and Dehydrobutyrine Intermediates. Aging Cell, 13(2): 226–234.

[5] Dizdaroglu M, Jaruga P, 2012, Mechanisms of Free Radical-Induced Damage to DNA. Free Radical Biology & Medicine, 46(4): 382–419.

[6] Mikhelson, V, Gamaley I, 2012, Telomere Shortening is a Sole Mechanism of Aging in Mammals. Current Aging Science, 5(3): 203–208.

[7] Unnikrishnan A, Freeman WM, Jackson J, et al., 2019, The Role of DNA Methylation in Epigenetics of Aging. Pharmacology & Therapeutics, 2019(195): 172–185.

[8] Hou Y, Dan X, Babbar M, et al., 2019, Aging as a Risk Factor for Neurodegenerative Disease. Nature Reviews (Neurology), 15(10): 565–581.

[9] Kritsilis M, Rizou VS, Koutsoudaki PN, et al., 2018, Aging, Cellular Senescence and Neurodegenerative Disease. International Journal of Molecular Sciences, 19(10): 2937.

[10] Liu RM, 2022, Aging, Cellular Senescence, and Alzheimer's Disease. International Journal of Molecular Sciences, 23(4): 1989.

[11] Palmer AK, Gustafson B, Kirkland JL, et al., 2019, Cellular Senescence: At the Nexus between Aging and Diabetes. Diabetologia, 62(10): 1835–1841.

[12] Costantino S, Paneni F, Cosentino F, et al., 2016, Aging, Metabolism and Cardiovascular Disease. The Journal of Physiology, 594(8): 2061–2073.

[13] Kowald A, Passos JF, Kirkwood TBL, 2020, On the Evolution of Cellular Senescence. Aging Cell, 19(12): e13270.

[14] Guarente L, 2014, Aging Research: Where do We Stand and Where are We Going. Cell, 159(1): 15–19.

[15] Liu H, Lu X, Hu Y, et al., 2020, Chemical Constituents of *Panax ginseng* and *Panax notoginseng* Explain why they Differ in Therapeutic Efficacy. Pharmacological Research, 2020(161): 105263.

[16] Chen X, Zhang J, Fang Y, et al., 2008, Ginsenoside Rg1 Delays Tert-Butyl Hydroperoxide-Induced Premature Senescence in Human WI-38 Diploid Fibroblast Cells. The Journals of Gerontology (Biological sciences and medical sciences), 63(3): 253–264.

[17] Shi AW, Gu N, Liu XM, et al., 2011, Ginsenoside Rg1 Enhances Endothelial Progenitor Cell Angiogenic Potency and Prevents Senescence in Vitro. The Journal of International Medical Research, 39(4): 1306–1318.

[18] Maria J, Ingrid Z, 2017, Effects of Bioactive Compounds on Senescence and Components of Senescence Associated Secretory Phenotypes in Vitro. Food and Function, 8(7): 2394–2418.

[19] Zhang Y, Cai W, Han G, et al., 2020, *Panax notoginseng* Saponins Prevent Senescence and Inhibit Apoptosis by Regulating the PI3K-AKT-mTOR Pathway in Osteoarthritic Chondrocytes. International Journal of Molecular Medicine 45(4): 1225–1236.

[20] Xu Y, Tan HY, Li S, et al., 2018, *Panax notoginseng* for Inflammation-Related Chronic Diseases: A Review on the Modulations of Multiple Pathways. The American Journal of Chinese Medicine, 46(5): 971–996.

[21] Huang YD, Cheng JX, Shi Y, et al., 2022, *Panax notoginseng*: A Review on Chemical Components, Chromatographic Analysis, *P. notoginseng* Extracts, and Pharmacology in Recent Five Years. China Journal of Chinese Materia Medica, 47(10): 2584–2596.

[22] Nogales C, Mamdouh ZM, List M, et al., 2022, Network Pharmacology: Curing Causal Mechanisms instead of Treating Symptoms. Trends in Pharmacological Sciences, 43(2): 136–150.

[23] Zhang R, Zhu X, Bai H, et al., 2019, Network Pharmacology Databases for Traditional Chinese Medicine: Review and Assessment. Frontiers in Pharmacology, 2019(10): 123.

[24] Wang YN, Wu W, Chen HC, et al., 2010, Genistein Protects against UVB-induced Senescence-like Characteristics in Human Dermal Fibroblast by p66Shc Down-Regulation. Journal of Dermatological Science, 58(1): 19–27.

[25] Black CN, Bot M, Révész D, et al., 2017, The Association between Three Major Physiological Stress Systems and Oxidative DNA and Lipid Damage. Psychoneuroendocrinology, 2017(80): 56–66.

[26] Lin J, Kumari S, Kim C, et al., 2016, RIPK1 Counteracts ZBP1-mediated Necroptosis to Inhibit Inflammation. Nature, 540(7631): 124–128.

[27] Saretzki G, Zglinicki TV, 2002, Replicative Aging, Telomeres, and Oxidative Stress. Annals of the New York Academy of Sciences, 2002(959): 24–29.

[28] Yousefzadeh M, Henpita C, Vyas R, et al., 2021, DNA Damage: How and Why We Age? Elife, 2021(10): e62852.

[29] Lin J, Epel E, 2022, Stress and Telomere Shortening: Insights from Cellular Mechanisms. Ageing Research Reviews, 2022(73): 101507.

[30] Murphy MP, 2009, How Mitochondria Produce Reactive Oxygen Species. The Biochemical Journal, 417(1): 1–13.

[31] Jauhari A, Baranov SV, Suofu Y, et al., 2020, Melatonin Inhibits Cytosolic Mitochondrial DNA-induced Neuroinflammatory Signaling in Accelerated Aging and Neurodegeneration. The Journal of Clinical Investigation, 130(6): 3124–3136.

[32] Kauppila TES, Kauppila JHK, Larsson NG, 2017, Mammalian Mitochondria and Aging: An Update. Cell Metabolism, 25(1): 57–71.

[33] Zhang D, Liu Y, Zhu Y, et al., 2022, A Non-Canonical cGAS-STING-PERK Pathway Facilitates the Translational Program Critical for Senescence and Organ Fibrosis. Nature Cell Biology, 24(5): 766–782.

[34] Perdomo G, Henry HD, 2009, Apolipoprotein D in Lipid Metabolism and its Functional Implication in Atherosclerosis and Aging. Aging (Albany NY), 1(1): 17–27.

[35] Bai R, Zhang T, Gao Y, et al., 2022, Rab31, a Receptor of Advanced Glycation End Products (RAGE) Interacting Protein, Inhibits AGE-induced Pancreatic Beta-cell Apoptosis through the pAKT/BCL2 Pathway. Endocrine Journal, 69(8): 1015–1026.

[36] Nautiyal J, Kanwar SS, Majumdar AP, et al., 2010, EGFR(s) in Aging and Carcinogenesis of the Gastrointestinal Tract. Current Protein & Peptide Science 11(6): 436–450.

[37] Chahal HS, Drake WM, 2007, The Endocrine System and Aging. The Journal of Pathology, 211(2): 173–180.

[38] Stein GH, Drullinger LF, Soulard A, et al., 1999, Differential Roles for Cyclin-Dependent Kinase Inhibitors p21 and p16 in the Mechanisms of Senescence and Differentiation in Human Fibroblasts. Molecular and Cellular Biology, 19(3): 2109–2117.

[39] Passos JF, Nelson G, Wang C, et al., 2010, Feedback between p21 and Reactive Oxygen Production is Necessary for Cell Senescence. Molecular Systems Biology, 2010(6): 347.

[40] Majumdar AP, Du J, 2006, Phosphatidylinositol 3-kinase/Akt Signaling Stimulates Colonic Mucosal Cell Survival during Aging. American Journal of Physiology (Gastrointestinal and Liver Physiology), 290(1): 49–55.

[41] Schmelz EM, Levi E, Du J, et al., 2004, Age-related Loss of EGF-receptor Related Protein (ERRP) in the Aging Colon is a Potential Risk Factor for Colon Cancer. Mechanisms of Aging and Development, 125(12): 917–922.

[42] Nygaard M, Soerensen M, Flachsbart F, et al., 2013, AKT1 Fails to Replicate as a Longevity-Associated Gene in Danish and German Nonagenarians and Centenarians. European Journal of Human Genetics, 21(5): 574–577.

[43] Bao J, Liu B, Wu C, 2020, Progress of Anti-aging Drugs Targeting Autophagy. Advances in Experimental Medicine and Biology, 2020(1207): 681–688.

[44] Zhao X, Wang T, Cai B, et al., 2019, MicroRNA-495 Enhances Chondrocyte Apoptosis, Senescence and Promotes the Progression of Osteoarthritis by Targeting AKT1. American Journal of Translational Research, 11(4): 2232–2244.

[45] Pawlikowska L, Hu D, Huntsman S, et al., 2009, Association of Common Genetic Variation in the Insulin/IGF1 Signaling Pathway with Human Longevity. Aging Cell, 8(4): 460–472.

[46] Li N, Luo H, Liu X, et al., 2016, Association Study of Polymorphisms in FOXO3, AKT1 and IGF-2R Genes with Human Longevity in a Han Chinese Population. Oncotarget, 7(1): 23–32.

Clinical Neuroscience Research, 2024, Volume 2, Issue 1
http://ojs.bbwpublisher.com/index.php/CNR

Research Progress on the Use of Music Therapy Combined with Transcranial Magnetic Stimulation to Treat Cognitive Impairment after Stroke

Chubo Xiang*, Wuming Huo

Capital Medical University, Beijing 100069, China

Corresponding author: Chubo Xiang, 2066937153@qq.com

Abstract: Stroke patients may develop different functional impairments, including cognitive impairment after treatment. To improve their condition, music therapy combined with transcranial magnetic stimulation therapy should be used in rehabilitation treatment to promote their cognitive and living ability, thereby improving the patient's quality of life and easing the burden on the patient's family. Therefore, it is necessary to first clarify the concept of cognitive impairment after stroke and then elaborate on music therapy and transcranial magnetic stimulation treatment. The respective roles played in rehabilitating patients with cognitive impairment after stroke and the value of their combined application are discussed for reference.

Keywords: Music therapy; Transcranial magnetic stimulation; Stroke; Cognitive impairment

Online publication: March 29, 2024

1. Introduction

Stroke is a common neurological disease with relatively high disability and mortality rates. With the support of contemporary medicine, the mortality rate of patients in the acute phase has dropped significantly. However, the disability rate is still not effectively managed. One of its sequelae is cognitive impairment, which seriously affects the patient's quality of life, and increases the burden on the patient's family. According to relevant studies, there are about 2 million new stroke patients in China every year, with an increasing rate of about 9% every year. Modern research on cerebrovascular disease emphasizes improving the therapeutic effect, prolonging the patient's life, and strengthening rehabilitation medicine intervention to optimize the patient's bodily functions [1]. Recently, with the development of non-drug therapies, music therapy, and transcranial magnetic stimulation treatments have garnered attention due to their unique therapeutic mechanisms and safety. Music therapy can improve the patient's emotional states and cognitive functions by stimulating their auditory perception and emotions. Transcranial magnetic stimulation, a non-invasive brain stimulation technology, can promote neurological recovery by regulating the brain's neural activity. However, the specific efficacy of music

therapy combined with transcranial magnetic stimulation in patients with post-stroke cognitive impairment still needs to be explored.

2. Overview of post-stroke cognitive impairment

Cognitive impairment is one of the common complications after stroke. It includes memory loss, executive dysfunction, decreased attention, language understanding, and expression difficulties. This disorder seriously affects the patient's quality of life and limits their social participation and ability to carry out daily activities. Brain damage caused by stroke mainly involves the loss of nerve cells and the destruction of neural networks. These changes directly affect cognitive function. At the same time, patients may also experience mood disorders, psychological stress, and social isolation, all of which may further exacerbate cognitive decline.

3. The effect of music therapy combined with transcranial magnetic stimulation on patients with post-stroke cognitive impairment

For post-stroke cognitive impairment, conventional treatments include drug therapy, cognitive training, and rehabilitation training. Pharmacological treatments mainly focus on improving blood circulation to the brain and neuroprotection, but their direct effect on improving cognitive function is limited. Cognitive training and rehabilitation can help restore cognitive abilities to a certain extent. Still, these methods usually require continuous training for long periods and the effects vary depending on individual differences. In addition, these methods have limited effect in improving the patient's quality of life and social functioning. Therefore, there is a need to explore more effective treatments. Music therapy combined with transcranial magnetic stimulation is an innovative treatment method that utilizes the music's rhythm, melody, and harmony to stimulate the patient's emotions and cognition, improving their mood and enhancing memory and concentration. Transcranial magnetic stimulation, as a non-invasive brain stimulation technology, can promote the recovery of neurological function by altering the excitability of subcortical neurons. This combined treatment model aims to jointly promote the recovery and reconstruction of brain function through the psychotherapeutic effect of music therapy and the biological effect of repetitive transcranial magnetic stimulation (rTMS), thereby improving the cognitive ability of patients with post-stroke cognitive impairment [2].

4. Application model of music therapy in patients with post-stroke cognitive impairment

When carrying out rehabilitation treatment for stroke patients, music therapy can be regarded as physical therapy and an important part of speech therapy to promote the gradual recovery of the patient's speech and motor functions. However, recent studies have shown that music therapy can also improve cognitive function, further enhancing the application value of music therapy in the rehabilitation treatment of stroke patients. Providing music therapy to stroke patients can lead to rapid growth of hippocampal nerves, which can enhance brain plasticity. After patients hear familiar melodies and lyrics, they may hum along unconsciously and even recall certain memories. Memory facilitates extensive connections within the brain's bilateral communication network, thus optimizing the patient's cognitive function. According to relevant studies, patients with cognitive impairment after stroke were given playing music or other reading materials. After 6 months of continuous intervention, the attention and memory of patients who listen to music or other reading materials significantly improved. The patient's long-term plastic changes in sensory perception occurred in the early stages of brain

injury, thereby gradually restoring cognitive functions. The process of applying music therapy is relatively simple and has high application value in the rehabilitation process of stroke patients [3].

Music therapy can be divided into active and passive treatment. When conducting active treatment, also known as participatory treatment, melodies or songs familiar to the patient were used to garner the patient's interest. Patients were encouraged to directly participate in singing, playing, or physical activities following the songs during treatment. When performing passive therapy, also known as receptive therapy, patients were provided with prepared recordings or improvisation. Generally speaking, there were no clear requirements for the passive therapy process. The primary goal was to promote comfort and happiness among patients and to develop a pleasant and ideal environment for therapy. A combination of active and passive methods of music therapy can provide patients with alternating treatment methods. Medical staff first communicated with patients and their families to understand the patient's preferred music type and then selected their favorite music for therapy. In this study, music therapy was used to treat 40 patients with post-stroke cognitive impairment in the experimental group. The cognitive function score of patients who received music therapy improved from 19.13 ± 2.51 points to 25.29 ± 2.04 points after treatment. In contrast, only conventional treatment was used for the control group. There was no significant difference between the scores before and treatment in the control group ($P > 0.05$). After treatment, the scores improved to 21.35 ± 1.80 points but were lower than those of the experimental group ($P < 0.05$) [4].

Music therapy can be applied in the form of individual therapy or group therapy. When selecting music and active therapy, individual treatment plans should be formulated according to the patient's needs and appropriate music should be selected. Generally, music with a strong sense of rhythm should be selected. Passive therapy mainly selects music based on the patient's preferences. When using a group therapy model, the preferences and feelings of all group members need to be considered [5]. In addition, the homogeneity principle can also be used to select music, that is, according to the patient's emotional state. When the patient is emotionally excited, they are provided with bright and joyful music to guide the patient into a state of appropriate suppression through negative induction. The non-homogeneous principle can also be applied when selecting music, that is, by providing patients with music that contradicts their emotions. For example, providing patients with anxiety and depression with strong rhythms and cheerful music may improve their mood.

5. Application model of transcranial magnetic stimulation in patients with post-stroke cognitive impairment

The method of transcranial magnetic stimulation was developed in 1985. It is painless and non-invasive. Not only is it simple to operate but it is also highly safe and effective. rTMS treatment has been shown to effectively improve the patient's health. This treatment causes physiological, biochemical, and functional changes in the patient, where the related biological effects remain after completion of treatment. Recently, this treatment method has been widely used in the treatment of cerebrovascular diseases, epilepsy, and Parkinson's disease. The stimulation effect will not be attenuated during actual treatment due to passage through body tissues. As the electric field of magnetic stimulation is parallel to the skin, this procedure is painless, which can increase the patient's compliance with treatment.

rTMS treatment can promote significant changes in the levels of various neurotransmitters. For example, treatment through the prefrontal cortex can promote endogenous dopamine release, and treatment through the left dorsolateral prefrontal cortex can enhance 5-HT/color in local brain areas. The metabolism of amino acids was studied by applying positron emission tomography (PET), single photon emission computed tomography (SPECT), thermal conductivity detector (TCD), and other detection methods to study the pathophysiological

and neurophysiological effects of rTMS. Healthy subjects were given rTMS therapy for 20 minutes, with the left motor cortex being stimulated, while the contralateral cortex was not stimulated. In contrast, the oxyhemoglobin content on the stimulated side increased significantly, and it was still effective 40 minutes after the treatment. At the same time, the deoxygenated hemoglobin level also declined slightly, lasting for 15 minutes. rTMS was also applied to stroke patients, which improved a variety of functional impairments [6]. The magnetic field stimulator used was the Korean transcranial magnetic stimulator (TAMAS). When the patient was supine, the dorsolateral cortex of the left prefrontal lobe was stimulated. The 10–20 International EEG recording system electrode placement method was used to determine the stimulation point. The treatment had a stimulation frequency of 5 Hz and an intensity of 80%–90% of the resting motor threshold. Each stimulation was performed in seconds followed by an interval of 6 seconds, 20 minutes a day, a total of 2,000 pulses, for 5 days a week. This treatment was carried out for 3 weeks. This treatment plan was conducive to improving the patient's cognitive function. In a study, 31 patients with post-stroke cognitive impairment in the experimental underwent this treatment plan. The experimental group's modified Barthel index (MBI) score improved from 41.61 ± 25.49 points to 59.81 ± 24.68 points after treatment. The MBI score of the control group that only received conventional treatment improved to 54.31 ± 22.19, which was lower than that of the experimental group ($P < 0.05$) [7].

6. Post-stroke cognitive impairment treated with music therapy combined with transcranial magnetic stimulation

The combination of music therapy and transcranial magnetic stimulation provides a multimodal intervention approach that improves the cognitive function of patients with post-stroke cognitive impairment. Transcranial magnetic stimulation can promote the reconstruction of damaged neural networks and functional recovery by stimulating neurons under the cerebral cortex. This dual stimulation helps accelerate the recovery process of cognitive function and can also repair the neurological damage caused by stroke to a certain extent. Emotional disorders are a common complication in post-stroke patients, which further affect the recovery of their cognitive functions [8]. Therefore, improving the patient's emotional state through music therapy can improve the patient's quality of life and create a favorable psychological environment for the recovery of cognitive functions [9]. According to relevant studies, 12 patients with post-stroke speech impairment were treated with music therapy combined with transcranial magnetic stimulation. Their aphasia quotient score was 23.46 ± 3.67 points and their spontaneous speech score was 4.33 ± 1.31, while the scores of the 13 patients in the sham stimulation group were 8.41 ± 2.20 points and 1.08 ± 0.76 points, respectively, ($P < 0.05$). It was seen that the effect of music therapy combined with transcranial magnetic stimulation significantly improved the patient's aphasia. Improving the patient's speech function can improve treatment confidence and compliance, laying an important foundation for alleviating and eliminating cognitive impairment [10].

Moreover, when applying music therapy, patients can engage in auditory experiences, participate, and interact with the song's chorus, rhythm coordination, and other activities. These highly interactive activities can promote the patient's social participation and improve their interpersonal skills. During rehabilitation, the patient's social communication skills can be improved, along with their sense of social participation and belonging. A supportive social environment through effective communication and cooperation with other patients can then be established, ultimately improving the patient's quality of life and rehabilitation outcomes.

7. Conclusion

Both music therapy and rTMS therapy play an important role in the rehabilitation treatment of stroke patients. They positively impacted the recovery of the patient's cognitive function. The combination of music therapy and rTMS therapy can jointly stimulate the patient's brain and nerve activities, thereby improving cognitive function. All in all, the patient's quality of life was improved.

Disclosure statement

The author declares no conflict of interest.

References

[1] Jian Q, Xu R, Yao Q, et al., 2023, Meta-Analysis of The Prevalence and Influencing Factors of Cognitive Impairment in Chinese Elderly Stroke Patients. Chinese General Medicine, 26(32): 4070–4079 + 4088.

[2] Jin R, Zhao X, He Y, et al., 2023, Network Meta-Analysis of The Effects of Non-Drug Intervention on Cognitive Function and Activities of Daily Living in Patients with Post-Stroke Cognitive Impairment. Chinese Journal of Practical Nursing, 39(30): 2394–2401.

[3] Liu J, Guo N, Li F, 2023, Research Progress on The Effects and Mechanisms of Music Therapy on Stroke-Related Cognitive Impairment. Chinese Journal of Health Management, 17(1): 67–71.

[4] Ruan C, Shao L, Lu P, 2022, The Value of Music Therapy in Improving Memory in Patients with Mild Cognitive Impairment After Stroke. Heilongjiang Medicine, 35(1): 236–238.

[5] Zhang D, Chen Y, Zhu H, 2022, The Impact of Music Therapy Intervention in The Comprehensive Nursing Combined Group Model on ICU Patients. Qilu Nursing Journal, 28(24): 38–41.

[6] Wang Z, Yu Q, Li K, et al., 2023, Effects of Repetitive Transcranial Magnetic Stimulation on Brain Functional Activities in Patients with Post-Stroke Cognitive Impairment and Depression. Chinese Journal of Physical Medicine and Rehabilitation, 45(10): 893–898.

[7] Liu X, Zhu L, Xu Y, et al., 2023, The Efficacy of Repetitive Transcranial Magnetic Stimulation Combined with Scalp Acupuncture in Treating Post-Stroke Cognitive Impairment. Journal of China Medical University, 52(2): 115–119.

[8] Li N, 2020, Observation of the Effects of Repetitive Transcranial Magnetic Stimulation (Rtms) Combined with Computer-Assisted Cognitive Training on Cognitive Function and Activities of Daily Living (ADL) in Patients with Post-Stroke Cognitive Impairment (PSCI). Contemporary Medicine, 26(9): 87–89.

[9] Wang Y, Zhang H, Chen M, et al., 2022, Effect of Family Collaborative Continuous Care Model Combined with Music Therapy on The Quality of Life of Patients with Alzheimer's Disease. Chinese Journal of Practical Neurological Diseases, 25(10): 1270–1274.

[10] Ji Y, 2020, Analysis of the Efficacy of Low-Frequency Repetitive Transcranial Magnetic Stimulation Combined with Music Therapy for Post-Stroke Aphasia, dissertation, Suzhou University, Jiangsu.

Clinical Neuroscience Research, 2024, Volume 2, Issue 1
http://ojs.bbwpublisher.com/index.php/CNR

Application of Cognitive Training Therapy for Alzheimer's Disease and Evaluation of its Efficacy

Sha Chang[1], Yu Zhang[2], Xiaohui Wang[1], Zhi Li[1], Le Wang[1]*

[1]Department of Neurology, Shaanxi Provincial People's Hospital, Xi'an 710068, Shaanxi Province, China
[2]Department of Gynecology, Shaanxi Provincial People's Hospital, Xi'an 710068, Shaanxi Province, China

***Corresponding author:** Le Wang, wangle.lewang@163.com

Abstract: *Objective:* The purpose of this study is to conduct in-depth research on the cognitive training treatment of Alzheimer's disease and evaluate its efficacy. *Methods:* 74 cases of Alzheimer's disease patients in the hospital were randomly selected for analysis and study from January 2023 to December 2023. The 74 patients were divided into two groups, 37 cases in the control group received conventional drug treatment, while 37 cases in the study group received conventional drug treatment combined with cognitive training. The cognitive functions of the two groups of patients before and after receiving the two different treatment methods were compared. *Results:* The cognitive impairment symptoms of patients in both groups were alleviated to a certain degree. The ADAS-Cog score of the study group was significantly lower than that of the control group, and the CDT, RVR, TMT-A, DS, FOME, and BD scores were higher than those of the control group, $P < 0.05$. *Conclusion:* After the combined intervention of medication and cognitive training therapy, the cognitive function of patients with Alzheimer's disease was significantly improved, which increased the patients' rehabilitation effect and quality of life, so this combined therapy is worth further research for widespread application.

Keywords: Cognitive function; Cognitive training; Alzheimer's disease

Online publication: May 14, 2024

1. Introduction

Alzheimer's disease is a common clinical neurodegenerative disease that has a main symptom of progressive cognitive decline and decreasing ability to perform daily living tasks. In addition, patients with Alzheimer's disease may also be accompanied by a variety of mental and behavioral abnormalities [1]. Currently, cholinesterase inhibitors are mainly used in the clinical treatment of early to middle-stage Alzheimer's disease. Although medication can improve cognitive function to a certain extent, it may also lead to the risk of functional impairment. Therefore, a comprehensive treatment plan should be formulated based on the patient's specific condition. Cognitive training is a standardized task training developed by professional therapists for patients suffering from symptoms of cognitive impairment involving memory, attention, and executive ability. This type of training can be performed in a variety of forms and has been confirmed through clinical studies to have a positive effect on improving cognitive function in patients with stroke, traumatic brain injury, and so

on [2–3]. Therefore, 74 patients with Alzheimer's disease were included in this study to research and explore the application value of the integrated intervention of medication and cognitive training.

2. Information and methods

2.1. General information

In this study, 74 cases of Alzheimer's disease patients in the hospital were randomly selected to be analyzed and studied from January 2023 to December 2023. Among the 74 patients, there were 34 males and 40 females, and the patients had a disease duration of 1–8 years, with an average of 4.12 ± 1.22 years. The 74 patients were divided into two groups. The control group consisted of 37 cases that underwent conventional drug treatment with an age range of 59–79 years old, and a mean of 69.12 ± 2.62 years. The study group consisted of 37 cases that underwent conventional medication combined with cognitive training treatment with an age range of 60–78 years, and a mean of 69.12 ± 2.32 years. The general data of patients is $P > 0.05$ at the start of the study.

2.2. Methods

The 37 cases of Alzheimer's disease in the control group received conventional drug treatment. The treatment involved the patients taking Donepezil tablets orally as prescribed by the doctor, with a dose of 5 mg each time, once a day for three months. At the same time, communication with patients was increased and necessary psychological support was provided. The patients in the study group received training treatment on this basis, with the following specific contents. First, the therapist explored with the patients the cognition of time, place, and people through the form of dialog. Secondly, the patients were asked to make associations with a specific word at the beginning of a word or make a list of nouns for a specific category of items, such as fruits and vegetables, at a specific time. This training method is not only effective in improving patients' cognitive flexibility but is also a key means of word fluency and categorization ability training. Thirdly, elements containing graphics such as numbers, letters, animals, and so on are made into recognition cards in the form of black and white superimpositions, which are then divided into different difficulty levels according to the difference in the number of superimpositions [4–5]. Subsequently, patients were asked to accurately recognize and name the specific graphics on each card, so that the patients' graphic recognition ability could be effectively improved [6–7]. Fourthly, patients are invited to observe a set of character pictures in detail and subsequently narrate the contents of the pictures in detail. During the process of observation and narration, the therapist will ask a series of relevant questions and require the patient to give accurate answers based on the content of the pictures. Questions of different levels of difficulty are designed according to the level of abstraction of the pictures. In low-difficulty questions, the patient mainly needs to recognize the subjects in the picture and their basic information, such as the gender of the person shown. These questions help train the patient's basic recognition skills. In contrast, high-level questions require patients to further analyze potential relationships between the people in the picture. These types of questions aim to develop patients' abstract generalization ability so that they can understand the relationships and connections between subjects while recognizing them [8]. After training with questions of different difficulties, patients can gradually improve their cognitive abilities. In addition, this training method has a significant effect on strengthening the patients' episodic and memory extraction ability. Based on strict adherence to the principle of error-free learning, individualized cognitive training tasks were developed for each patient with different baseline cognitive abilities. In addition, if the patient exudes frustration or a bad mood, the therapist will prioritize giving him or her the necessary psychological support and comfort rather than continuing cognitive training [9–10].

2.3. Observation indicators

The cognitive function of the two groups of patients before and after treatment was systematically evaluated using the cognitive subscale (ADAS-Cog), covering language, memory, attention, and manipulation. The severity of cognitive impairment was negatively correlated with the scores, meaning the lower the scores, the less severe the cognitive impairment. The clock drawing test (CDT) assessed the executive function; the verbal retrieve test (RVR) assessed the semantic memory storage function; the connection test-A (CT-A) assessed the cognitive function of the two groups of patients; the trail-making test-A (TMT-A) assesses attention and motor speed; the digit span test (DS) assesses immediate memory capacity; the fuld object memory evaluation (FOME) assesses delayed memory functioning; and the block design test (BD) assesses visuospatial functioning. Tables were utilized for the presentation.

2.4. Statistics and methods

All research data were analyzed by the SPSS 23.0 system. Count data were expressed by ($x \pm s$, %) and the differences between the two groups were compared by t and x^2 tests. If $P < 0.05$, it indicates that the experiment has significant value.

3. Results

The data shows that the cognitive impairment symptoms of the two groups of patients have improved. As shown in Table 1, the ADAS-Cog score of the study group is significantly lower than that of the control group, and the scores of CDT, RVR, TMT-A, DS, FOME, and BD are higher than those of the control group, with $P < 0.05$.

Table 1. Comparison of various cognitive function scores between the two groups of patients ($x \pm s$)

Cognitive function score	Before treatment			After treatment		
	Study group	Control group	*P*-value	Study group	Control group	*P*-value
Language	8.44 ± 1.32	8.32 ± 1.31	$P > 0.05$	4.11 ± 1.42	6.73 ± 1.68	$P < 0.05$
Memory	13.23 ± 3.16	13.29 ± 3.21	$P > 0.05$	8.12 ± 2.31	10.65 ± 2.44	$P < 0.05$
Attention	3.25 ± 1.25	3.21 ± 1.27	$P > 0.05$	2.17 ± 0.26	2.87 ± 0.76	$P < 0.05$
Manipulation	3.34 ± 1.28	3.43 ± 1.24	$P > 0.05$	2.11 ± 0.76	2.99 ± 0.21	$P < 0.05$
CDT	2.12 ± 0.32	2.11 ± 0.26	$P > 0.05$	2.98 ± 0.61	2.39 ± 0.56	$P < 0.05$
RVR	15.35 ± 2.32	15.22 ± 2.36	$P > 0.05$	18.62 ± 2.59	16.88 ± 2.37	$P < 0.05$
TMT-A	81.25 ± 6.36	81.63 ± 6.62	$P > 0.05$	89.47 ± 5.36	84.87 ± 5.52	$P < 0.05$
DS	3.34 ± 1.28	3.43 ± 1.24	$P > 0.05$	2.11 ± 0.76	2.99 ± 0.21	$P < 0.05$
FOME	6.46 ± 0.76	4.44 ± 0.77	$P > 0.05$	7.76 ± 0.89	7.32 ± 0.80	$P < 0.05$
BD	5.52 ± 1.32	5.49 ± 1.34	$P > 0.05$	6.88 ± 0.98	6.56 ± 0.91	$P < 0.05$

4. Discussion

The main cause of cognitive decline or impairment symptoms in patients with Alzheimer's disease is closely related to the neurobiological changes in their brain tissue. In the early stage of the disease, most patients show a decrease in localized cerebral blood flow, with the frontal-parietal and temporal regions being the most severely affected [11–12]. According to relevant studies, cognitive training therapy can activate the cortex of the frontal-

parietal region, temporal region, and other brain regions of the patients, thus enhancing cerebral blood flow and strengthening the local metabolism in the brain. After systematic categorical fluency training in clinical practice, the cerebral blood flow in the left frontal region of patients can be significantly improved, thus optimizing brain function. At the same time, the implementation of word fluency training can increase the local cerebral blood flow mainly in the temporal region, which can further improve the brain's ability to process verbal information. Both training methods help to improve the cognitive function of the brain [13]. In addition, cognitive processes such as episodic memory and memory extraction are correlated with neurobiological changes in the medial temporal and limbic lobes of the patient's brain. Functional training in executive aspects, such as stereotypical switching and inhibitory control ability, can effectively influence the functional performance of the frontal lobe-related cortex of patients [14–15].

The results of this study indicated that both groups of patients receiving treatment showed improvement in cognitive impairment symptoms, and there was a significant reduction in ADAS-Cog scores in the study group compared with the control group. The CDT, RVR, TMT-A, DS, FOME, and BD scores were higher in the study group than those in the control group ($P < 0.05$). This indicates that cognitive training can effectively promote the increase of cerebral blood flow in patients, and can improve the metabolic function of brain areas, thus improving the cognitive ability and quality of life of patients to a certain extent.

In summary, the combination of drug therapy and cognitive training for Alzheimer's disease patients has shown remarkable clinical effects. This comprehensive treatment method can not only effectively promote the improvement of cognitive function, but also help to control the progression of the disease, which is worthy of widespread clinical application.

Disclosure statement

The authors declare no conflict of interest.

References

[1] Li CX, Fang Y, Jiang N, et al., 2021, Cognitive Improvement of Mild to Moderate Alzheimer's Disease Patients by Adaptive Cognitive Training. Journal of Hunan Institute of Technology (Natural Science Edition), 34(04): 43–46.

[2] Wu LY, 2023, Early Diagnosis and Treatment of Alzheimer's Disease. Population and Health, 2023(09): 89–92.

[3] Wang L, He Y, Li YM, et al., 2023, Application of Cognitive Intervention based on VR Technology Combined with Individualized Chemical Recreational Therapy in Patients with Mild-to-moderate Alzheimer's Disease. Contemporary Nurses, 30(11): 37–41.

[4] Zhang RF, Zhu JZ, Hu JQ, et al., 2023, Effects of Regression Family Intervention on Cognitive Function and Quality of Life in Patients with Alzheimer's Disease. Journal of Nursing, 38(22): 106–110.

[5] Zheng YJ, Zhang YQ, Gong W, 2023, Effects of Recreational Cognitive Training Combined with Psychological Liaison Care on Patients with Mild to Moderate Alzheimer's Disease. Psychology Monthly, 18(22): 204–206.

[6] Li N, Wang CL, Fang XN, et al., 2023, Evidence-based Practice of Rehabilitation Training for Patients with Mild to Moderate Alzheimer's Disease. China Practical Medicine, 18(24): 152–157.

[7] Xu QC, Du MZ, 2023, Effects of Virtual Technology Combined with Conventional Cognitive Rehabilitation Training on Cognitive Function in Patients with Alzheimer's Disease. Medical Theory and Practice, 36(24): 4298–4300.

[8] Han GH, Pang XL, Sun HL, et al., 2021, Quality Evaluation of Meta-analytic Reports of Cognitive Interventions for Alzheimer's Disease Patients in China. Chinese Family Medicine, 19(11): 1946–1950.

[9] Ni Z, Sun GQ, Jiang ML, 2023, Effects of Multisensory Stimulation Combined with Early Cognitive Rehabilitation

Training on Cognitive Ability and Mental Status of Patients with Alzheimer's Disease. Zhejiang Medicine, 45(04): 404–407 + 415.

[10] Lin XY, Ye H, Chen H, 2023, Effects of Cognitive-perceptual Dysfunction Training Combined with Occupational Therapy on the Recent Rehabilitation Effect and Prognosis of Patients with Alzheimer's Disease. Chinese and Foreign Medical Research, 21(05): 149–153.

[11] Wang J, Yuan J, Wang L, 2022, Clinical Efficacy of Aripiprazole and Donepezil Combined with Functional Training in the Treatment of Alzheimer's Disease and its Effect on Patients' Cognitive Function and Behavioral Ability. Journal of Clinical Rational Drug Use, 15(27): 73–76.

[12] Cai LL, Huang ZH, Yu ZG, 2022, Effects of Cognitive Function Training Combined with Daily Living Ability Training on Patients with Alzheimer's Disease. Chinese Contemporary Medicine, 29(19): 90–93.

[13] Xiao GX, 2023, Clinical Efficacy of Transcranial Direct Current Stimulation Combined with Cognitive Training in Alzheimer's Disease and its Neural Mechanism, thesis, Anhui Medical University.

[14] Hu FX, 2022, Effects of Comprehensive Rehabilitation Training Combined with Donepezil Hydrochloride on Cognitive Function and Quality of Life in Patients with Mild-to-moderate Alzheimer's Disease. Reflexology and Rehabilitation Medicine, 3(07): 171–173.

[15] Zhao XY, Huang XX, Wan QQ, 2021, An Integrative Review of Exercise Combined with Cognitive Training in Patients with Mild Cognitive Impairment and Alzheimer's Disease. Chinese Nursing Education, 18(12): 1098–1105.

Clinical Neuroscience Research, 2024, Volume 2, Issue 1
http://ojs.bbwpublisher.com/index.php/CNR

The Efficacy of Manual Nerve Mobilization Combined with Traction Therapy in the Treatment of Nerve Root Cervical Spondylosis

Lei Zhou*, Kaixing Du, Jing Chen, Jieran Li

Meishan People's Hospital, Meishan, Sichuan 620010, China

Corresponding author: Lei Zhou, 18783383705@163.com

Abstract: *Objective*: This study aimed to evaluate the therapeutic effect of the manual nerve mobilization technique combined with traction therapy on nerve root cervical spondylosis and to investigate its effect on symptomatic improvement and functional recovery of patients. *Methods*: 101 patients diagnosed with nerve root cervical spondylosis were selected and randomly divided into two groups. The control group received conventional medication and physical therapy, while the observation group was treated with manual nerve mobilization combined with traction therapy. The manual nerve mobilization technique uses a delicate and gentle technique to reduce pain and inflammation by loosening the soft tissues around the compressed nerve roots. Traction therapy was used to relieve pressure on the cervical discs pull on the nerve roots, and restore the normal physiologic curvature of the cervical spine. All patients were assessed for pain scores and neck mobility before and after treatment. *Results*: At the end of the treatment, the pain scores of the patients in the observation group were significantly reduced and neck mobility was significantly improved, with a significant difference compared with the control group ($P < 0.001$). No serious adverse events occurred in the patients of the observation group after the completion of treatment. *Conclusion*: Manual nerve mobilization combined with traction therapy has good efficacy in the treatment of nerve root cervical spondylosis. This therapy can effectively reduce patients' pain and improve neck motor function. Therefore, the promotion and application of this therapy in rehabilitation therapy will play a positive role in the recovery of patients with radiculopathy.

Keywords: Manual nerve mobilization; Traction therapy; Radiculopathy; Efficacy

Online publication: March 29, 2024

1. Introduction

Neurogenic cervical spondylosis is a common type of cervical spondylosis, which is caused by cervical spine lesions compressing the nerve roots. This condition is mostly seen in middle-aged and elderly people, with poor posture as the main trigger [1]. Symptoms of nerve root cervical spondylosis mainly manifest as neck and shoulder pain, accompanied by radiating upper limb pain and numbness, and in severe cases, muscle atrophy and weakness. Conventional management includes cervical traction, physical therapy, acupuncture, medication,

and so on. Surgery may be required for severe cases. However, the treatment effect of nerve root cervical spondylosis varies with individuals and is prone to recurrence [2]. Therefore, prevention is key and can be achieved by maintaining the correct sitting posture, avoiding prolonged use of cell phones or computers with the head down, and performing regular neck exercises to strengthen the neck muscles [3].

2. Information and methods

2.1. General information

Patients diagnosed with nerve root type cervical spine were selected from May 2022 to December 2023 in the hospital rehabilitation department of the study for a total of 101 cases with 56 male cases and 45 female cases. The age range of the patients was between age 37 years 2 months to 74 years 9 months. The patients were randomly divided into two groups, 51 cases in the control group with 29 males and 22 females, and an average age of 55.6 ± 3.2 years. The second group is the observation group with 50 cases, consisting of 27 males and 23 females, and an average age of 53.8 ± 3.4 years. There was no statistical difference in the general information of patients in the two groups as shown in **Table 1** ($P > 0.05$), and they were comparable.

Table 1. Basic information on cases in the control group and observation group

Groups	Number of cases (*n*)	Sex		Average age (years)
		Male	Female	
Control group	51	29	22	55.6 ± 3.2
Observation group	50	27	23	53.8 ± 3.4

2.2. Inclusion and exclusion criteria

All the enrolled patients met the diagnostic criteria of neurogenic cervical spondylosis according to the guideline recommendations [4]. The diagnosis of neurogenic type was based on the following. The patients have more typical radicular symptoms, such as numbness and pain, and the range was consistent with the area innervated by the cervical spinal nerves. The head pressure test or brachial plexus pull test has positive results. The imaging findings are consistent with the clinical manifestations. The closure of the pain point is not effective, this test may not be performed if the diagnosis is clear. Apart from the diseases caused by extra cervical vertebrae, such as thoracic outlet syndrome, tennis elbow, carpal tunnel syndrome, elbow tube syndrome, frozen shoulder, biceps tenosynovitis, and so on, the patient's family members should sign the informed consent for treatment.

The exclusion criteria include the following. The patient is suffering from diseases or illnesses that prohibit any exercise. The weight of traction causes excessive strain on the spine. The patient is showing symptoms of acute strains, sprains, and acute inflammation. The patient is suffering from vascular disease. The symptoms of patients aggravated during traction.

2.3. Treatment method

The study selected 101 patients diagnosed with neurogenic cervical spondylosis and randomly divided them into two groups. The control group (n=51) received conventional drugs and physical therapy, while the observation group (n=50) was treated with manual nerve mobilization combined with traction therapy. The manual nerve mobilization technique was performed twice a day for about half an hour each time to reduce pain and inflammatory reaction by loosening the soft tissues around the compressed nerve roots with a fine and gentle

technique. Traction therapy was performed once a day for 20 minutes each time to relieve the pressure of the cervical disc and the pull of the nerve root, and to restore the normal physiological curvature of the cervical spine.

2.4. Clinical observation and evaluation methods

The two groups of patients were evaluated for pain scores and neck mobility before and after treatment.

The pain scoring used the numerical rating system (NRS) with 0–10 to represent different degrees of pain, with 0 being no pain and 10 being severe pain. The pain level grading criteria are, 0: no pain, 1–3: mild pain, 4–6: moderate pain, and 7–10: severe pain.

Appropriate scores were selected according to the degree of neck activity limitation of the patients. The neck mobility score grading is as follows, 0: without any activity limitation, 1: mild activity limitation, only affecting some specific movements, 2: moderate activity limitation, affecting daily activities but coping with them, 3: severe activity limitation, unable to carry out routine activities, 4: complete activity limitation, unable to carry out normal activities.

2.5. Statistical analysis

SPSS 20.0 statistical software was used for data processing, and the measurement data were expressed as ± *s*, and the *t*-test was used, the count data were tested by χ^2 test. $P < 0.05$ was regarded as the difference was statistically significant.

3. Results

The pain score of the observation group after treatment was lower than that of the control group, $p<0.05$, as shown in **Table 2**.

Table 2. Comparison of pain scores between the two groups of patients before and after treatment

Groups	Comparison of pain scores (points)		*t*	*P*
	Pre-treatment	Post-treatment		
Observation group	5.14 ± 1.14	2.31 ± 0.66	15.305	0.001
Control group	5.11 ± 1.15	3.76 ± 0.68	7.163	0.001
t	0.132	10.875	-	-
P	0.896	0.001	-	-

After treatment, the neck mobility score of the observation group was lower than that of the control group, with a *P*-value of < 0.05, as shown in **Table 3**.

Table 3. Comparison of neck mobility scores between the two groups of patients before and after treatment

Groups	Comparison of neck mobility scores (points)		*t*	*P*
	Pre-treatment	Post-treatment		
Observation group	3.14 ± 0.54	1.04 ± 0.31	24.027	0.001
Control group	3.12 ± 0.53	2.65 ± 0.42	4.933	0.001
t	0.188	21.949	-	-
P	0.851	0.001	-	-

4. Discussion

Cervical spondylosis is a common disease in clinical practice, among which neurogenic cervical spondylosis is a common type of cervical spondylosis. Due to the compression of nerve roots by cervical spondylotic lesions, the patients often suffer from symptoms such as pain, activity limitation, and sensory abnormalities. Manual nerve mobilization and traction therapy are commonly used therapies in rehabilitation, and they have good efficacy in the treatment of radiculopathy [5]. The purpose of this paper is to explore the effect of manual nerve mobilization combined with traction therapy in the treatment of neurogenic cervical spondylosis and to discuss its efficacy in depth. The nerve mobilization technique, also known as the neural tension technique, is a manipulative technique for the treatment of pain caused by nerve tissues. It is based on the anatomical structure and physiological function of nerves and applies force to the abnormal nerve tissues through specific manipulation and limb movement to produce extension and tension changes, as well as promotes microcirculation and impulse conduction between nerve tissues, reduces neural adhesion, improves neural tension, and enhances nerve function. Thus, it can improve the therapeutic effect of pain, numbness, sensory abnormalities, muscle weakness, and so on [6]. Traction therapy, on the other hand, stretches the cervical vertebrae through external force to increase the volume of the cervical spinal space and intervertebral foramina, thus reducing the compression of the nerve roots, relieving pain, and improving the function of the cervical vertebrae [7]. The combined application of manual nerve mobilization and traction therapy can utilize both of their advantages, complement each other, and improve the therapeutic effect. In this study, a randomized controlled trial of 49 patients with nerve root-type cervical spondylosis found that manual nerve mobilization combined with traction therapy was superior to traction therapy alone in terms of pain relief, improvement of cervical motor function, and quality of life. After treatment, the pain scores and neck mobility scores of the combination therapy group were significantly lower than those of the control group, and the recurrence rate of the combination therapy group was also significantly lower than that of the control group during the follow-up period. These results suggest that manual nerve mobilization combined with traction therapy has better efficacy in the treatment of neurogenic cervical spondylosis [8–9]. This study found that manual nerve mobilization combined with traction therapy has significant advantages in the treatment of radiculopathy of the cervical spine, which can effectively reduce patients' pain and improve neck motor function [10]. However, the efficacy and safety of this therapy need to be further confirmed with long-term follow-up and larger studies. In addition, the development of personalized treatment plans for different patients should also be the focus of future research [11].

In conclusion, this study demonstrated that manual nerve mobilization combined with traction therapy has good efficacy in the treatment of neurogenic cervical spondylosis. Therefore, the promotion and application of this therapy in rehabilitation will play a positive role in the recovery of patients with neurogenic cervical spondylosis. However, long-term follow-up and larger studies are needed to further validate the effectiveness and safety of this therapy. Meanwhile, personalized treatment plans for different patients are also an important direction for future research.

Disclosure statement

The authors declare no conflict of interest.

References

[1] Huang L, Jiang T, Lin XD, et al., 2023, Analyzing the Efficacy of Acupuncture Therapy Combined with Auricular Point Pressure Bean in the Treatment of Nerve Root-Type Cervical Spondylosis based on a Novel Quantitative Muscle Evaluator. Journal of Guangzhou University of Traditional Chinese Medicine, 40(12): 3072–3077.

[2] Wu Y, Zhang SF, Wang WJ, 2023, Clinical effect of Acupuncture and Moxibustion Combined with Tuina in the Treatment of Neurogenic Cervical Spondylosis in the Elderly. Chinese Journal of Gerontology, 43(22): 5532–5534.

[3] Liang LB, Zuo XT, Mo HF, et al., 2021, Observation on the Curative Effect of Manual Nerve Loosening Combined with Suspension Training Technique in the Treatment of Cervical Radiculopathy. The Journal of Cervicodynia and Lumbodynia, 42(6): 881–883.

[4] Xu QX, Shi GL, Tian WJ, 2023, Warm Acupuncture and Moxibustion Combined with Cervical Fukang Granules for the Treatment of Neurogenic Cervical Spondylosis in 30 Cases. Guangming Traditional Chinese Medicine, 38(22): 4421–4423.

[5] Liu WF, Jin Y, Zhao LJ, et al., 2023, Clinical Study on the Treatment of Lumbar Intervertebral Disc Herniation by Multidimensional Traction. Chinese Orthopedics, 35(11): 1–4 + 9.

[6] Cai SP, Li ZY, Li SC, et al., 2023, Clinical Observation on the Treatment of Neurogenic Cervical Spondylosis by Electrothermal Needling Combined with Picking Four Sutures. Journal of Guangzhou University of Traditional Chinese Medicine, 40(11): 2820–2825.

[7] Liu ZH, 2023, Comparison of Clinical Effect and Safety of Proximal Femoral Anti-spin Intramedullary Nail Fixation and Tibial Tuberosity Distraction in Treating Intertrochanteric Femur Fracture in the Elderly. Heilongjiang Medicine, 36(05): 1161–1163.

[8] Li C, Li J, Mao ZT, et al., 2023, Clinical Efficacy of Orthopedic Method under Long's Traction in the Treatment of Cervicogenic Frozen Shoulder. Journal of Guangzhou University of Traditional Chinese Medicine, 40(09): 2225–2230.

[9] Liang LB, Zuo XT, Mo HF, et al., 2021, The Efficacy of Unarmed Nerve Release Combined with Suspension Training Technique in the Treatment of Nerve Root Cervical Spondylosis. Journal of Neck and Low Back Pain, 42(06): 881–883.

[10] Wang Y, Pei F, Kang LR, et al., 2015, Clinical Observation on Treatment of Peripheral Nerve Injury of Lower Extremity by Cluster Acupuncture at Head Point Combined with Nerve Loosening. Journal of Clinical Acupuncture and Moxibustion, 2015(5): 5–8.

[11] Pei F, Wang Y, 2012, Research Progress of Peripheral Nerve Release. China Rehabilitation, 27(06): 462–464.

Clinical Neuroscience Research, 2024, Volume 2, Issue 1
http://ojs.bbwpublisher.com/index.php/CNR

Prediction of Futile Recanalization Following Mechanical Thrombectomy for Acute Ischemic Stroke Using Quantitative Electroencephalography: Temporal Delta/Alpha Power Ratio as an Independent Predictor

Min Wang, Li Li, Shengli Chen*, Lina Zhang*

Chongqing University Three Gorges Hospital, Chongqing 404100, China
Min Wang and Li Li contributed equally to this work.

Corresponding authors: Shengli Chen, chen001696@163.com; Lina Zhang, syxs891114@163.com

Abstract: *Objective*: Previous studies have reported associations between quantitative electroencephalography (QEEG) parameters and acute ischemic stroke (AIS). However, the relationship between QEEG parameters and clinical outcomes in AIS patients with complete intracranial recanalization post-thrombectomy has been rarely explored. This study aims to evaluate the relationship between the QEEG parameter, specifically the regional delta/alpha power ratio (DAR), and futile recanalization (FR) in AIS patients with anterior circulation large vessel occlusion undergoing mechanical thrombectomy. *Methods*: A retrospective study was conducted on AIS patients with anterior circulation large artery occlusion who underwent mechanical thrombectomy and achieved complete vessel recanalization (mTICI 2b or 3) between May 2020 and October 2021. Patients with complete recanalization were categorized into effective recanalization and FR groups based on their modified Rankin scale (mRS) scores at three months. The FR group was defined as having an mRS score of 3–6 at three months, while the effective recanalization group had an mRS score of 0–2. Univariate analysis was performed to identify factors associated with FR, and factors with $P < 0.05$ were further analyzed using binary logistic regression to determine independent predictors of FR. Receiver operating characteristic (ROC) curve analysis was employed to assess the predictive ability of identified factors for FR. *Results*: Among 152 patients, 81 had effective recanalization, while 71 had FR, resulting in an FR rate of 46.7%. Univariate analysis revealed that baseline characteristics such as admission NIH stroke scale (NIHSS) score, neutrophil ratio, hemorrhagic transformation rate, number of thrombectomy passes, and time to recanalization were higher, whereas ASPECTS score was lower in the FR group compared to the effective recanalization group, all with statistical significance ($P < 0.05$). Electrophysiologically, DAR values in the affected frontal and temporal regions were significantly higher in the FR group compared to the effective recanalization group ($P < 0.05$). After adjusting for potential confounders, multivariable adjusted regression analysis demonstrated that regional DAR (odds ratio [OR] 1.205 [95% CI 1.041–1.396], $P = 0.013$), neutrophil ratio (OR 1.040 [95% CI 1.040–1.081], $P = 0.042$), ASPECTS score (OR 0.556 [95% CI 0.397–0.780], $P = 0.001$), and admission NIHSS score (OR 1.209 [95% CI 1.064–1.373], $P = 0.004$) were independent predictors of FR. ROC analysis indicated that combining regional DAR, especially temporal DAR, with other clinical factors could effectively predict adverse outcomes. *Conclusion*: Baseline characteristics

including NIHSS score, ASPECTS score, and neutrophil ratio are independent predictors of FR, while electrophysiological characteristics, particularly temporal DAR of regional DAR, are closely associated with adverse outcomes at three months post-mechanical thrombectomy in AIS patients with anterior circulation large vessel occlusion. This shows that models incorporating temporal DAR can effectively predict FR.

Keywords: Acute ischemic stroke; Quantitative electroencephalography; Delta/alpha power ratio; Mechanical thrombectomy; Futile recanalization

Online publication: March 29, 2024

1. Introduction

Acute ischemic stroke (AIS) is one of the leading causes of death and disability in China. More than one-third of patients suffer from large vessel occlusion, which represents a severe subtype of AIS with a poor prognosis and imposes significant societal and economic burdens [1]. The primary treatment modality for large vessel occlusive AIS involves intravascular therapy within the time window (<6 h) or beyond the extended time window (6-24 h) using perfusion imaging to re-establish blood flow through the occluded vessel, thus salvaging the ischemic penumbra [2–4]. However, multiple studies have indicated that 46% to 55% of patients undergoing intravascular therapy within the time window and 41% to 43% of patients undergoing intravascular therapy beyond the time window fail to achieve functional independence at 90 days post-recanalization (mRS 3–6), termed as futile recanalization (FR) [2–3, 5]. Clinical outcomes of completely recanalized patients with similar characteristics may vary. Current research suggests that predictive factors for FR may include the patient's clinical characteristics, time to initiation and intraoperative management of intravascular therapy, collateral circulation and hemodynamics, core infarct volume, cerebral edema, and baseline brain white matter hyperintensity, yet other predictors of adverse outcomes remain unclear [5–16].

For patients with poor prognosis due to extensive cerebral infarction, there is a significant enlargement of the ischemic core area, accompanied by decreased cerebral blood flow perfusion and more severe irreversible neuronal damage. Electroencephalography (EEG) can reflect changes in cortical neuronal metabolism and electrical activity. When cerebral blood flow (CBF) is impaired, faster frequency waves on EEG gradually decrease, while slower frequency waves increase. As cerebral blood flow perfusion continues to decline to the ischemic threshold, neurons undergo irreversible damage, resulting in an electrically silent EEG. By analyzing EEG frequency, rhythm, amplitude, waveform, and other variables, through frequency domain or time domain analysis, specific quantitative parameters are derived using particular function models, termed Quantitative Electroencephalogram (QEEG) [17–18]. Subsequently, direct observation of the distribution and changes in alpha, beta, theta, delta, and gamma frequency bands of EEG waves is conducted [18]. A review emphasizes that specific QEEG indices can assist clinicians in making clinical decisions regarding stroke. Continuous monitoring informs the efficacy of acute endovascular reperfusion therapy. Brief recording aids in prognosis prediction, clinical diagnosis, and treatment assistance [19]. QEEG can reveal neuronal activity in the ischemic penumbra of AIS, providing potential information for salvaging hypoperfused brain tissue of the penumbra [19–23]. Currently, most studies have identified the delta-alpha power ratio (DAR) as the QEEG-related index that shows the greatest value in AIS monitoring [19, 21, 24–25].

QEEG exhibits superior detection and localization capabilities compared to EEG. Delta lesions identified by QEEG have been demonstrated to correlate with lesion locations in neuroimaging studies, including MRI [19, 26]. Early studies suggested that in patients with ischemic stroke (IS) due to occlusion of the middle

cerebral artery (MCA) and internal carotid artery (ICA), delta activity in EEG is most prominent at the ipsilateral frontotemporal central electrode as shown in **Figure 1** [19, 27]. Subsequent observations in MCA-AIS revealed maximal delta power at electrodes overlying the anterior hemisphere, with a few studies reporting the significance of ipsilateral single frontal area delta activity reduction (DAR) in AIS patients with anterior circulation large vessel occlusion [20, 25]. However, there is no clear data regarding the prognostic value of DAR in the anterior-temporal single electrode for AIS prognosis. Therefore, this study assesses the relationship between regional DAR (frontal DAR and temporal DAR) and clinical outcomes in AIS patients with complete reperfusion after endovascular thrombectomy of anterior circulation large vessel occlusion and utilizes ROC curves to evaluate the optimal regional quantitative EEG parameters combined with other factors for predicting FR after thrombectomy.

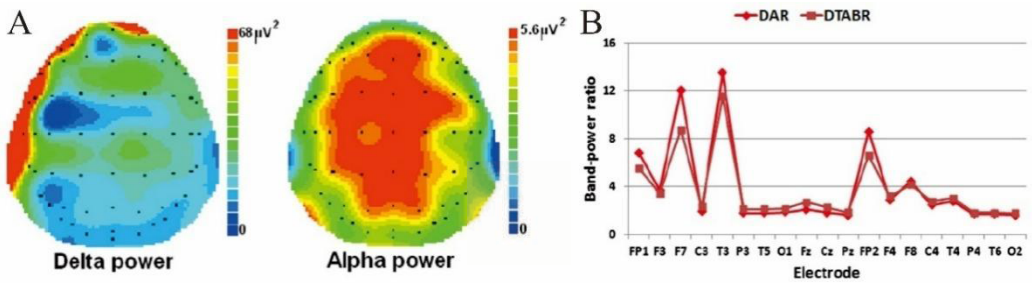


Figure 1. EEG data was obtained from a 7-hour post-stroke AIS (left middle cerebral artery) female patient with an NIHSS score of 7. Panel A: Topographic maps of average delta (left) power and alpha (right) power distribution. Panel B: Shows DAR (delta activity reduction) and (Delta+theta)/(alpha+beta) power ratio (DTABR) for each electrode. Values are highest at ipsilateral frontal and anterior temporal electrodes

2. Clinical data and methods

2.1. Study population

AIS patients with anterior circulation large vessel occlusion who underwent mechanical thrombectomy treatment either within or outside the time window after perfusion imaging assessment between January 2020 and October 2021 at the affiliated Three Gorges Hospital of Chongqing University were included, with signed informed consent.

2.1.1. Inclusion criteria

The inclusion criteria include the following. All patients diagnosed clinically according to the Diagnostic Criteria for Cerebral Infarction revised at the 2019 National Conference on Cerebrovascular Diseases and confirmed by head CT and/or MRI; age between 18 and 80 years; deficit symptoms consistent with occluded vessels; anterior circulation large vessel occlusion confirmed by cervical CTA or DSA (middle cerebral artery M1 or internal carotid artery); first-time stroke with no history of previous cerebral infarction; able to undergo EEG examination; emergency mechanical thrombectomy performed within or outside the time window after perfusion imaging assessment, achieving mTICI 2b or 3 reperfusion grade.

2.1.2. Exclusion criteria

The exclusion criteria include the following. CTA or DSA indicating concomitant contralateral large vessel stenosis or occlusion; concurrent ischemic lesions outside the territory of the ipsilateral or contralateral internal carotid artery or middle cerebral artery, such as brainstem infarction, occipital lobe infarction,

cerebellar infarction, or multiple infarctions in both cerebral hemispheres; hemorrhagic diseases of the brain, cerebrovascular malformations, intracranial space-occupying lesions, arterial aneurysms, etc.; patients with unstable vital signs; history of previous stroke, epilepsy, or other neurological disorders such as encephalitis or drug poisoning; use of sedatives or psychotropic drugs before EEG monitoring, which may affect EEG results.

2.2. Research methods

Data collection was based on previous studies and experience, gathering general patient information, as detailed below.

2.2.1. Demographic data

Demographic data includes gender, age, history of alcohol consumption, history of smoking, and so on. The definitions are as follows.

History of alcohol consumption: Drinking frequency of ≥ 3 times per week, or alcohol intake exceeding 100 mg of alcohol concentration (50° or above), or consuming one can of beer (500 ml) per occasion.

History of smoking: Having smoked for more than 6 months cumulatively in the past, with a daily smoking habit of ≥ 1 cigarette, and a personal history of smoking within one month before the onset of the current stroke.

2.2.2. Clinical data

Collection of medical history (hypertension, diabetes, atrial fibrillation, history of previous stroke), admission clinical characteristics (National Institutes of Health Stroke Scale (NIHSS) score, pre-stroke modified Rankin Scale (mRS) score), site and etiology of infarction, Alberta Stroke Program Early CT Score (ASPECTS), blood glucose level, neutrophil ratio, and treatment details (treatment methods, number of thrombectomy procedures, hemorrhagic transformation) were included as baseline information. The relevant assessment criteria are as follows.

History of hypertension: Previously diagnosed with hypertension or currently taking antihypertensive medication; under resting conditions, systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg measured on three separate occasions.

History of diabetes: Previously diagnosed with diabetes or currently taking antidiabetic medication; fasting blood glucose ≥ 7.0 mmol/L; glycated hemoglobin (HbA1c) ≥ 6.5%; oral glucose tolerance test: 2-hour postprandial blood glucose ≥ 11.1 mmol/L.

2.2.3. EEG data

Digital video EEG recordings were performed using equipment from Beijing Taiyang Company within 6–24 hours after mechanical thrombectomy. Electrodes were placed according to the international 10/20 system at FP1, FP2, F3, F4, F7, F8, T3, T4, T5, T6, O1, O2, P3, P4, C3, C4, Fz, Cz, and Pz locations. The referenced electrode was used as the baseline. After degreasing the skin, electrodes were attached using conductive gel and secured with medical-grade net caps. The paper speed was set at 3 cm/s, with a high-frequency filter of 35 Hz and a low-frequency filter of 0.5 Hz. EEG data were recorded for 30 minutes, with a stable and artifact-free baseline of 1800 ms selected. Through the fast Fourier transform (FFT), absolute power values in the delta, theta, alpha, and beta frequency bands were calculated based on the power spectrum generated by each electrode. Regional delta and alpha absolute power ratios were then calculated to determine hemisphere-specific DAR, including F-DAR and T-DAR, in the frontal and temporal regions.

2.3. Statistical methods

Data processing and analysis were performed using statistical product and service solutions (SPSS) 25.0 software. Continuous variables for two groups of patients (effective reperfusion group, mRS 0–2; FR group, mRS 3–6) were expressed as mean ± standard deviation (x ± s), while categorical variables were expressed as percentages (%). Normality tests for quantitative EEG parameters were conducted using Q-Q and P-P probability plots, indicating that DAR values in each hemisphere region were normally distributed. For single-factor analysis, independent *t*-tests were used for continuous data, and rank-sum tests and chi-square tests (χ^2) were used for categorical data comparison between the two groups. Factors with $P < 0.05$ in single-factor analysis were determined as independent risk factors for FR using binary logistic regression analysis. The predictive ability of these risk factors for FR was evaluated using ROC curves and the area under the curve of ROC (AUC).

3. Results

3.1. Univariate analysis

Data from a total of 152 AIS patients who underwent mechanical thrombectomy for complete recanalization of anterior circulation large vessel occlusion were collected, among which the FR rate was 46.7%. Among them, 81 cases were classified into the effective recanalization group with a mean age of 66.1 ± 12.2 years, and 71 cases were classified into the FR group with a mean age of 69.7 ± 11.5 years based on the mRS score at 3 months post-treatment. **Table 1** summarizes the descriptive analysis of baseline data for both groups of patients. The FR group showed significantly higher admission NIHSS score ($P < 0.001$), neutrophil ratio ($P = 0.011$), hemorrhagic transformation rate ($P < 0.001$), number of thrombectomy passes ($P < 0.001$), and time to recanalization ($P = 0.01$) compared to the effective recanalization group, while ASPECTS score ($P < 0.001$) was lower in the FR group than the effective recanalization group, all with statistical significance. **Table 2** displays the regional DAR descriptive analysis of the two groups of patients, showing the baseline values of F-DAR and T-DAR on the affected side and ipsilateral side in the FR group were higher than those in the effective recanalization group, with statistically significant differences observed in the affected side F-DAR ($P = 0.04$) and T-DAR ($P = 0.02$) baseline values compared to the effective recanalization group ($P < 0.05$).

Table 1. Univariate analysis of effective recanalization and FR groups after endovascular treatment for acute ischemic stroke

Variables	Effective recanalization group (*n* = 81)	Variables (*n* = 71)	*P* < 0.05
Demographics			
Age (x ± s)[a]	66.1 ± 12.243	69.7 ± 11.523	0.068
Gender (*n*, %)[b]			
Male	44 (54.3)	36 (50.7)	
Female	37 (45.7)	35 (49.3)	
Medical history			
History of hypertension (*n*, %)[b]	39 (48.1)	38 (53.5)	0.509
History of diabetes (*n*, %)[b]	15 (18.5)	15 (21.1)	0.687

Table 1 (Continued)

Variables	Effective recanalization group (n = 81)	Variables (n = 71)	$P < 0.05$
Atrial fibrillation (n, %)[b]	40 (49.4)	36 (50.7)	0.871
History of stroke (n, %)[b]	4 (4.9)	9 (12.7)	0.089
Admission evaluation			
NIHSS Score [c] (median)[b]	11 (9,15)	15 (14,16)	< 0.000
Pre-stroke mRS Score (n, %)[b]			0.797
0	78 (96.3)	65 (91.5)	
Others	3 (3.7)	6(8.4)	
Blood glucose (x±s)[a]	7.5 ± 2.4	8.2 ± 2.8	0.132
Neutrophil ratio (x±s)[a]	76.6 ± 12.2	81.2 ± 9.9	0.011
Imaging			
ASPECTS score (median)[c]	7 (5.5,8)	5 (5,6)	< 0.000
Infarcted vessels (n, %)[b]			0.191
ICA	17 (21)	23 (32.4)	
MCA-M1	54 (66.7)	40 (56.3)	
MCA-M2	7 (8.6)	5 (7)	
ICA+MCA	3 (3.7)	3 (4.2)	
Disease characteristics			
Onset time (x ± s)[a]	5.8 ± 4.3	6.8 ± 4.8	0.193
TOAST classification (n, %)[b]			
Large artery atherosclerosis	39 (48.1)	30 (42.3)	0.722
Cardioembolism	36 (44.4)	35 (49.3)	
Others	6 (7.4)	6 (8.5)	
Treatment (n, %)[b]			0.577
Thrombolysis & Thrombectomy	19 (23.5)	14 (19.7)	
Thrombectomy alone	62 (76.5)	57 (80.3)	
Number of thrombectomy passes (median)[c]	2 (1,2)	2 (2,3)	< 0.000
Time to recanalization (x ± s) [a]	115.8 ± 42.5	143. 3 ± 58.8	0.01
Hemorrhagic transformation (n, %) [b]	15 (18.5)	38 (53.5)	< 0.000

Note: x ± s: mean ± standard deviation; a: t-test; b: chi-square test (χ^2); c: Mann-Whitney U test; n: frequency

Table 2. Electrophysiological analysis of effective recanalization and FR groups after endovascular treatment for acute ischemic stroke

Electrophysiological factors	Effective recanalization group (n = 81)	FR group (n = 71)	t	$P < 0.05$
IH-F	1.947 ± 1.746	3.219 ± 3.288	2.919	0.04
IH-T	2.818 ± 2.452	4.528 ± 3.997	3.221	0.02
CH-F	1.710 ± 1.639	2.655 ± 2.886	2.434	0.17

CH-T	2.218 ± 2.147	3.185 ± 3.178	2.165	0.32

Note: IH-F: Ipsilateral hemisphere frontal area; IH-T: Ipsilateral hemisphere temporal area; CH-F: Contralateral hemisphere frontal area; CH-T: Contralateral hemisphere temporal area.

3.2. Multivariate analysis of factors associated with FR after endovascular treatment for acute ischemic stroke

The baseline data with **P** < 0.05 from the univariate analysis were subjected to binary logistic regression analysis. The chi-square value was 62.05, with a significance level of less than 0.01, indicating statistical significance at the 1% level. This suggests that the model has statistical significance. The log(-2)-likelihood value was 148.008, Cox-Snell *R* square was 0.335, and Nagelkerke *R* square was 0.448, indicating a high level of model fit. Therefore, the model provides a relatively ideal interpretation of the original data. The Hosmer-Lemeshow test yielded a chi-square value of 3.673, with a *P*-value of 0.878, indicating a good fit for the predicted model. Furthermore, the regional DAR (F-DAR, T-DAR) with $P < 0.05$ was combined with clinical baseline data for binary logistic analysis as shown in **Table 3**. The results showed that each group's model had statistical significance ($P < 0.00$), and their predictive fit was good ($P > 0.05$).

Table 3. Multivariate analysis of baseline information and electrophysiological characteristics after endovascular treatment for acute ischemic stroke

	Baseline information *n*[d]	Baseline information [d] +IH-F	Baseline information [d] +IH-T
Chi-square (model summary)	62.050	66.747	69.077
Sig	< 0.00	< 0.00	< 0.00
log(-2)-likelihood value	148.008	143.311	140.981
Cox-Snell *R* square	0.335	0.355	0.365
Nagelkerke *R* Square	0.448	0.475	0.488
Chi-Square (Hosmer-Lemeshow Test)	3.767	5.106	10.749
Sig (Hosmer-Lemeshow Test)	0.878	0.746	0.216

3.3. ROC analysis

Through ROC analysis, the predictive performance of baseline data in multivariate analysis for FR was evaluated, yielding an AUC of 0.848, with a sensitivity of 77.5% and specificity of 79%. Upon incorporating electrophysiological data of regional DAR, the optimal predictive performance was observed when combining ipsilateral T-DAR with baseline data of AUC = 0.859, sensitivity = 88.9%, and specificity = 88.9%. Subsequently, combining ipsilateral F-DAR with baseline data also showed good performance of AUC = 0.855, sensitivity = 86.4%, and specificity = 86.4%. However, all these performances were superior to baseline data alone as shown in **Figure 2** and **Table 4**.

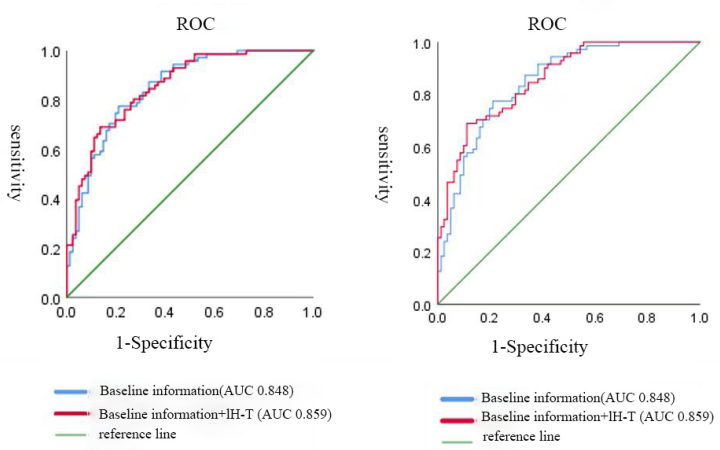


Figure 2. ROC Curve analysis of baseline information and electrophysiological characteristics following endovascular treatment for acute ischemic stroke; IH-F: Ipsilateral hemisphere-frontal DAR; IH-T: Ipsilateral hemisphere temporal DAR; CH-F: Contralateral hemisphere- frontal DAR; CH-T: Contralateral hemisphere temporal DAR

Table 4. Multifactor analysis of baseline information and electrophysiological characteristics following endovascular treatment for acute ischemic stroke

Factors	Baseline information [d]	Baseline information [d] +IH-F	Baseline information [d] +IH-T
Correct percentage (%)	75.7	74.6	75.0
AUC (95%CI)	0.848 (0.788, 0.908)	0.855 (0.797, 0.913)	0.859 (0.802, 0.915)
Threshold (%)	42.9	58.7	54.5
Sensitivity (%)	77.5	86.4	88.9
Specificity (%)	79	86.4	88.9
Sig	< 0.00	< 0.00	< 0.00

Note: IH-F: Ipsilateral hemisphere- frontal DAR; IH-T: Ipsilateral hemisphere temporal DAR; CH-F: Contralateral hemisphere- frontal DAR; CH-T: Contralateral hemisphere temporal DAR.

The ROC curve confirmed that the combination of baseline data with DAR in the affected temporal region was the optimal model. Binary logistic regression analysis revealed that regional DAR IH-T (odds ratio, 1.205 [95% CI: 1.041–1.396], P = 0.013), neutrophil ratio (odds ratio, 1.040 [95% CI: 1.040–1.081], P = 0.042), ASPECTS score (odds ratio, 0.556 [95% CI: 0.397–0.780], P = 0.001), and NIHSS score (odds ratio, 1.209 [95% CI: 1.064–1.373], P = 0.004) were independent predictive factors for FR (**Figure 3**).

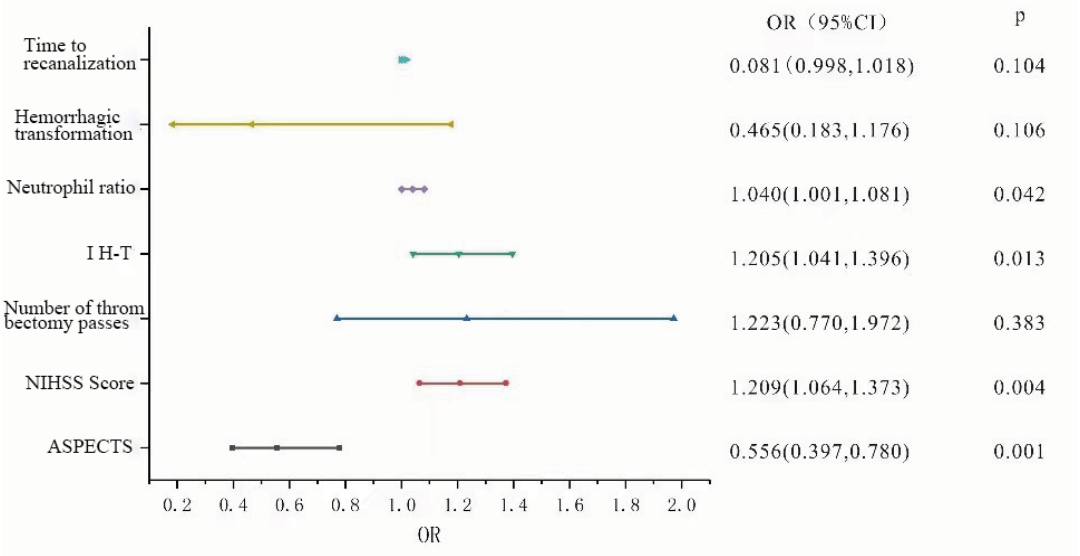


Figure 3. Multifactor analysis of baseline information and electrophysiological characteristics following endovascular treatment for acute ischemic stroke; OR: odds ratio; IH-T: Ipsilateral hemisphere temporal

4. Discussion

Mechanical thrombectomy is the standard treatment for anterior circulation large vessel occlusion AIS [28]. With advancements in thrombectomy devices, the rate of successful reperfusion can reach 71%–84%. However, vascular reperfusion as demonstrated by angiography does not necessarily indicate complete cerebral tissue reperfusion [5]. In this study, data from 152 patients with anterior circulation large vessel occlusion AIS was collected, showing the effective reperfusion rate after mechanical thrombectomy was 53.3%. Nearly half of the patients ultimately failed to achieve functional independence at 90 days. Therefore, predicting FR is crucial for

making rational decisions regarding subsequent treatment for AIS patients.

Consistent with prior studies, this study concludes that NIHSS score, ASPECTS score, and neutrophil ratio are associated with poor outcomes. As clinical indicators reflecting the severity of neurological impairment and assessing prognosis, patients with NIHSS scores > 15 and ASPECTS scores ≤ 5 after successful reperfusion often indicate a poor prognosis. Biologically, experimental studies have found that in the pathological examination of proximal large vessel occlusion, early accumulation of platelets, fibrinogen, and neutrophils mostly occurs in the downstream microcirculation of the venous compartment. This phenomenon is referred to as downstream microvascular thromboinflammation (DMT). DMT can exacerbate cerebral ischemic injury, promote blood-brain barrier disruption, and facilitate hemorrhagic transformation [29–30]. This partially explains why neutrophil count is correlated with adverse clinical outcomes in these studies. This research also suggests that in patients with elevated neutrophil levels, irreversible cerebral infarction progresses rapidly after vessel occlusion, rendering reperfusion procedures often ineffective.

This study combined brain functional values to jointly evaluate the prognosis of patients with large-area cerebral infarction. In the QEEG, the regional DAR baseline in the FR group was higher than that in the successful reperfusion group ($P < 0.05$). Among them, DAR in the temporal region was identified as the optimal predictor for poor prognosis in patients with anterior circulation acute ischemic stroke before successful reperfusion. Combining baseline DAR in the temporal region with the affected side effectively predicts FR.

DAR is the relative ratio between slow and faster frequencies. Research has demonstrated the strongest negative correlation between δ power (1–3 Hz) and regional cerebral blood flow (rCBF), while α power (8–13 Hz) exhibits a relatively strong positive correlation with rCBF [19, 25]. The ratio between slow and fast frequencies essentially quantifies abnormalities, increasing the overall signal strength of slow activities, thus better reflecting the distribution, proportion, and amplitude changes of frequency bands. As cerebral perfusion decreases, brain cell metabolism also declines, cortical function deteriorates, and slow waves (delta or theta waves) increase in EEG recordings. Moreover, as perfusion decreases, cortical function declines and brain wave frequency slows down. Therefore, a higher slow wave index indicates more significant local brain tissue ischemia, indicating less local cerebral perfusion [17, 22, 27, 31]. In 1983, DAR was reported as the most reliable QEEG index for assessing poor prognosis in ischemic stroke from EEG recordings obtained from 11 electrodes [32]. In animal experiments, a close relationship between SEEG parameter alpha/delta power ratio and motor function recovery was observed following occlusion of the middle cerebral artery, monitored via EEG [33]. Some scholars have proposed that QEEG within the first 72 hours of stroke onset may be a powerful tool for predicting short-term and long-term prognosis in patients with acute ischemic stroke, with the highest prediction accuracy observed within 24 hours [23, 34]. Bentes et al. suggested that alpha, beta relative power, and DAR are optimal QEEG prediction indices [19, 34–35]. This study retrospectively analyzed QEEG within 24 hours postoperatively and concluded that DAR is an independent prognostic factor for FR, where a higher slow wave index indicates a poorer prognosis for patients.

In 2006, delta activity observed in patients with middle cerebral artery (MCA) infarction confirmed by MRI was found to originate from cortical regions within the blood supply area of the brain, particularly the anterior or lateral temporal lobe and lateral frontal lobe, with the highest DAR values observed in the temporal region [19, 36]. Subsequent studies reported that in patients with large vessel AIS, significant delta wave oscillations were observed in the ipsilateral hemisphere, particularly in the fronto-central and fronto-temporal electrodes, several hours after stroke onset, with the frontal region exhibiting the most pronounced average power [19, 37]. Although recent studies have utilized single-channel frontal DAR to assess AIS, the results have shown that frontal DAR can distinguish between AIS and non-AIS patients. Additionally, dynamic changes in

frontal DAR during AIS treatment can evaluate treatment efficacy [20, 25, 37]. However, there is currently no clear data on the prognostic value of quantitative EEG parameters in the frontal and temporal regions for anterior circulation large vessel AIS. This study compared the average power of T-DAR in the ipsilateral hemisphere between the FR group and the successful reperfusion group post-thrombectomy and found that it had the greatest predictive ability for FR. It was demonstrated that for regional QEEG indices, ipsilateral hemisphere T-DAR had the optimal predictive efficiency, with a 20% increase in FR occurrence rate for every doubling of DAR value. Moreover, the combination of baseline data, NIHSS score, ASPECTS score, and neutrophil ratio, plays an important role in AIS prognosis and clinical management decisions. Furthermore, it was suggested in 2013 that the presence of delta activity in the contralateral hemisphere, as measured by EEG and magnetoencephalography, is an important prognostic factor after stroke, indicating a significant deterioration in cerebral pathophysiology [38]. A study in 2021 by Ferreira et al. reported significant delta activity in the contralateral frontal region in rats after middle cerebral artery occlusion [39]. However, this study did not observe differences in contralateral regional DAR between the two groups, and further research and analysis are needed to elucidate the role and specific mechanisms of contralateral slow waves.

A limitation of this study is its single-center design. The study focused on patients with occlusion of the M1 segment of the middle cerebral artery and/or internal carotid artery, but due to variations in the time of onset, the location and size of infarction differed among patients. The study did not conduct a comparative analysis after stabilization of the condition post-treatment, which may reduce its representativeness. Furthermore, similar to other QEEG studies, effectively identifying and excluding EEG artifacts may pose a challenge. Artifacts such as muscle interference affecting faster activities or eye movement interference affecting delta activities may be present. The difficulty in removing artifacts may limit the utility of QEEG.

5. Conclusion

Current research suggests that factors influencing FR may include patients' clinical characteristics, the initiation time and intraoperative procedures of endovascular treatment, collateral circulation and hemodynamics, core infarct volume, brain edema, and baseline cerebral white matter hyperintensities. This study indicates that admission NIHSS score, ASPECTS score, and neutrophil ratio are independent predictors of FR. Additionally, among electrophysiological features, temporal single-channel Delta/Alpha Ratio (DAR) is an independent predictor of poor prognosis after mechanical thrombectomy in patients with anterior circulation large vessel occlusion ischemic stroke. The predictive model combining quantitative EEG data can enhance the prediction ability of FR. Therefore, the relevant information from EEG should be considered in the assessment of FR. Further investigation into electrophysiological predictors of FR after endovascular treatment can help formulate effective interventions to reduce FR occurrence and improve the post-treatment prognosis of AIS patients. More extensive multicenter prospective studies are warranted to validate these findings and develop a reliable FR risk prediction model.

Funding

This work was supported by the General Project of Chongqing Natural Science Foundation (Grant No. cstc2020jcyj-msxmX0017) and Major project of Science and Technology Research plan of Chongqing Education Commission (KJZD-M202100102)

Disclosure statement

The authors declare no conflict of interest.

References

[1] Vos T, Lim S S, Abbafati C, et al., 2020, Global Burden of 369 Diseases and Injuries in 204 Countries and Territories, 1990–2019: A Systematic Analysis for the Global Burden of Disease Study 2019. The Lancet, 396(10258): 1204–1222.

[2] Albers GW, Marks MP, Kemp S, et al., 2018, Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. The New England Journal of Medicine, 378(8): 708–718.

[3] Nogueira RG, Jadhav AP, Haussen DC, et al., 2018, Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. The New England Journal of Medicine, 378(1): 11–21.

[4] Zaidat OO, Yoo AJ, Khatri P, et al., 2013, Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. Stroke, 44(9): 2650–2663.

[5] Deng G, Xiao J, Yu H, et al., 2022, Predictors of Futile Recanalization after Endovascular Treatment in Acute Ischemic Stroke: A Meta-analysis. Journal of Neurointerventional Surgery, 14(9): 881–885.

[6] Zhou T, Yi T, Li T, et al., 2022, Predictors of Futile Recanalization in Patients Undergoing Endovascular Treatment in the DIRECT-MT Trial. Journal of Neurointerventional Surgery, 14(8): 752–755.

[7] Waqas M, Levy EI, 2021, Editorial. Toward Reducing Futile Recanalization in Stroke: Automated Prediction of Final Infarct Volume. Neurosurgical Focus, 51(1): E14.

[8] Pan H, Lin C, Chen L, et al., 2021, Multiple-Factor Analyses of Futile Recanalization in Acute Ischemic Stroke Patients Treated With Mechanical Thrombectomy. Frontiers in Neurology, 12: 704088.

[9] Lattanzi S, Norata D, Divani AA, et al., 2021, Systemic Inflammatory Response Index and Futile Recanalization in Patients with Ischemic Stroke Undergoing Endovascular Treatment. Brain Sciences, 11(9): 1164.

[10] Kaginele P, Beer FA, Joshi K C, et al., 2021, Brain Atrophy and Leukoaraiosis Correlate with Futile Stroke Thrombectomy. Journal of Stroke and Cerebrovascular Diseases, 30(8): 105871.

[11] Zang N, Lin Z, Huang K, et al., 2020, Biomarkers of Unfavorable Outcome in Acute Ischemic Stroke Patients with Successful Recanalization by Endovascular Thrombectomy. Cerebrovascular Diseases, 49(6): 583–592.

[12] Sivan-Hoffmann R, Gory B, Rabilloud M, et al., 2016, Patient Outcomes with Stent-Retriever Thrombectomy for Anterior Circulation Stroke: A Meta-Analysis and Review of the Literature. The Israel Medical Association Journal, 8(9): 561–566.

[13] Pedraza MI, Lera DM, Bos D, et al., 2020, Brain Atrophy and the Risk of Futile Endovascular Reperfusion in Acute Ischemic Stroke. Stroke, 51(5): 1514–1521.

[14] Kitano T, Todo K, Yoshimura S, et al., 2020, Futile Complete Recanalization: Patients Characteristics and its Time Course. Scientific Reports, 10(1): 4973.

[15] McCarthy DJ, Tonetti DA, Stone J, et al., 2021, More Expansive Horizons: A Review of Endovascular Therapy for Patients with Low NIHSS Scores. Journal of Neurointerventional Surgery, 13(2): 146–151.

[16] Hussein HM, Saleem MA, Qureshi AI, 2018, Rates and Predictors of Futile Recanalization in Patients Undergoing Endovascular Treatment in a Multicenter Clinical Trial. Neuroradiology, 60(5): 557–563.

[17] Liu XY, 2018, Clinical Electroencephalography. People's Medical Publishing House, Beijing.

[18] Marc NM, 1997, Assessment of Digital EEG, Quantitative EEG, and EEG Brain Mapping: Report of the American Academy of Neurology and the American Clinical Neurophysiology Society. Neurology, 49: 277–292.

[19] Finnigan S, Putten VMJ, 2013, EEG in Ischaemic Stroke: Quantitative EEG can Uniquely Inform (sub-)acute Prognoses and Clinical Management. Clinical Neurophysiology, 124(1): 10–19.

[20] Sheikh N, Wong A, Read S, et al., 2013, QEEG may Uniquely Inform and Expedite Decisions Regarding Intra-arterial Clot Retrieval in Acute Stroke. Clinical Neurophysiology, 124(9): 1913–1914.

[21] Foreman B, Claassen J, 2012, Quantitative EEG for the Detection of Brain Ischemia. Critical Care, 16(2): 216.

[22] Mishra M, Banday M, Derakhshani R, et al., 2011, A Quantitative EEG Method for Detecting Post Clamp Changes during Carotid Endarterectomy. Journal of Clinical Monitoring and Computing, 25(5): 295–308.

[23] Friedman D, Claassen J, 2010, Quantitative EEG and Cerebral Ischemia. Clinical Neurophysiology, 121(10): 1707–1708.

[24] Leon CNJ, Martin RJF, Damas LJ, et al., 2009, Delta-alpha Ratio Correlates with Level of Recovery after Neurorehabilitation in Patients with Acquired Brain Injury. Clinical Neurophysiology, 120(6): 1039–1045.

[25] Finnigan S, Wong A, Read S, 2016, Defining Abnormal Slow EEG Activity in Acute Ischaemic Stroke: Delta/alpha ratio as an Optimal QEEG Index. Clinical Neurophysiology, 127(2): 1452¬–1459.

[26] Finnigan SP, Rose SE, Chalk JB, 2006, Rapid EEG Changes Indicate Reperfusion after Tissue Plasminogen Activator Injection in Acute Ischaemic Stroke. Clinical Neurophysiology, 117(10): 2338–2339.

[27] Phan TG, Gureyev T, Nesterets Y, et al., 2012, Novel Application of EEG Source Localization in the Assessment of the Penumbra. Cerebrovascular Diseases, 33(4): 405–407.

[28] Powers W J, Rabinstein AA, Ackerson T, et al., 2018, Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke, 49(3): e46–e110.

[29] Desilles JP, Syvannarath V, Meglio DL, et al., 2018, Downstream Microvascular Thrombosis in Cortical Venules Is an Early Response to Proximal Cerebral Arterial Occlusion. Journal of the American Heart Association, 7(5): e007804.

[30] Laridan E, Denorme F, Desender L, et al., 2017, Neutrophil Extracellular Traps in Ischemic Stroke Thrombi. Annals of Neurology, 82(2): 223–232.

[31] Sundt TM, Sharbrough FW, Anderson RE, et al., 1974, Cerebral Blood Flow Measurements and Electroencephalograms during Carotid Endarterectomy. Journal of Neurosurgery, 41(3): 310–320.

[32] Sainio K, Stenberg D, Keskimäki I, et al., 1983, Visual and Spectral EEG Analysis in the Evaluation of the Outcome in Patients with Ischemic Brain Infarction. Electroencephalography and Clinical Neurophysiology, 56(2): 117–124.

[33] Zhang SJ, Ke Z, Li L, et al., 2013, EEG Patterns from Acute to Chronic Stroke Phases in Focal Cerebral Ischemic Rats: Correlations with Functional Recovery. Physiological Measurement, 34(4): 423–435.

[34] Schleiger E, Wong A, Read S, et al., 2016, Improved Cerebral Pathophysiology Immediately Following Thrombectomy in Acute Ischaemic Stroke: Monitoring via Quantitative EEG. Clinical Neurophysiology, 127(8): 2832–2833.

[35] Bentes C, Peralta AR, Viana P, et al., 2018, Quantitative EEG and Functional Outcome following Acute Ischemic Stroke. Clinical Neurophysiology, 129(8): 1680–1687.

[36] Jordan KG, 2004, Emergency EEG and Continuous EEG Monitoring in Acute Ischemic Stroke. Journal of Clinical Neurophysiology, 21: 341–352.

[37] Schleiger E, Sheikh N, Rowland T, et al., 2014, Frontal EEG delta/alpha Ratio and Screening for Post-stroke Cognitive Deficits: The Power of Four Electrodes. International Journal of Psychophysiology, 94(1): 19–24.

[38] Assenza G, Zappasodi F, Pasqualetti P, et al., 2013, A Contralesional EEG Power Increase Mediated by Interhemispheric Disconnection Provides Negative Prognosis in Acute Stroke. Restorative Neurology and Neuroscience, 31(2): 177–188.

[39] Ferreira LO, Mattos BG, Jóia DMV, et al., 2012, Increased Relative Delta Bandpower and Delta Indices Revealed by Continuous qEEG Monitoring in a Rat Model of Ischemia-Reperfusion. Frontiers in Neurology, 2021(12): 645138.

Integrated Services Platform of International Scientific Cooperation

Innoscience Research (Malaysia), which is global market oriented, was founded in 2016.Innoscience Research focuses on services based on scientific research. By cooperating with universities and scientific institutes all over the world, it performs medical researches to benefit human beings and promotes the interdisciplinary and international exchanges among researchers.

Innoscience Research covers biology, chemistry, physics and many other disciplines. It mainly focuses on the improvement of human health. It aims to promote the cooperation, exploration and exchange among researchers from different countries. By establishing platforms, Innoscience integrates the demands from different fields to realize the combination of clinical research and basic research and to accelerate and deepen the international scientific cooperation.

Cooperation Mode

Clinical Workers

In-service Doctors

Foreign Researchers

China Collaborators

Oversea Collaborators

Hospital

University

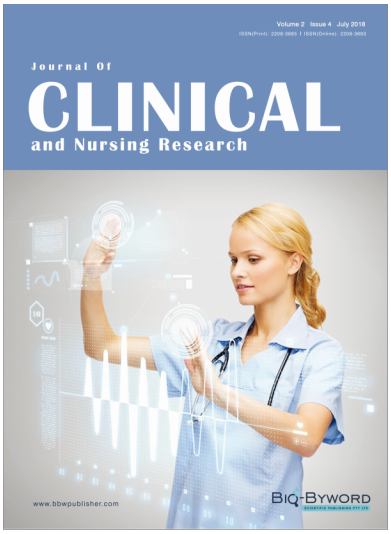
Scientific institutions

Our Journals

The *Journal of Architectural Research and Development* is an international peer-reviewed and open access journal which is devoted to establish a bridge between theory and practice in the fields of architectural and design research, urban planning and built environment research.

Topics covered but not limited to:

- Architectural design
- Architectural technology, including new technologies and energy saving technologies
- Architectural practice
- Urban planning
- Impacts of architecture on environment



Journal of Clinical and Nursing Research (JCNR) is an international, peer reviewed and open access journal that seeks to promote the development and exchange of knowledge which is directly relevant to all clinical and nursing research and practice. Articles which explore the meaning, prevention, treatment, outcome and impact of a high standard clinical and nursing practice and discipline are encouraged to be submitted as original article, review, case report, short communication and letters.

Topics covered by not limited to:

- Development of clinical and nursing research, evaluation, evidence-based practice and scientific enquiry
- Patients and family experiences of health care
- Clinical and nursing research to enhance patient safety and reduce harm to patients
- Ethics
- Clinical and Nursing history
- Medicine

Journal of Electronic Research and Application is an international, peer-reviewed and open access journal which publishes original articles, reviews, short communications, case studies and letters in the field of electronic research and application.

Topics covered but not limited to:

- Automation
- Circuit Analysis and Application
- Electric and Electronic Measurement Systems
- Electrical Engineering
- Electronic Materials
- Electronics and Communications Engineering
- Power Systems and Power Electronics
- Signal Processing
- Telecommunications Engineering
- Wireless and Mobile Communication