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ORIGINAL RESEARCH

Correlation Analysis of Serum 3-NT, NPASDP-4, and S100β Protein Levels with Cognitive Function in Patients Diagnosed with Cerebral Infarction

Zuhao Xu, MM; Xiaorong Weng, MM; Liping Cao, MD; Disai Liang, MD; Fengshan Zeng, MM; Shaolan Chen, BM; Yi Zhang, BM; Haiwen Huang, BM; Min Gao, MD

ABSTRACT

Objective • To observe the levels of serum 3-nitrotyrosine (3-NT), neuronal PAS domain protein 4 (NPASDP-4), and S100β protein in patients diagnosed with cerebral infarction and analyze their correlation with cognitive dysfunction in these patients.

Methods • The study included a cohort of 158 patients suffering from cerebral infarction who were admitted to the Liwan District Hospital of Traditional Chinese Medicine between January 2021 and December 2022. After stabilizing vital signs, all patients underwent the Montreal Cognitive Assessment (MoCA) to assess their cognitive function. Based on the assessment results, they were divided into two groups: the cognitive dysfunction group (121 cases) and the normal cognitive function group (37 cases). The baseline characteristics and serum levels of 3-NT, neuronal PAS domain protein 4 (NPASDP-4), and S100β protein were compared in the patient cohorts. Furthermore, the correlation between these three indicators and cognitive function in patients suffering from cerebral infarction was analyzed. A logistic regression model was constructed to analyze how serum levels of 3-NT, NPASDP-4, and S100β protein levels affected cognitive function in patients suffering from cerebral infarction. ROC curve analysis was conducted to assess the predictive value of serum 3-NT, NPASDP-4, and S100β protein levels for cognitive function in patients suffering from cerebral infarction.

Results • Among the 158 patients with cerebral infarction, 121 (76.58%) had cognitive dysfunction, while 37 (23.42%) had normal cognitive function. The levels of 3-NT, NPASDP-4, and S100β protein were found to be significantly higher in the cognitive dysfunction group compared to the normal cognitive function group (t = 5.788, 7.774, 6.460; P = .000, .000, .000). The point-biserial correlation analysis results showed a positive correlation between serum levels of 3-NT, NPASDP-4, and S100β protein and the occurrence of cognitive dysfunction in patients suffering from cerebral infarction (r=0.420, 0.529, 0.424; P = .000, .000, .000). The logistic regression model demonstrated that serum levels of 3-NT(95%*CI*: 1.299-2.603), NPASDP-4(95%*CI*: 1.487-3.386), and S100β protein(95%*CI*: 1.153-8.746) were risk factors for cognitive dysfunction in patients suffering from cerebral infarction (*OR*=1.839, 2.244, 1.429; P = .001, .000, .240). ROC curve analysis demonstrated that serum 3-NT, NPASDP-4, and S100β protein levels exhibited a certain predictive value for cognitive function in patients with cerebral infarction (AUC = 0.789, 0.881, 0.820).

Conclusion • Serum levels of 3-NT, NPASDP-4, and S100β protein are closely related to the cognitive function of patients with cerebral infarction, and abnormal changes in these levels may exacerbate cognitive dysfunction in these patients. (*Altern Ther Health Med.* 2024;30(4):54-59)

Zuhao Xu, MM, Associate chief physician**; Disai Liang, MD,** Chief physician**; Fengshan Zeng, MM,** Resident doctor**; Shaolan Chen, BM; Yi Zhang, BM; Haiwen Huang, BM; Min Gao, MD,** Chief Physician**;** Department of Neurology, Fifth Clinical Medical College, Guangzhou University of Chinese Medicine, Guangzhou, China; **Xiaorong Weng, MM,** Associate chief physician**;** Liwan District Hospital of Traditional Chinese Medicine, Guangzhou, China; **Liping Cao, MD,** Associate Chief Physician**;** Department of Neurology, The First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine, Guizhou, China.

Corresponding author: Min Gao, MD
E-mail: 37279883@qq.com

INTRODUCTION

Cerebral infarction is a common clinical cerebrovascular disorder characterized by a high incidence rate, disability rate, and mortality rate. Its main clinical manifestations include facial paralysis, language impairments, sensory deficits, etc., which can lead to varying degrees of cognitive

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dysfunction in patients.[1,2] Studies have indicated that cognitive function affects limb function, social activities, and overall well-being in patients with cerebral infarction.[3] Therefore, accurate assessment of cognitive function in such patients and the timely implementation of corresponding interventions are of great significance for improving the prognosis. 3-nitrotyrosine (3-NT) is a protein oxidation product and serves as an important marker for evaluating oxidative stress levels in clinical settings.[3] Relevant research has highlighted the critical role of 3-NT in the occurrence and progression of unstable atherosclerotic plaques and is also one of the key contributing factors in the progression of ischemic brain diseases.[4] Neuronal PAS domain protein 4 (NPASDP-4) is a transcription factor that regulates neuronal growth and development, particularly playing a crucial role in inhibitory synapse development and participating in stress-induced hippocampal damage, leading to cognitive impairment.[5,6] S100β protein belongs to calcium-binding acidic proteins and is widely distributed in glial cells of the central nervous system, capable of reflecting early brain injury conditions.[7] Based on the above research, it is inferred that serum levels of 3-NT, NPASDP-4, and S100β protein may play a certain role in cognitive impairment in patients with cerebral infarction. Therefore, this study aimed to examine the levels of serum 3-NT, NPASDP-4, and S100β protein in patients suffering from cerebral infarction and analyze their correlation with cognitive dysfunction. The purpose is to provide a reference for the early evaluation of cognitive function and the formulation of treatment plans for patients with this condition. The results of the study are presented below.

MATERIALS AND METHODS

Study Subjects

A cohort of 158 patients with cerebral infarction were admitted to the Liwan District Hospital of Traditional Chinese Medicine between January 2021 and December 2022 were included in the study. Inclusion criteria were as follows: (1) Patients with cerebral infarction meeting the relevant diagnostic criteria outlined in *Diagnostic Essentials of Various Cerebrovascular Diseases*[8] and confirmed by imaging examination; (2) First onset of cerebral infarction; (3) Patients with clear consciousness and normal cognitive function before the onset of the disease; (4) Patients whose vital signs stabilized after acute-phase treatment; (5) Patients or their family members provided informed consent and were willing to cooperate in the study. Exclusion criteria were as follows: (1) History of cranial or brain trauma; (2) Concomitant central nervous system infections, hydrocephalus, intracranial tumors, or subarachnoid hemorrhage; (3) Coexisting psychiatric disorders such as mental retardation, bipolar disorder, schizophrenia, anxiety disorder, or depression; (4) Coexisting thyroid dysfunction or other endocrine system disorders; (5) History of abuse of antipsychotic drugs; (6) Coexisting malignant tumors or other severe diseases.

Methods

Cognitive Function Assessment. After stabilizing the vital signs of the patients, the cognitive function of the patients was evaluated using the Montreal Cognitive Assessment (MoCA).[9] The MoCA consists of seven domains: naming (3 points), orientation (6 points), delayed recall (5 points), language (3 points), attention (6 points), visuospatial and executive abilities (5 points), and abstraction (2 points), resulting in a total score of 30 points. A higher score reflects better cognitive function. Following the study by Gong Juan et al.,[10] individuals with a score of less than 26 points will be considered to have cognitive impairment, while those with a score of 26 points or higher will be considered to have normal cognitive function. Out of the 158 patients with cerebral infarction, 121 cases (76.58%) experienced cognitive dysfunction, while 37 cases (23.42%) had normal cognitive function.

Detection of Serum Levels of 3-NT, NPASDP-4, and S100β Protein

Upon admission, each patient underwent venipuncture to collect a 4ml blood sample and then subjected to centrifugation at 3500 rpm for 15 minutes to isolate the upper layer, which contains the serum. The levels of 3-NT, NPASDP-4, and S100β protein were determined using a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA). The test kits used were from Wuhan Huamei Biotech Co., Ltd., and all relevant procedures were strictly carried out according to the instructions provided with the test kits.

Outcome Measures

(1) The cognitive function status in patients with cerebral infarction was observed after stabilizing their vital signs. (2) Patients who developed cognitive dysfunction were included in the cognitive dysfunction group, while patients with normal cognitive function were included in the normal cognitive function group. Baseline data were compared within the two groups, including gender (male, female), age, body mass index (BMI), underlying conditions (diabetes, hypertension, hyperlipidemia), smoking history (yes, no), alcohol consumption history (yes, no), and blood lipid levels [total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C)]. Blood samples for lipid level measurements were collected in sterile tubes containing anticoagulants, inverted 5-10 times to mix thoroughly, and then analyzed using an automated biochemistry analyzer (Beckman Coulter, AU5800) to measure TC, TG, LDL-C, and HDL-C levels. (3) Comparison of serum levels of 3-NT, NPASDP-4, and S100β protein between the two groups.

Statistical analysis

Data processing was conducted using Statistic Package for Social Science (SPSS) version 23.0 software (IBM, Armonk, NY, USA). Measurement data were presented as $\bar{x} \pm s$ and analyzed using *t* tests. Count data were presented as n (%) and

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Table 1. Comparison of Baseline Characteristics between the Cognitive Dysfunction Group and Normal Cognitive Function Group

Indicators		Cognitive Dysfunction Group (n = 121)	Normal Cognitive Function Group (n = 37)	Statistical values	*P* value
Gender(%)	Male	63 (52.07)	20 (54.05)	χ^2=0.045	.832
	Female	58 (47.93)	17 (45.95)		
Age ($\bar{x} \pm s$, year)		64.86±5.73	65.12±6.08	t=0.238	.812
BMI ($\bar{x} \pm s$, kg/m^2)		25.78±2.13	25.89±2.21	t=0.273	.786
Underlying conditions (%)	Diabetes	17 (14.05)	3 (8.11)	χ^2=0.447	.504
	Hypertension	39 (32.23)	8 (21.62)	χ^2=1.526	.217
	Hyperlipidemia	21 (17.36)	5 (13.51)	χ^2=0.304	.581
Smoking history(%)	Yes	32 (26.45)	7 (18.92)	χ^2=0.864	.353
	No	89 (73.55)	30 (81.08)		
Alcohol consumption history(%)	Yes	28 (23.14)	6 (16.22)	χ^2=0.804	.370
	No	93 (76.86)	31 (83.78)		
TC ($\bar{x} \pm s$, mmol/L)		4.94±0.87	4.86±0.82	t =0.496	.621
TG ($\bar{x} \pm s$, mmol/L)		1.61±0.63	1.58±0.60	t =0.256	.798
LDL-C ($\bar{x} \pm s$, mmol/L)		3.02±0.75	2.97±0.71	t =0.359	.720
HDL-C ($\bar{x} \pm s$, mmol/L)		1.38±0.48	1.43±0.53	t =0.541	.589

analyzed using the χ^2 test. The correlation between categorical variables and continuous variables was analyzed using point-biserial correlation analysis. A logistic regression model was constructed to assess the influence of serum levels of 3-NT, NPASDP-4, and S100β protein on cognitive function in patients suffering from cerebral infarction. ROC curve analysis was conducted to assess the predictive value of serum levels of 3-NT, NPASDP-4, and S100β protein for cognitive function in patients suffering from cerebral infarction. Statistical significance was set at $P < .05$ for all analyses.

RESULTS

Comparison of Baseline Characteristics between the Cognitive Dysfunction Group and Normal Cognitive Function Group

No statistically significant differences were observed in baseline characteristics, including gender, age, body mass index (BMI), underlying conditions, smoking history, alcohol consumption history, TC, TG, LDL-C, and HDL-C between the normal cognitive function group and the cognitive dysfunction group ($P > .05$). (Table 1)

Comparison of Serum Levels of 3-NT, NPASDP-4, and S100β Protein between the Cognitive Dysfunction Group and Normal Cognitive Function Group

The cognitive dysfunction group had significantly higher levels of 3-NT, NPASDP-4, and S100β protein compared to the normal cognitive function group ($P < .05$). (Table 2 and Figure 1)

Correlation between Serum Levels of 3-NT, NPASDP-4, and S100β Protein and Cognitive Function in Patients Suffering from Cerebral Infarction

The point-biserial correlation analysis results indicated that serum levels of 3-NT, NPASDP-4, and S100β protein showed a positive correlation with the occurrence of cognitive dysfunction in patients suffering from cerebral infarction ($r > 0$, $P < .05$). (Table 3 and Figure 2)

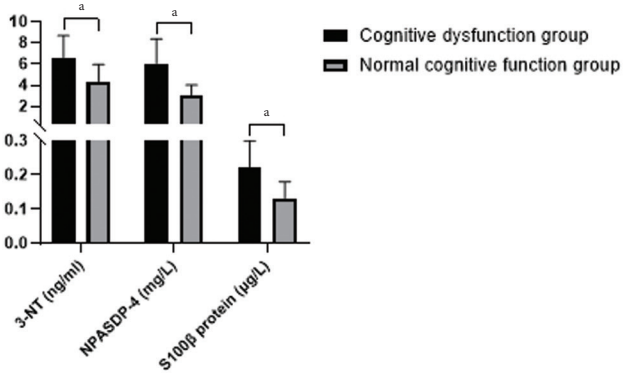
Table 2. Comparison of Serum Levels of 3-NT, NPASDP-4, and S100β Protein between the Cognitive Dysfunction Group and Normal Cognitive Function Group ($\bar{x} \pm s$)

Groups	3-NT (ng/ml)	NPASDP-4 (mg/L)	S100β Protein (μg/L)
Cognitive Dysfunction Group (n=121)	6.51±2.17	6.04±2.32	0.22±0.08
Normal Cognitive Function Group (n=37)	4.26±1.69	2.98±1.04	0.13±0.05
t	5.788	7.774	6.460
P value	.000	.000	.000

Indicators	Cognitive Dysfunction Group (n = 121)	Normal Cognitive Function Group (n = 37)	t	*P* value
3-NT (ng/ml)	6.51±2.17	4.26±1.69[a]	5.788	.000
NPASDP-4	6.04±2.32	2.98±1.04[a]	7.774	.000
S100β Protein (μg/L)	0.22±0.08	0.13±0.05[a]	6.460	.000

[a]Compared to the cognitive dysfunction group, $P < .05$

Figure 1. Comparison of Serum Levels of 3-NT, NPASDP-4, and S100β Protein between the Cognitive Dysfunction Group and Normal Cognitive Function Group.



[a]$P < .001$

Table 3. Correlation between Serum Levels of 3-NT, NPASDP-4, and S100β Protein and Cognitive Function in Patients Suffering from Cerebral Infarction (r/P).

Indicators	r	*P* value
3-NT	0.420	.000
NPASDP-4	0.529	.000
S100β Protein	0.424	.000

Figure 2. Correlation between Serum Levels of 3-NT, NPASDP-4, and S100β Protein and Cognitive Function in Patients Suffering from Cerebral Infarction.

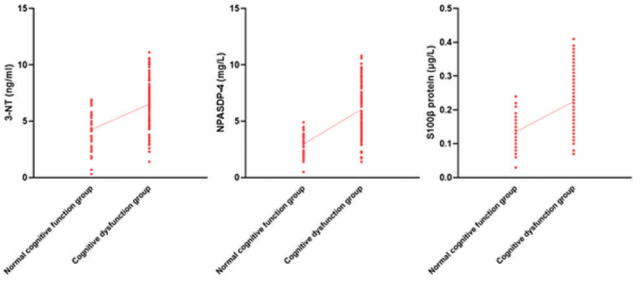


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Table 4. Impact of Serum Levels of 3-NT, NPASDP-4, and S100β Protein on Cognitive Function in Patients with Cerebral Infarction

Independent variables	*β*	Standard error	*Wald* χ^2	*P* value	*OR*	95%*CI*
3-NT	0.609	0.177	11.789	.001	1.839	1.299-2.603
NPASDP-4	0.808	0.210	14.809	.000	2.244	1.487-3.386
S100β Protein	16.195	3.386	22.879	.000	1.429	1.153-8.746
Constant	-1.656	1.409	1.382	.240	0.191	-

Figure 3. Clinical Feature Forest Plot Based on Multivariate Logistic Regression Analysis.

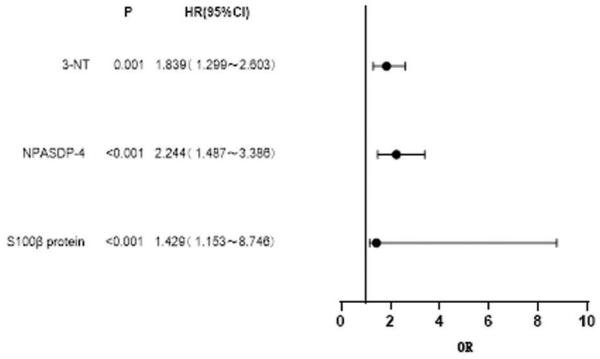

Figure 4. ROC Curve of Serum Levels of 3-NT, NPASDP-4, and S100β Protein for Predicting Cognitive Function in Patients Suffering from Cerebral Infarction.

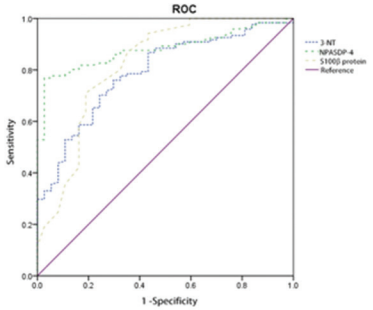

Table 5. Predictive Value of Serum Levels of 3-NT, NPASDP-4, and S100β Protein for Cognitive Function in Patients with Cerebral Infarction.

Test variables	AUC	Standard error	*P* value	95%*CI*	cut-off value	Sensitivity	Specificity	Jaccard Index
3-NT	0.789	0.040	.000	0.711-0.867	4.820 ng/ml	0.785	0.649	0.434
NPASDP-4	0.881	0.027	.000	0.828-0.933	3.660 mg/L	0.860	0.703	0.563
S100β Protein	0.820	0.045	.000	0.732-0.908	0.165 μg/L	0.802	0.676	0.478

Impact of Serum Levels of 3-NT, NPASDP-4, and S100β Protein on Cognitive Function in Patients Suffering from Cerebral Infarction

Using serum levels of 3-NT, NPASDP-4, and S100β protein as independent variables (all considered as continuous data) and the cognitive function status of patients with cerebral infarction as the dependent variable (1 = cognitive dysfunction, 0 = normal cognitive function), a logistic regression model was established. The results showed that serum levels of 3-NT(95%*CI*: 1.299-2.603), NPASDP-4(95%*CI*: 1.487-3.386), and S100β protein (95%*CI*: 1.153-8.746) were risk factors for cognitive dysfunction in patients with cerebral infarction (*OR* >1, *P* < .05). (Table 4 and Figure 3)

Predictive Value of Serum Levels of 3-NT, NPASDP-4, and S100β Protein for Cognitive Function in Patients Suffering from Cerebral Infarction

Using serum levels of 3-NT, NPASDP-4, and S100β protein as test variables and the cognitive function status of patients with cerebral infarction as the state variable (1=cognitive dysfunction, 0=normal cognitive function), ROC curves were generated (Figure 4). The results showed that serum levels of 3-NT, NPASDP-4, and S100β protein had certain predictive value for cognitive function in patients with cerebral infarction (AUC=0.789, 0.881, 0.820). (Table 5)

DISCUSSION

Mechanisms of Cognitive Dysfunction in Patients Suffering from Cerebral Infarction

Cognitive function refers to an individual's ability to perceive, acquire, store, and intelligently process information, including language comprehension, calculation, memory, executive functions, and so on. Cognitive dysfunction, on the other hand, refers to the pathological process in which the above functions are impaired, resulting in a single or a series of functional changes.[10] After the occurrence of cerebral infarction, a large area of infarction can lead to abnormal brain cortical structure and function. The cerebral cortex is the higher center of consciousness in the brain, and damage to the cortex will inevitably lead to impairment of consciousness, thereby causing varying degrees of cognitive dysfunction.[11] In recent years, advancements in medical technology have led to a reduction in the mortality rate of patients with cerebral infarction. However, the number of patients with cognitive dysfunction has gradually increased. If effective intervention measures are not taken promptly, cognitive dysfunction can progress to dementia. Therefore, early assessment of cognitive function in patients suffering from cerebral infarction is of great significance in guiding subsequent treatment.

Relationship between Serum 3-NT Levels and Cognitive Function in Patients Suffering from Cerebral Infarction

Oxidative stress plays an important role in cerebral amyloid angiopathy, cerebral dysfunction, and cerebral arteriosclerosis. Oxidative stress can disrupt the metabolism of nitric oxide, which is dependent on vascular endothelial cells, thereby affecting cerebral vascular relaxation function and disrupting the balance between pro-inflammatory and anti-inflammatory responses, as well as oxidative and antioxidative processes, leading to cerebral vascular damage.[12,13] 3-NT is a relatively stable marker used in clinical assessment of oxidative stress, and it accurately reflects the level of oxidative stress in the body.[14] Previous studies have suggested that 3-NT promotes atherosclerosis and is involved in the formation of unstable plaques.[15] The study findings demonstrated that patients with cerebral infarction and

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cognitive dysfunction had significantly elevated serum levels of 3-NT compared to those with normal cognitive function. Furthermore, the findings of point-biserial correlation analysis confirmed a positive correlation between 3-NT levels and the occurrence of cognitive dysfunction in patients with cerebral infarction. In other words, higher serum 3-NT concentrations were associated with more severe cognitive dysfunction in patients. As a product of oxidative stress, 3-NT can directly affect the denaturation of intracellular proteins and proteinases, damage DNA, induce chronic inflammatory reactions, disrupt the blood-brain barrier, aggravate cerebral vascular dysfunction, and lead to the necrosis and apoptosis of cholinergic neurons and other intracranial neurons, ultimately affecting cognitive function in patients.

Relationship between Serum NPASDP-4 Levels and Cognitive Function in Patients Suffering from Cerebral Infarction

NPASDP-4 is mainly present in the hippocampal tissue as an activity-dependent transcription factor. It plays a vital regulatory role in various processes, including synaptic plasticity transcriptional regulation, dendritic cell skeleton formation, and neuronal cell survival in the hippocampal tissue, exhibiting certain neuroprotective effects.[16] Under the action of intracellular calcium ions (Ca2+), NPASDP-4 can selectively induce inhibitory synapse formation and regulate function-dependent genes, promoting the restoration of inhibitory synapses under pathological conditions.[17] An animal study conducted by Laurence[18] suggested that the level of NPASDP-4 in neurons is related to cognitive function in mice. The study findings indicated that the serum levels of NPASDP-4 were elevated in the cognitive dysfunction group compared to the normal cognitive function group. Moreover, the logistic regression analysis indicated that elevated serum NPASDP-4 levels were a risk factor for the occurrence of cognitive dysfunction in patients with cerebral infarction. After cerebral infarction, the brain tissue experiences severe hypoxia and ischemia, leading to the release of a large amount of excitatory amino acids at abnormal concentrations, causing ion influx into neurons and neuronal damage, thereby triggering the expression of NPASDP-4. However, NPASDP-4 can further aggravate brain hypoxia and ischemia in patients with cerebral infarction, severely disrupting the physiological and psychological balance of the body, inhibiting the generation of neuronal cells, causing morphological changes in the hippocampal tissue, and consequently resulting in cognitive dysfunction.

Relationship between Serum S100β Protein Levels and Cognitive Function in Patients Suffering from Cerebral Infarction

S100β protein is primarily produced by astrocytes in the central nervous system and is a major component of glial cell cytoplasm. It participates in the regulation of various biological functions, accurately reflecting glial cell function, and has an impact on the interaction between glial cells and neurons. Additionally, the S100β protein can regulate the levels of inflammatory cytokines and nitric oxide synthase, thereby modulating neuronal inflammatory damage.[19,20] A study by Ozturk et al.[21] demonstrated a significant association between S100β protein levels and cognitive dysfunction following robot-assisted laparoscopic radical prostatectomy. Other research also indicated that serum S100β protein levels in patients suffering from cognitive dysfunction following cerebral infarction when compared to those with normal cognitive function, and these studies also established a strong correlation between serum S100β protein levels and cognitive function in these patients.[22] The study findings indicated that the cognitive dysfunction group exhibited significantly higher serum S100β protein levels than the normal cognitive function group. Moreover, elevated serum S100β protein levels were identified as a risk factor for cognitive dysfunction in patients suffering from cerebral infarction, which aligns with the findings of the aforementioned studies. Under normal physiological concentrations, S100β protein has inhibitory effects on glutamate toxicity and acts as an antioxidant, promoting axonal growth and repair in neurons and exerting neuroprotective effects. However, when S100β protein levels are abnormally elevated, it can become neurotoxic, exacerbate oxidative stress and inflammatory responses, and cause neuronal death and cell apoptosis. During the occurrence of cerebral infarction, the disruption of the blood-brain barrier, central nervous system demyelination, activation and proliferation of brain glial cells, neuronal damage, and spontaneous inflammatory reactions may lead to an increase in S100β protein content in cerebrospinal fluid, which then enters the bloodstream. This process triggers a cascade of events, including the release of a large amount of calcium ions (Ca2+), elevated nitric oxide levels, and the generation of free radicals and other harmful substances, ultimately leading to neuronal apoptosis and cognitive dysfunction. Finally, the ROC curve analysis confirmed that serum levels of 3-NT, NPASDP-4, and S100β protein can serve as predictors for cognitive function in patients suffering from cerebral infarction. The mechanism underlying cognitive impairment in patients with cerebral infarction is complex. Clinically, early prediction of the risk of cognitive dysfunction can be achieved by observing serum markers such as 3-NT, NPASDP-4, and S100β protein. High-risk patients can then be actively treated with neurotrophic drugs and neuroprotective agents to prevent the occurrence of cognitive dysfunction.

In conclusion, serum levels of 3-NT, NPASDP-4, and S100β protein are closely related to the cognitive status of patients with cerebral infarction. Abnormal changes in the levels of these markers can exacerbate cognitive dysfunction in patients. Clinically, the observation of serum 3-NT, NPASDP-4, and S100β protein levels can serve as a predictive indicator for patients' cognitive function and take early intervention measures to improve patient prognosis.

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CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

AUTHOR CONTRIBUTIONS

ZX, XW, and MG designed the study and performed the experiments, LC, DL, and FZ collected the data, SC, YZ, and HH analyzed the data, and ZX, XW, and MG prepared the manuscript. All authors read and approved the final manuscript.

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This study did not receive any funding in any form.

ETHICAL COMPLIANCE

This study was approved by the ethics committee of Fifth Clinical Medical College, Guangzhou University of Chinese Medicine. Signed written informed consent was obtained from the patients and/or guardians.

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