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Discussing the predictive value of serum alkaline phosphatase combined with the NINDS-CSN 5-minute test scale for cognitive impairment after acute ischemic stroke

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ABSTRACT

Background: Post-stroke cognitive impairment (PSCI) is one of the causes of the current disease burden of stroke. Early prediction of it is conducive to early intervention and treatment. Research has found that serum alkaline phosphatase (ALP) is involved in the pathophysiological process of stroke. Meanwhile, the NINDS-CSN 5-minute test can be used for early screening of PSCI. This study aims to explore whether the combination of ALP and the NINDS-CSN 5-minute test scale has predictive value for PSCI.

Method: This prospective cohort study included 100 patients who were initially diagnosed with acute ischemic stroke (AIS) at the Neurology Department of Chengfei Hospital from January 2023 to May 2024 were selected as the research subjects. Serum ALP tests and the NINDS-CSN 5-minute test were completed within 2 weeks after the onset of the disease. Three months and six months after AIS, the MMSE and NINDS-CSN 5-minute assessments were conducted again to determine whether PSCI had occurred. Statistical analysis was performed using SPSS 26.0 software. Logistic regression analysis was employed to explore the influencing factors of PSCI. The predictive efficacy of serum ALP and the NINDS-CSN5-minute test for PSCI was evaluated through the ROC curve.

Result: The results of this study revealed that both serum ALP levels and the NINDS-CSN 5-minute assessment scale significantly influenced the prediction of PSCI (ALP: $P < 0.01$; NINDS-CSN 5-minute: $P < 0.01$), with both showing a strong association with cognitive dysfunction following ischemic stroke. However, no significant differences were found in terms of age, gender, or infarction location. When evaluated individually, ALP demonstrated a high diagnostic value for predicting PSCI (AUC 0.835; 95%CI: 75.39% - 91.69%), while the NINDS-CSN 5-minute assessment had a relatively lower diagnostic value (AUC 0.780; 95%CI: 69.04% - 86.92%). Notably, the combination of ALP and the NINDS-CSN 5-minute test yielded a superior diagnostic performance (AUC: 0.905; 95%CI: 84.6%-96.2%), enhancing the predictive accuracy for PSCI.

Conclusion: The Combination of ALP and NINDS-CSN 5-minute test scale has a relatively high diagnostic value for predicting cognitive impairment after PSCI.

Keywords: alkaline phosphatase; NINDS-CSN 5-minute; Stroke; Cognitive impairment; Influencing factors .
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INTRODUCTION

Ischemic strokes account for 60–70% of all strokes, which are a frequent cerebrovascular illness and one of the world's major causes of mortality and disability.[1] China now has the highest lifetime risk of stroke and the highest disease burden worldwide.[2] About one-third of stroke patients suffer from post-stroke cognitive impairment (PSCI), which has a significant negative impact on their survival time and quality of life.[3] Additionally, PSCI contributes significantly to the overall burden of stroke and has emerged as a prominent area of interest for global stroke research and clinical care.[4] With an incidence rate as high as 58%, cognitive impairment is a typical stroke consequence that has a major influence on patients' everyday lives and social adaptation. According to studies, PSCI not only elevates the risk of dementia but also lowers the efficacy of rehabilitative therapies and increases the risk of psychiatric conditions like anxiety and depression.[5] PSCI, which can range from mild to severe, is quite frequent following a stroke, particularly in the first year. Up to one-third of stroke victims develop dementia within five years, despite the fact that cognitive impairment can occasionally be reversed in the early stages following a stroke.[6] Since there is presently no cure for PSCI, early detection and prevention are especially crucial. Neuropsychological evaluation measures like the Mini-Mental State Examination (MMSE), the Montreal

Cognitive Evaluation (MoCA), and the NINDS-CSN 5-minute test are currently used in clinical practice to screen for and identify PSCI early. The NINDS-CSN 5-minute test is one of the easiest of them to finish quickly and easily. However, there are several drawbacks to utilizing this method alone to evaluate post-stroke cognitive impairment, including low sensitivity and an easy correlation with the patient's educational attainment.[7] Therefore, exploring biomarkers that can evaluate PSCI is of great significance. Recently, many researchers have closely linked serum alkaline phosphatase with PSCI. Alkaline phosphatase (ALP) is an enzyme that catalyzes the hydrolysis of pyrophosphate and is often used as a marker for bone, liver, and obesity-related diseases. Moreover, studies have found that ALP is involved in the pathophysiological process of stroke.[8] According to studies, persons who have had an acute ischemic stroke may be at an independent risk for cognitive impairment if their baseline serum ALP level is relatively high.[9] Another study, however, found that although the serum ALP levels were higher in AIS patients, the specificity was 78.9% and the sensitivity was just 49.5%. Furthermore, there was no discernible relationship between this and the functional outcome or the NIHSS score a year later.[10] Therefore, this study aims to explore whether the combination of ALP and the NINDS-CSN 5-minute test scale can enhance the predictive value for cognitive impairment after ischemic stroke, providing a reliable basis for earlier clinical intervention and treatment, reducing the impact of cognitive impairment on patients, and improving their quality of life.

METHODS

Study participant

This study included 100 patients with acute ischemic stroke (AIS) who were first diagnosed in the Department of Neurology of Chengfei Hospital between January 2023 and May 2024 and had no cognitive impairment at the time of enrollment (with no previous diagnosis of acute cerebral infarction). Among them, 45 cases had cognitive impairment, 54 cases did not have cognitive impairment, and 1 case was lost to follow-up.

Inclusion criteria of this study include (1) diagnosis of ischemic stroke that meets the criteria outlined in the Chinese Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke 2018 issued by the Neurology Branch of the Chinese Medical Association;[11] (2) confirmation of diagnosis via magnetic resonance imaging (MRI) or other imaging techniques, along with assessment of neurological deficits; (3) time since onset less than 14 days; and (4) complete clinical data available. While the exclusion criteria of this study includes (1) patient wth history of transient ischemic attack (TIA), prior stroke, or traumatic brain injury; (2) severe liver or kidney dysfunction, severe inflammation, or malignancy; (3) history of cognitive impairment due to other causes such as Alzheimer's disease or depression; (4) history of psychiatric disorders or impaired consciousness preventing cooperation; or (5) refusal by the patient or family members to participate.

Eligible patients will be divided into the "Post-stroke Cognitive Impairment Group" (coded with "Yes") and the "Post-stroke Non-cognitive Impairment Group" (coded with "No") based on whether they experienced cognitive impairment or not.

Collection of basic information

After enrollment, basic clinical data were collected, including age, gender, and infarction location. Within two weeks after the onset of the disease, the fasting serum ALP and the 5-minute test score of the NINDS-CSN were collected. The cognitive function assessment results of all study subjects were collected 3 months and 6 months after the stroke.

Serological Indicators (ALP)

All the research subjects had their venous blood samples (5 ml) collected on an empty stomach within 2 weeks after ischemic stroke. The ALP level was detected using the NPP substrate-AMP buffer solution method (Beckman AU5800 automatic biochemical analyzer). The normal reference range is 50 - 135 U/ml.

Cognitive function assessment

Cognitive function outcomes were evaluated for all study subjects at 3 months and 6 months after the stroke. Two neurology doctors who have undergone strict training used the NINDS-CSN 5-minute and MMSE assessment methods to evaluate the patients' cognitive status. The content of the scale includes 9 dimensions: executive function, language fluency, orientation, calculation, abstraction, delayed recall, visual perception, naming, and attention. The NINDS-CSN 5-minute total score is 12 points. An 8-point score is the cut-off value. A score lower than 8 indicates the presence of cognitive dysfunction. The total score of the MMSE scale ranges from 0 to 30. The normal threshold classification criteria are as follows: illiterate > 17 points, primary school graduate > 20 points, junior high school graduate and above > 24 points. A score lower than the threshold value for the education level group indicates the presence of cognitive dysfunction. Outcome determination: Satisfying any one of the conditions is sufficient to consider the presence of post-stroke cognitive impairment.

Statistical analysis

The SPSS 26.0 software was used to perform the independent sample t-test, Wilcoxon rank sum test, and chi-square test. The t-test was performed if the measurement data had a normal distribution; if not, the rank sum test was utilized. The chi-square test was used to assess the count data. After an ischemic stroke, the factors that contribute to cognitive dysfunction were examined using logistic regression analysis. The statistical results showed that $P < 0.05$ indicated that the data differences were statistically significant. The application (ROC) curve was used to evaluate the predictive value of serum ALP and NINDS-CSN 5-minute for cognitive dysfunction after ischemic stroke.

RESULTS

Basic Information of the Study Subjects

Based on the analysis of the basic data of the research subjects, there was no statistically significant difference in age, gender, and the distribution of infarction sites between the stroke post-cognitive impairment group and the stroke post-non-cognitive impairment group ($P > 0.05$), as shown in **Table 1**.

Logistic regression analysis

Post-stroke cognitive impairment was the dependent variable, while the independent factors were the ALP, gender, age, infarction site, and NINDS-CSN 5-minute. Based on the Logit regression analysis, the model formula obtained is: ln(p/(1-p)) = 3.774 + 0.080*ALP + 0.598*gender + 0.009*infarction site + 0.004*age - 1.273*NINDS-CSN 5-minute (where p represents the probability of post-stroke cognitive impairment being 1, and 1-p represents the probability of post-stroke cognitive impairment being 0), as shown in Table 2.

The regression coefficient value of ALP is 0.080, and it shows a significant level of 0.01 (z = 4.085, p = 0.000 < 0.01), indicating that ALP has a significant positive impact on post-stroke cognitive impairment. The odds ratio (OR value) is 1.084, meaning that when ALP increases by one unit, the change (increase) in post-stroke cognitive impairment is 1.084 times greater. The regression coefficient value of NINDS-CSN 5-minute is -1.273, and it shows a significant level of 0.01 (z = -4.059, p = 0.000 < 0.01), indicating that NINDS-CSN 5-minute has a significant negative impact on post-stroke cognitive impairment. The odds ratio (OR value) is 0.280, meaning that when NINDS-CSN 5-minute increases by one unit, the reduction in post-stroke cognitive impairment is 0.280 times. However, there was no significant difference in terms of gender, age, and infarction location (P > 0.05), which indicates that these three factors do not have an impact on the cognitive impairment after stroke. In conclusion, ALP has a significant positive impact on post-stroke cognitive impairment, while NINDS-CSN 5-minute has a significant adverse effect on post-stroke cognitive impairment. However, gender, infarction location, and age do not have any impact on post-stroke cognitive impairment. (Table 2).

Predictive value analysis

The results of ROC curve analysis showed: As shown in Figure 1 and Table 3, the AUC value of ALP alone for predicting PSCI was 0.835, indicating that ALP has a relatively high diagnostic value for post-stroke cognitive impairment. As shown in Figure 2, the AUC value of ALP alone

Table 1. Basic information about the research object

Variables	Total (n = 99)	no (n = 54)	yes (n = 45)	Statistic	P
Age, M (Q_1, Q_3)	70.00 (57.50, 80.00)	69.50 (54.00, 80.00)	70.00 (64.00, 79.00)	Z=-0.77	0.441
Gender n(%)				χ^2=0.15	0.701
Male	64 (64.65)	34 (62.96)	30 (66.67)		
Female	35 (35.35)	20 (37.04)	15 (33.33)		
Infarct location n(%)				χ^2=1.88	0.171
Supra-tentorial	89 (89.90)	46 (85.19)	43 (95.56)		
Infratentorial	10 (10.10)	8 (14.81)	2 (4.44)		

Note: Z=Mann-Whitney test; χ^2=Chi-square test; M=Median, Q_1=1st Quartile; Q_3=3rd Quartile; ALP=Alkaline Phosphatase; NINDS-CSN 5-minute=National Institute of Neurological Disorders and Stroke–Canadian Stroke Network 5-minute Protocol

Table 2. Summary of Logistic Regression Analysis Results

Variables	β	S.E	z	χ^2	p	OR	95% CI
ALP	0.080	0.020	4.085	16.689	<0.01	1.084	1.043 ~ 1.126
Gender	0.598	0.617	0.969	0.939	0.333	1.819	0.542 ~ 6.101
Infarction site	0.009	0.016	0.582	0.338	0.561	1.009	0.978 ~ 1.042
Age	0.004	0.024	0.176	0.031	0.860	1.004	0.959 ~ 1.052
NINDS-CSN 5-minute	-1.273	0.314	-4.059	16.474	<0.01	0.280	0.151 ~ 0.518
Intercept	3.774	3.986	0.947	0.897	0.344	43.553	0.018 ~ 107542.111

Note: Dependent variable = Post-stroke cognitive impairment; McFadden R 方 = 0.427; Cox & Snell R 方 = 0.445; Nagelkerke R 方 = 0.595

Table 3. Results of the Optimal Cut-off Value on ROC Curve

Variables	AUC	Optimal threshold value	Sensitivity	Specificity	Cut-off
Joint diagnosis	0.905	0.678	0.956	0.722	0.292
NINDS-CSN 5-minute	0.780	0.433	0.711	0.722	10.000
ALP	0.835	0.611	0.889	0.722	75.000

Table 4. Model summary table

Item	parameter name	parameter values
Model parameter setting	data preprocessing	None
	Training set ratio	0.8
	Number of decision trees	100
	Standard for node splitting	gini
	Minimum number of nodes to split	2
	Minimum number of nodes in a leaf	1
	Maximum depth of tree	no limit
	Maximum feature count limit	auto
	Whether there is a return sampling	Yes
	Whether to perform off-site data testing	Yes
Model evaluation effect	Accuracy rate	85.000%
	Accuracy (overall)	89.091%
	Overall recall rate	85.000%
	f1-score	0.851

for predicting PSCI was 0.780, indicating that the diagnostic predictive value of CSN for ALP was relatively lower than that of ALP. As shown in Figure 3 and Table 3, the AUC value corresponding to the combined diagnosis of PSCI using ALP and the 5-minute NINDS-CSN test scale is 0.905, with a sensitivity of 0.956 and a specificity of 0.722. The diagnostic value is extremely high. Therefore, the combined application of the two methods has a greater value in predicting post-stroke cognitive impairment compared to their use alone.

Confusion Matrix

Taking ALP and NINDS-CSN 5-minute items as independent variables and post-stroke cognitive impairment as the dependent variable, with a training set ratio of 0.8, 100 decision trees, a node splitting criterion of gini, and no limit on the maximum depth of the tree, a random forest model was constructed. From Table 4 and Figure 4, it can be seen that the final model achieved an accuracy rate of 85.00% on the test set, a precision rate (combined) of 89.09%, a recall rate (combined) of 85.00%, and an F1-score (combined) of 0.85. The model performance is acceptable.

DISCUSSION

With the accelerating aging of China's population, the incidence of ischemic stroke has been increasing annually, posing a serious threat to patients' lives and health. Patients with ischemic stroke often exhibit varying degrees of cognitive impairment, clinically manifested as declines in short-term memory, attention, verbal communication ability, and recognition capacity, significantly affecting their quality of life. This has become a focal issue in clinical research.[12] Stroke prevalence in China is 1114.8 per 100,000, with an annual incidence of 246.8 per 100,000 and a fatality rate of 149.49 per 100,000, according to the China Stroke Report 2020.[13] China now has the highest lifetime risk of stroke and the highest disease burden worldwide.[2] Approximately one-third of stroke patients experience post-stroke cognitive impairment (PSCI).[3] PSCI refers to cognitive dysfunction that occurs within six months after a stroke event and persists for more than three

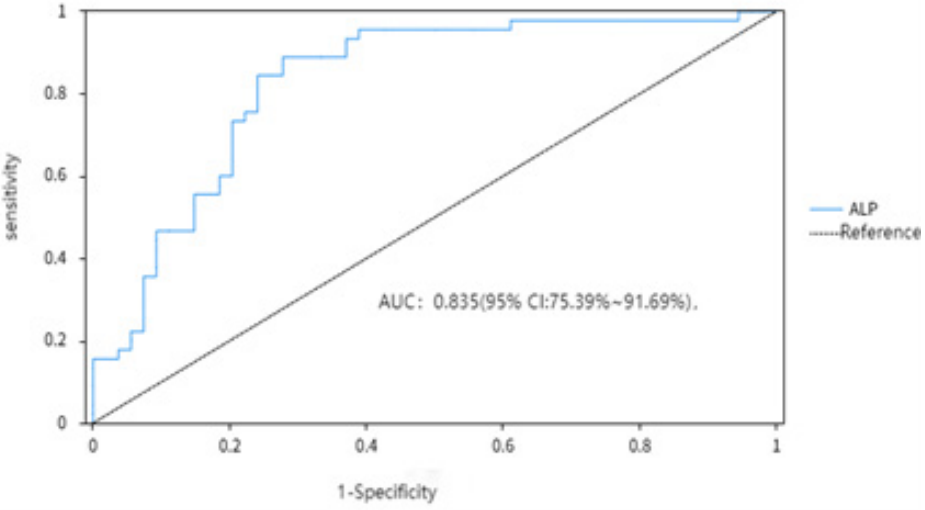

Figure 1. The value of ALP in predicting PSCI alone

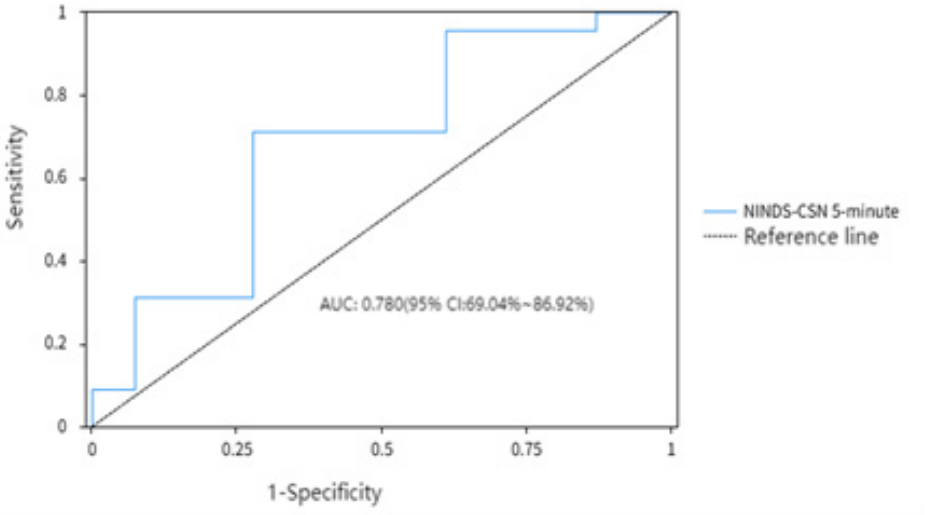

Figure 2. The value of the NINDS-CSN 5-minute test in predicting PSCI alone

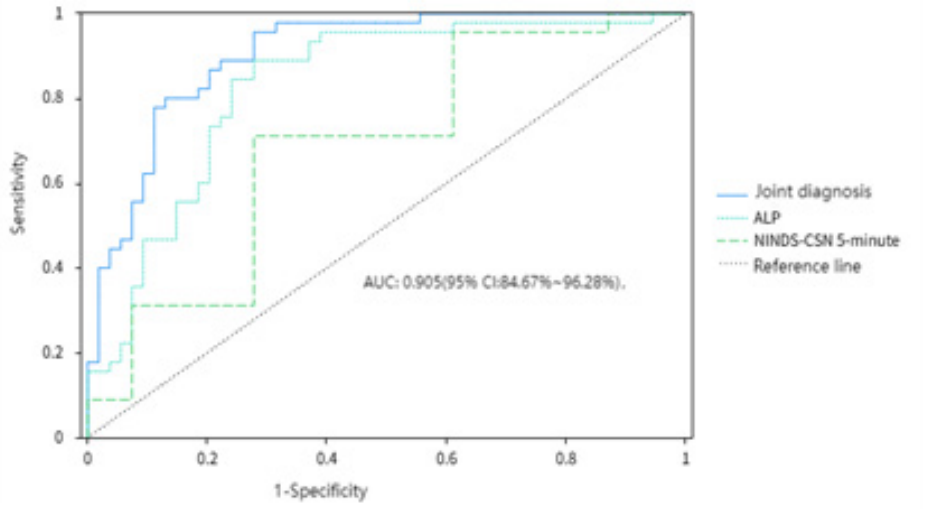

Figure 3. The value of the combined 5-minute prediction of ALP and NINDS-CSN 5-minute for PSCI

months. Cognitive changes in PSCI represent a dynamic process: during the acute phase of stroke and shortly afterward, cognitive function may decline rapidly and transiently. By 3 to 6 months post-stroke, when the recovery of neurological functions such as motor and language abilities reaches a plateau, cognitive impairment becomes more prominent. Therefore, the diagnosis of PSCI requires a neuropsychological assessment 3 to 6 months after the stroke for confirmation.[14] PSCI is a major contributor to the burden of stroke-related disorders and a primary focus of international stroke research and clinical intervention because of the significant impact it has on patients' quality of life and survival time.

Early identification and intervention of cognitive dysfunction are crucial for improving patients' quality of life and rehabilitation outcomes. ALP is a membrane-bound metalloenzyme currently known to be closely associated with atherosclerosis, vascular homeostasis, and inflammatory responses. It is also involved in the occurrence and progression of cognitive dysfunction after stroke. Research suggests that this may be due to ALP's anti-inflammatory effects, which promote its translocation from cell membranes into the bloodstream, leading to elevated ALP levels. Overexpression of ALP reduces the inhibitory effect of inorganic pyrophosphate on bone salt formation, resulting in decreased inorganic pyrophosphate levels, thereby inducing vascular calcification and atherosclerosis. These changes ultimately lead to ischemic cerebral alterations such as leukoaraiosis and cerebral infarction, accelerating the development of neurodegenerative diseases and consequent cognitive decline.[15]

Alzheimer's disease (AD) patients' brains and plasma have been shown to display higher levels of an ALP isoform, specifically tissue-nonspecific alkaline phosphatase (TNAP), which is encoded by the Alpl gene (also known as Akp2). This change is linked to increased TNAP activity in AD patients' brains and plasma, indicating that TNAP could be a new plasma biomarker for AD and moderate cognitive impairment (MCI).[16]

The NINDS-CSN 5-minute test, a subtest of the MoCA, is used as a clinical screening tool for cognitive impairment. This study explores the combination of ALP levels and the NINDS-CSN 5-minute test to identify clinically accessible values for predicting cognitive impairment in AIS patients. The goal is to establish indicators during hospitalization that can foresee the risk of PSCI, guiding earlier clinical interventions to mitigate or reduce the impact of cognitive impairment on patients.

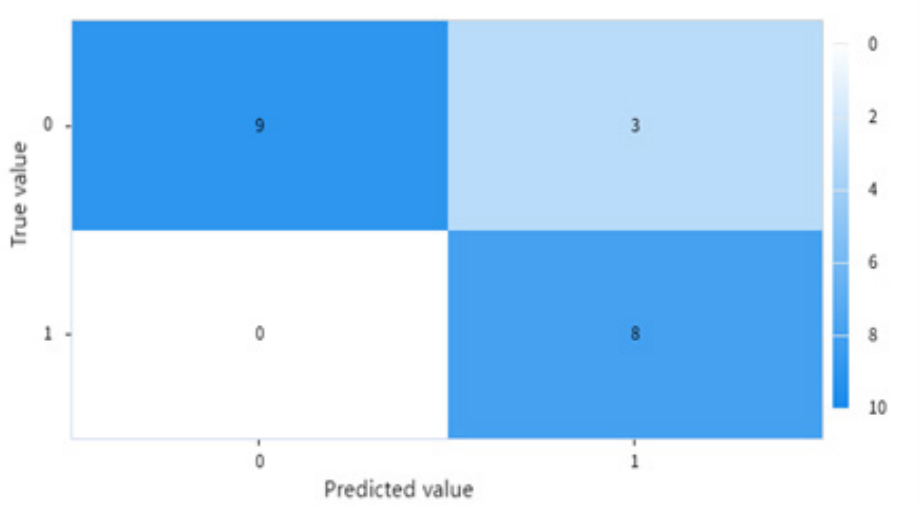

Figure 4. Mixed matrix

This study, through ROC curve analysis, found that when the critical values of serum ALP and NINDS-CSN 5-minute were 75 U/L and 10 points respectively, they had a high sensitivity and specificity in predicting cognitive function after ischemic stroke, The combination of the two methods has a very high value for predicting cognitive impairment after acute ischemic stroke (AUC: 0.905) (**Figure 3**, **Table 3**), and its sensitivity is as high as 95.6%. Thus, indicators for the foreseeable risk of cognitive dysfunction after AIS during hospitalization can be used to guide earlier clinical intervention, attempting to mitigate or reduce the impact of cognitive impairment on patients.

There is a lack of support from previous related studies, and there are certain limitations in the data collection tools, methods, and techniques. This may also lead to certain randomness in the clinical trial results. Therefore, in future research, it is preferable to conduct multi-center studies, increase the sample size, extend the research duration, optimize the sample selection, and employ more effective data analysis techniques. This will make the research more rigorous, reliable, and persuasive.

CONCLUSION

In conclusion, the combination of serum ALP levels and the NINDS-CSN 5-minute test demonstrates strong potential as a reliable diagnostic tool for predicting post-stroke cognitive impairment (PSCI). The integrated use of these two methods proves more effective than relying on either one alone, providing valuable insights for early identification of cognitive dysfunction following ischemic stroke. These findings highlight the importance of early clinical screening, which can facilitate timely intervention, alleviate the long-term burden of stroke, and significantly enhance patient quality of life. However, the study's limitations, including its small sample size and single-center design, suggest the need for further research to validate these results and minimize potential selection biases.

ETHICAL CLEARANCE

This research was approved by the ethics committee of Chengfei Hospital with ethics review number 20220151 (November 24, 2022).

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CONFLICT OF INTEREST

All authors of this paper declare that they have no conflicts of interest.

AUTHOR CONTRIBUTION

Longfei Nong contributes to manuscript editing and design. Xiaoling Song contributes to manuscript editing and data acquisition. Xiaolan Chen contributes to manuscript editing and data analysis.

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