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Development and study of S100 calcium-binding protein B and neuron-specific enolase-based predictive model for epilepsy secondary to cerebral infarction

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ABSTRACT

This study aimed to develop and validate a predictive model based on S100 calcium-binding protein B (S100B) and neuron-specific enolase (NSE) as the core of epilepsy secondary to cerebral infarction. For this aim, 156 cases of cerebral infarction from June 2018 to December 2019 were selected. According to the ratio of 7:3, 109 cases were used for training and 47 cases were used for validation. The factors influencing cerebral infarction secondary to epilepsy were analyzed by a univariate analysis comparing the general data of the two groups and binary logistic regression, and the prediction model was established and validated. Results showed that there was no statistically significant comparison of general information between the training and validation groups ($p>0.05$). The comparison of NIHSS score, lesion location, lesion size, infarct staging, involved arterial system, large infarct, NSE, and S100B levels between the two groups was significant ($P<0.05$). The difference between the two groups will be secondary epilepsy= 1, non-epilepsy=0 as dependent variables and factors with significant differences in the univariate analysis as covariates for logistic regression analysis showed that NIHSS score > 15, cortical lesion, lesion size ≥ 5cm, carotid circulation involvement, large infarct, S100B, NSE were risk factors for secondary epilepsy in cerebral infarction. In conclusion, serum S100B and NSE levels were abnormally elevated in patients with epilepsy secondary to cerebral infarction, NIHSS score > 15, cortical lesions, lesion size ≥ 5 cm, carotid circulation involvement, large infarct, S100B and NSE are risk factors for epilepsy secondary to cerebral infarction, and the AUC area of S100B and NSE is large, based on S100B and NSE as The prediction model based on S100B and NSE has good predictive value.

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Introduction

The incidence of cerebral infarction in China is on the rise with increasing ageing and the incidence of epilepsy secondary to cerebral infarction is also increasing year by year(1). Cerebral infarction is caused by atherosclerosis and thrombosis of the blood supply to the brain and has a high rate of disability and death. Epilepsy secondary to cerebral infarction is caused by abnormal neuronal discharges in the brain due to metabolic diseases, congenital diseases, intracranial injuries or infections, resulting in sudden, recurrent and transient disorders of the brain's nervous system. (2)

During the onset and progression of epilepsy secondary to cerebral infarction, it can cause damage to nerve cells and affect cognitive dysfunction(3) .

Cognitive function is an advanced function of the human brain, and the brain is an information network composed of many glial cells and neurons, of which glial cells can effectively nourish neurons, and feedback influences the neuronal information conversion mechanism, but the excessive secretion of glial cells can affect the neuronal response, and then damage the brain nerves (4), and S100 calcium-binding protein B (S100B) astrocyte secretion has the best active ingredient It is also one of the most specific biochemical indicators of brain injury (5-6). Serum neuron-specific enolase (NSE) levels have been found to correlate with the degree of neuronal damage and can be used clinically as an important indicator of neurological damage (7).

The study showed that(8), serum S100B and NSE levels in the secondary epilepsy group were higher than those in the non-secondary epilepsy group, suggesting that S100B and NSE are closely related to the occurrence of epilepsy secondary to cerebral infarction. Secondary epilepsy in patients with cerebral infarction leads to a state of hypoxia and ischemia in brain tissue, which aggravates the degree of blood-brain barrier damage, resulting in a large outflow of S100B and NSE from neurons through the severely damaged blood-brain barrier into the blood(9). S100B and NSE may affect epilepsy secondary to cerebral infarction, but the predictive value of S100B and NSE on epilepsy secondary to cerebral infarction needs to be further investigated, therefore this study The present study aims to develop a predictive model of S100B and NSE in epilepsy secondary to cerebral infarction, with a view to early detection and prevention of epilepsy secondary to cerebral infarction.

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Materials and Methods

General information

156 cases of cerebral infarction in our hospital from June 2018 to December 2019 were selected as the study population. According to the ratio of 7:3, 109 cases were used for training and 47 cases were used for validation. Each group was divided into a secondary epilepsy group and a non-epilepsy group according to the secondary epilepsy condition.

This study has been approved by the Ethics Committee.

Inclusion criteria: (i) meeting the diagnostic criteria in the Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke(10) ; (ii) confirmed by cranial imaging; (iii) first cerebral infarction; (iv) complete clinical data; (v) normal cognitive function before the disease.

Exclusion criteria: (i) history of epilepsy; (ii) combined subdural haematoma, hydrocephalus, intracranial tumour; (iii) history of craniocerebral trauma or surgery; (iv) recent use of anti-epileptic drugs; (v) central nervous system infection; (vi) visual and hearing impairment; (vii) impaired function of vital organs such as the kidneys and lungs.

Methodology

Collection of general information

General patient information was collected on age, sex, smoking, alcohol consumption, diabetes, hypertension, National Institutes of Health Stroke Scale (NIHSS) score(11), lesion site, lesion size, infarct staging, type of occlusion, the arterial system involved, and large infarcts.

Detection of serum NSE and S100B levels

All patients were tested by enzyme-linked immunosorbent assay for serum NSE and S100B kits purchased from Guangzhou Yijin Biotechnology Co.

Observation indicators

To compare general information, factors influencing epilepsy secondary to cerebral infarction, predictive value, prediction model and validation between the two groups.

Statistical methods

SPSS 22.0 was used for the statistical analysis of the data. The measurement data were tested for normality, and data that conformed to a normal distribution were expressed as (±s), and comparisons between groups were made using the independent samples t-test. Data that did not conform to a normal distribution were expressed using the median (quartiles) and the Mann-Whitney U test was used for comparison between groups. Categorical counts were expressed as percentages, and comparisons between groups of unordered categorical data were made using the χ^2 or Fisher exact test; comparisons between groups of ordered categorical data were made using the Mann-Whitney U test. Factorial logistic regression analysis was used to analyse the factors influencing secondary epilepsy in patients with cerebral infarction, and the predictive value was evaluated by the AUC area under the ROC curve; $P<0.05$ was considered a statistically significant difference.

Results

General information

There was no statistically significant comparison of general information between the training and validation groups ($p>0.05$, Table 1).

The training group was divided into a secondary epilepsy group (n=28) and a non-epilepsy group (n=81) based on secondary epilepsy. The comparison of age, gender, smoking, alcohol consumption, diabetes, hypertension and type of occlusion between the two groups in the training group was not statistically significant, with $P>0.05$. The comparison of NIHSS score, lesion site, lesion size, infarct staging, involved arterial system, large infarct, NSE and S100B levels between the two groups was statistically significant ($P<0.05$, Table 2).

Multi-factor analysis and development of predictive models

Logistic regression analysis with secondary epilepsy = 1 and non-epilepsy = 0 as dependent variables and factors that differed significantly on univariate analysis as covariates showed that NIHSS score > 15, cortical lesion, lesion size ≥ 5 cm, carotid circulation involvement, large infarct, S100B, and NSE were risk factors for secondary epilepsy in cerebral infarction (Tab. 3).

$Log(P)$ = NIHSS score × 5.489 + cortical lesion × 6.244 + lesion size × 6.029 + carotid circulation involvement × 11.726 + large infarct × 19.341 + S100B × 25.393 + NSE × 0.695 - 41.992.

Table 1. Comparison of general information.

Indicators		Training group (n=109)	Validation group (n=47)	t/χ^2	P
Age (years)		50.89±3.22	50.66 = 1±3.16	0.412	0.681
Gender (example)	Male	56	25	0.043	0.835
	Female	53	22		
Smoking (examples)	Yes	48	25	0.282	0.595
	None	51	22		
Alcohol consumption (examples)	Yes	71	36	2.001	0.157
	None	38	11		
Diabetes (cases)	Yes	46	18	0.207	0.649
	None	63	29		
Hypertension (cases)	Yes	76	36	0.949	0.330
	None	33	11		

Table 2. Comparison of general information.

Indicators		Secondary epilepsy group (n=28)	Non-epileptic group (n=81)	t/χ^2	P
Age (years)		50.62±3.21	51.14±3.12	0.755	0.452
Gender (example)	Male	15	43	0.002	0.964
	Female	13	38		
Smoking (examples)	Yes	16	46	0.001	0.974
	None	12	35		
Alcohol consumption (examples)	Yes	13	41	0.146	0.702
	None	15	40		
Diabetes (cases)	Yes	11	36	0.226	0.635
	None	17	45		
Hypertension (cases)	Yes	19	53	0.055	0.815
	None	9	28		
NIHSS score (cases)	>15 points	20	32	8.499	0.000
	≤15 points	8	49		
Site of lesion (cases)	Cortices	17	25	7.828	0.005
	Subcortical	11	56		
Lesion size (cases)	≥5 cm	18	28	7.534	0.006
	<5 cm	10	53		
Infarct typing (cases)	Cardiogenic	19	29	8.675	0.003
	Non-cardiac	9	52		
Type of occlusion (example)	Cerebral embolism type	14	40	0.099	0.952
	Small artery occlusion	10	31		
	Other types	4	10		
Involved arterial system (cases)	Carotid circulation	18	27	8.224	0.004
	Basilar artery circulation	10	54		
Massive infarction (cases)	Yes	17	26	7.133	0.008
	None	11	55		
S100B (μg/L)		0.81±0.21	0.49±0.18	7.763	0.000
NSE (μg/L)		34.62±4.65	27.11±4.87	7.114	0.000

Table 3. Multi-factor analysis

	β	SE	Wals	P	OR	OR95% Confidence interval	
						Lower limit	Upper limit
NIHSS score > 15	5.489	4.350	4.592	0.007	1.032	1.002	20.859
Cortical lesions	6.244	3.547	4.098	0.038	1.002	1.000	2.031
Lesion size ≥ 5cm	6.029	6.969	5.290	0.021	1.008	1.005	1.093
Involvement of the carotid circulation	11.726	5.442	4.643	0.031	123732.803	2.886	5.30E+09
Massive infarction	19.341	8.948	4.673	0.031	2.51E+08	6.075	1.04E+16
S100B	25.393	11.137	5.199	0.023	1.07E+11	35.335	3.22E+20
NSE	0.695	0.329	4.480	0.034	2.005	1.053	3.817
Constants	-41.992	17.252	5.924	0.015	0		

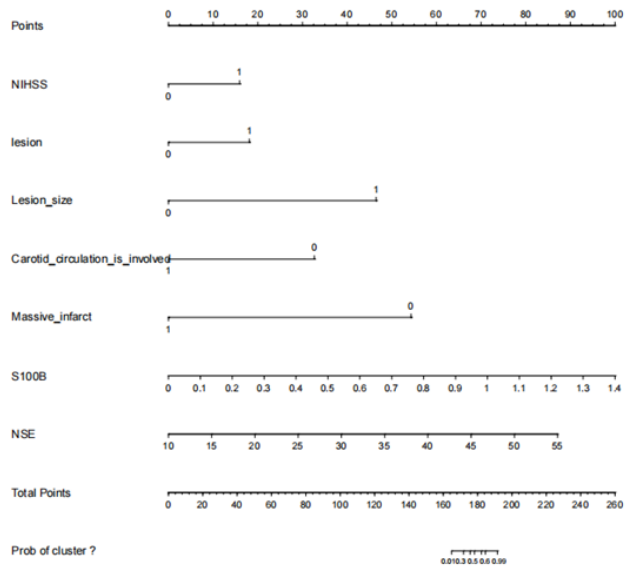

Figure 1. Column line diagram.

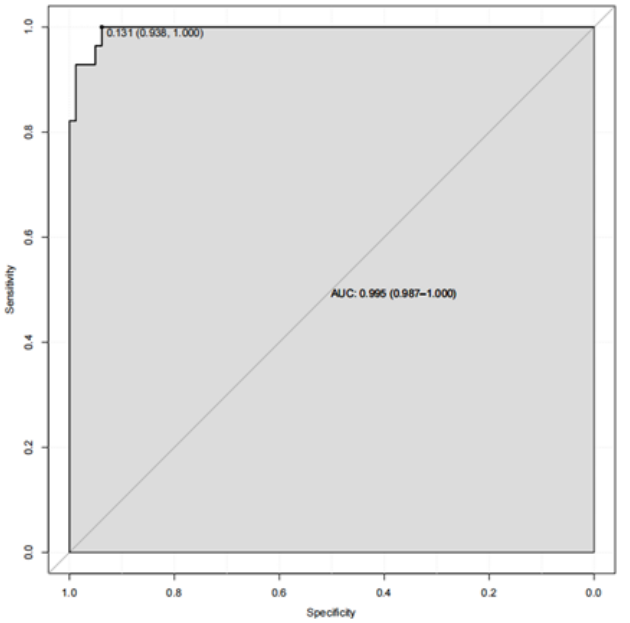

Figure 2. Training group ROC curves.

The column line graph model was established for the training group (Figure 1), and the area under the ROC curve of the column line graph prediction model based on S100B and NSE for the training group was 0.995 (95% CI:0. 987 ~1), and the AUC of S100B and NSE was 0.959 and 0.847 (Figure 2). The ROC curve was plotted for the validation group patients using the column line graph to predict the survival probability of the validation group, and the model AUC area was 0.967 (95% CI:0. 922 ~1) (Figure 3).

The slope of the calibration curve for the training group was close to 1 (Figure 4) and the test of goodness of fit was p>0.05, with a high agreement between the predicted and actual events. In the validation group, the slope of the calibration curve deviates from 1 (Figure 5), which may be due to the small sample size or too many independent variables.

The decision analysis curves for the training group and the validated prediction model (Figures 6 and 7), with the

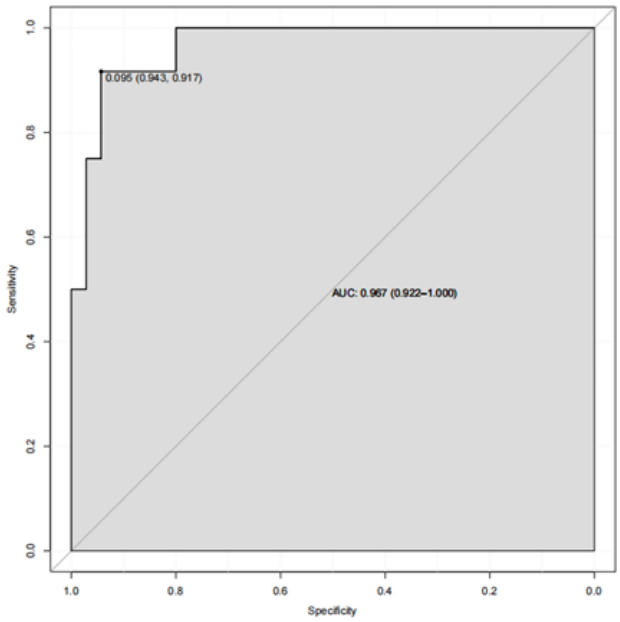

Figure 3. ROC curves for the validation group.

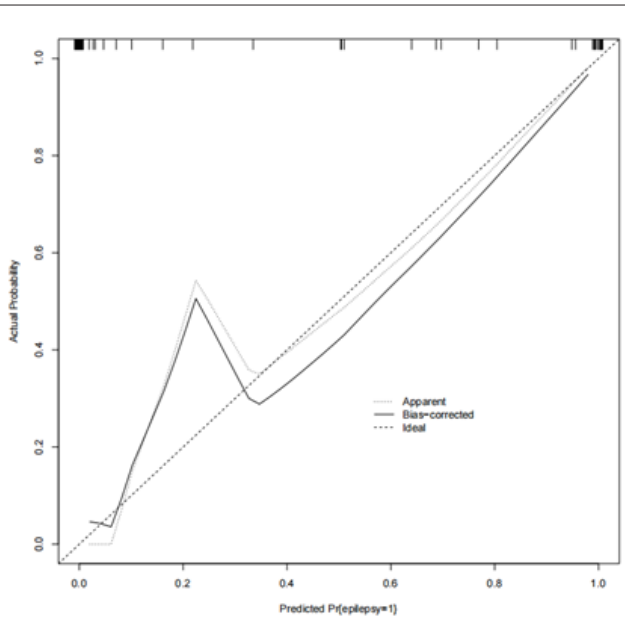

Figure 4. Training group column line graph calibration curve.

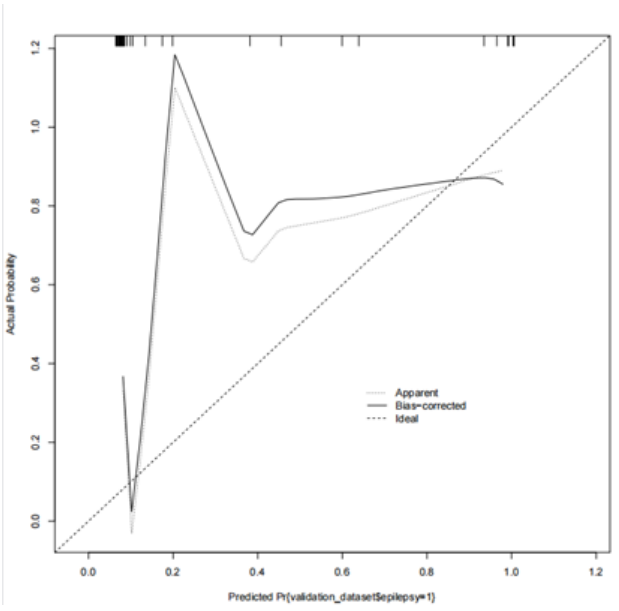

Figure 5. Calibration curve for the validation group column line graph.

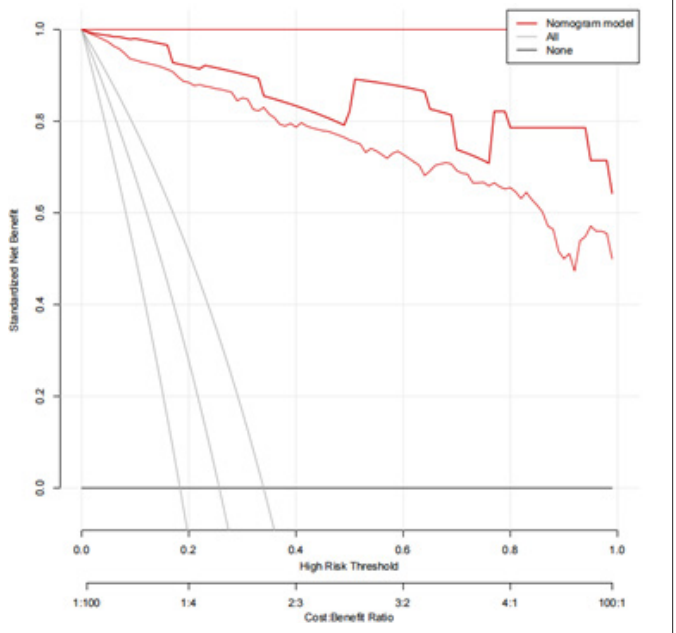

Figure 6. Training group DCA curve.

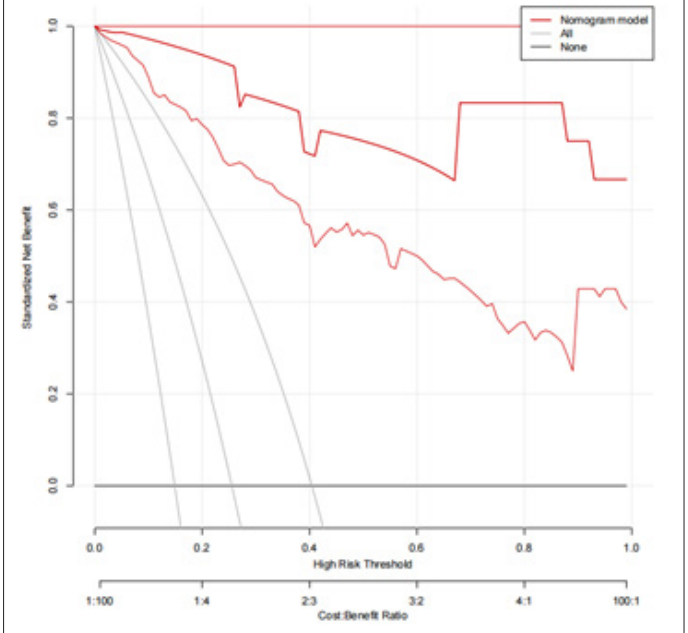

Figure 7. Validation group DCA curve.

x-axis indicating the threshold probabilities and the y-axis indicating the net returns, and the solid black line indicating the net returns using the column line graph prediction model, further confirm the validity of the column line graph prediction model.

Discussion

Epilepsy secondary to cerebral infarction is mainly due to the long-term undersupply of brain tissue, the permeability of nerve cell membranes is significantly enlarged, the cortex is severely damaged, and the ion concentration inside and outside the cell is difficult to maintain equilibrium, which eventually causes epileptic activity(12). There are many causes of epilepsy secondary to cerebral infarction(13), this study focuses on the analysis of the effect of S100B and NSE levels on epilepsy secondary to cerebral infarction and the development of a predictive model with S100B and NSE as the core to reduce the incidence of epilepsy secondary to cerebral infarction.

A total of patients with cerebral infarction were selected for training and validation in this study, and patients in the training group were divided into those with secondary epilepsy and those without epilepsy. There was no statistically significant comparison of age, gender, smoking, alcohol consumption, diabetes, hypertension, and type of occlusion between the two groups, and their association with the occurrence of epilepsy secondary to cerebral infarction was not significant. There was a statistically significant difference in the comparison of NIHSS score, lesion site, lesion size, infarct staging, involved arterial system, large infarct, NSE, and S100B levels between the two groups. significantly abnormal NSE and S100B levels may be significant for the occurrence of epilepsy secondary to cerebral infarction, NIHSS score, lesion site, lesion size, infarct staging, involved arterial system, and Large infarcts.

Further multifactorial analysis of factors influencing epilepsy secondary to cerebral infarction showed that NIHSS score > 15, cortical lesions, lesion size ≥ 5 cm, carotid circulation involvement, large infarct, S100B, and NSE were all risk factors for epilepsy secondary to cerebral infarction, as also shown in the study by Liu J et al.(14) , serum S100B protein levels measured in 93 non-epileptic patients were: 1.32±0.51 μg/L and serum S100B protein level measured in 7 epileptic patients was: 2.23±0.43 μg/L; serum S100B protein level was significantly higher in epileptic patients than in non-epileptic patients.

S100B can promote local cell proliferation, repair neural damage and regulate neural cell stability, but its overexpression can damage neural cells and is detrimental to recovery(15). (16)When cerebrovascular disease or ischemic encephalopathy occurs in the body, glial cell damage will release S100B into the cells, and the serum S100B level will increase. S100B levels are abnormally elevated(17). NSE is an important regulatory enzyme in the glycolytic pathway and is mainly found in neurons and neuroendocrine cells. When a brain injury occurs, NSE can be released from damaged cells in the lesion into the cerebrospinal fluid and enter the bloodstream through the damaged blood-brain barrier, resulting in elevated serum NSE levels(18).

Arca G et al. (19) also showed that abnormally high serum S100B and NSE levels increase the stress of brain proteins, which subsequently damage glial cells and neurons and even promote apoptosis, resulting in more dramatic damage to tissue in cognitively functional areas of the brain, leading to more severe cognitive dysfunction. Serum S100B and NSE levels reflect the degree of neurological damage in patients with cerebral infarction. High serum S100B and NSE levels indicate severe neurological damage and an increased risk of epilepsy. Another study reported a correlation between seizure frequency and infarct size after cerebral infarction. Large infarcts indicate the presence of occlusion or rupture of larger cerebral vessels, which increases the degree of hypoxia, ischaemia and oedema in brain tissue, thereby increasing the risk of epilepsy[20] . Involvement of the carotid circulatory system can affect the blood supply to the frontal, parietal and temporal areas, leading to limb twitching; also the anterior circulatory system is more complex and brain infarction triggers tissue remodelling leading to abnormal discharges

that can trigger epilepsy. It has also been shown[21] that NIHSS scores > 15 and lesion size ≥ 5 cm are also among the risk factors for epileptogenesis, with larger lesions and higher NIHSS scores being associated with higher epileptogenic findings, which is consistent with the present study. Cortical nerve cells are densely packed, mainly with astrocytes, pyramidal cells and axonal cells. Cortical involvement affects cortical neuronal function, decreases neuronal stability, leads to abnormal ion flow, causes excessive depolarization of neurons, and eventually causes abnormal discharges and triggers epilepsy. This results in a higher risk of secondary epilepsy in patients with a cortical infarct.

In addition, the training group derived the model formula by building the prediction model, and the predictive value of the model was good, with an AUC of 0.995, including AUC of 0.959 and 0.847 for S100B and NSE respectively, and AUC of 0.967 for the validation group model. The slope of the calibration curve of the column line plot of the training group was close to 1, and the test of goodness of fit was P>0.05, and the agreement between the predicted and actual events was high. In the validation group, the slope of the calibration curve deviated from 1, which may be due to the small sample size or too many independent variables. The decision analysis curves of the training group and the validated prediction model further confirmed the validity of the column line plot prediction model.

In summary, abnormally elevated serum S100B and NSE levels, NIHSS score > 15, cortical lesions, lesion size ≥ 5 cm, carotid circulation involvement, large infarct, S100B and NSE are risk factors for epilepsy secondary to cerebral infarction in patients with cerebral infarction, and the AUC area of S100B and NSE is large, based on S100B and NSE The prediction model established as the core has a better predictive value. However, this study still has certain limitations, such as the sample size of this study is too small, and the selection of more independent variables for the factors affecting patients with epilepsy secondary to cerebral infarction, which affects the model validation, resulting in the results may not be accurate enough.

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