Expression and significance of S-100β, CysC and NF-κB in patients with acute cerebral infarction

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Abstract. The present study aimed to explore the expression and significance of S100 protein β (S100β), cystatin C (CysC), and nuclear factor kappa B (NF-κB) in patients with acute cerebral infarction (ACI). ACI patients (n=120) were selected as the experimental group at Xuzhou Central Hospital from August 2016 to August 2018. Ninety healthy subjects who underwent a physical examination at Xuzhou Central Hospital during the same period were selected as the control group. The expression levels of S-100β, CysC and NF-κB were compared between the two groups. Serum S-100β, CysC and NF-κB levels were compared between ACI patients with different degree of nervous functional defects, different infarct size and different prognosis. ROC curve analysis was used for the diagnosis of ACI by serum S-100β, CysC and NF-κB levels. Serum S-100β, CysC and NF-κB levels in the experimental group were higher than those in the control group (P<0.05). The levels of serum S-100β, CysC and NF-κB in patients with different neurological deficits were significantly different. The levels of serum S-100β, CysC and NF-κB in the severe and medium type infarction group were significantly higher than those in the mild type infarction group (both P<0.05). The levels of serum S-100β, CysC and NF-κB in the severe type infarction group were higher than those in the medium type infarction group (P<0.05). There were significant differences in serum S-100β, CysC and NF-κB levels in patients with different infarct sizes. The levels of serum S-100β, CysC and NF-κB in patients with large and medium size infarction were higher than those in the small size infarction group (both P<0.05). The levels of serum S-100β, CysC and NF-κB in patients with large size infarction were higher than those in patients with medium size infarction (P<0.05). Serum S-100β, CysC and NF-κB levels in patients of the worsening group were significantly higher than those in patients of the non-worsening group. The levels of S-100β, CysC, NF-κB in ACI patients were significantly higher than those in healthy subjects. Increased levels of S-100β, CysC and NF-κB can be used as ideal indexes for diagnosing cerebral infarction and studying the condition.

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Introduction

Acute cerebral infarction (ACI) is an acute ischemic stroke. It refers to the sudden decrease or interruption of blood supply to part of the brain cells, resulting in hypoxia of local tissue and depletion of energy (1). Eventually, cells in this area lose their activity and undergo tissue necrosis, further resulting in the loss of nerve function (2,3). ACI has high morbidity and lethality in cerebrovascular disease, which has a serious impact on the psychological and physiological aspects of patients. It reduces the quality of life of patients and brings a serious economic burden to families and society (4). The pathogenesis of ACI is markedly complex. Hypertension, diabetes mellitus and other diseases have a certain impact on the occurrence of the disease (5). At present, the diagnosis of ACI mainly depends on clinical manifestations (6), signs, and imaging examination. However, some patients may not exhibit significant imaging changes 24 h later (7). Due to the influence of time, imaging application is limited (8). Especially some diseases, including migraine and epileptic seizures, have similar symptoms as a stroke (9), which has a certain influence on the diagnosis of diseases.

It has been reported (10) that S100 protein β (S100β) plays an important role in cell division, differentiation and apoptosis. It is mainly expressed in glial cells in the central nervous system and participates in the production process of cerebrovascular disease (11). Specifically, the release of S-100β by glial cell necrosis will lead to the increase of peripheral blood concentration (12). According to a previous study (13), there is a close relationship between the change of S100β level and the size of cerebral infarction, and the degree of nervous functional defects. Cystatin C (CysC) has been used as a serum factor index for assessing glomerular filtration rate. In recent years, it has received increased attention due to its effect in human vascular diseases and has been revealed to be directly involved in the atherosclerosis process (14). The most common factor of occurrence of ACI is atherosclerosis (10). Nuclear factor κB (NF-κB) (15) is a nuclear transcription activating factor that has been widely studied in recent years. It is closely related to immune

response, inflammatory response as well as other processes. Research has confirmed that (16) NF-κB can induce the activation of inflammatory factors in acute cerebral hemorrhage, which can lead to further damage of brain tissue.

Therefore, the present study aimed to research the expression and significance of S-100β, CysC and NF-κB in ACI. It is of great significance to explore the diagnostic biomarkers related to cerebral infarction in the treatment of disease and prognosis.

Materials and methods

Baseline data. ACI patients (n=120) that were hospitalized at the Department of Neurology of Xuzhou Central Hospital (Xuzhou, China) from August 2016 to August 2018 were selected as the experimental group. There were 68 males and 52 females, 52-76 years old, with a mean age of (62.25±2.18). Healthy (n=90)subjects who underwent a physical examination at Xuzhou Central Hospital during the same period were selected as the control group. There were 53 males and 37 females, 51-76 years old, with a mean age of (62.36±2.07). There were no significant differences between the two groups with regard to age and sex.

Inclusion and exclusion criteria. The inclusion criteria were the following: i) patients who met the diagnostic criteria for acute ischemic stroke in China (17) and diagnosed by CT and MRI; ii) patients who had the disease for the first time; iii) patients admitted to the hospital within 24 h from onset; and iv) patients who received no thrombolytic therapy.

The exclusion criteria were the following: i) patients complicated with cerebral hemorrhage, malignant tumor, head trauma, severe infection, and autoimmune disease; ii) patients who received thrombolytic and surgical therapy; iii) patients with hepatic renal dysfunction; iv) patients with communication and cognitive dysfunction; and v) patients who did not cooperate with the experiment.

All patients agreed to participate in the experiment and signed the informed consent form. The present study was approved by the Ethics Committee of Xuzhou Central Hospital (approval no. XZXY-LJ-20190305-007).

Methods. All patients were treated according to the 'single disease type quality control indexes for cerebral infarction' (18). They were administered antiplatelet aggregation and anti-arteriosclerosis therapeutic agents, such as aspirin, clopidogrel and statins. The blood pressure and blood glucose levels were controlled, brain edema was relieved, and a protective agent of brain cells and symptomatic supportive treatment was applied. The degree of nervous functional defects was assessed by the National Institutes of Health Stroke Scale (NIHSS) (19). According to the NIHSS, the 120 ACI patients were divided into the severe type infarction group (NIHSS score was >15 points, 27 cases), the medium type infarction group (NIHSS score was 4-15 points, 56 cases) and the mild type infarction group (NIHSS score was <4 points, 37 cases). According to the focal volume of cerebral infarction (20), patients were divided into three groups: the small size infarction group (<5 cm^3, 39 cases), the medium size infarction group (5-10 cm^3, 58 cases), and the large size infarction group (>10 cm^3, 23 cases). The prognosis information was obtained by phone 6 months after patients were discharged, and the patients were divided into a worsening group (36 cases) and a non-worsening group (84 cases) according to whether their conditions were aggravated.

Experimental materials. Peripheral venous blood (2 ml) was collected from patients in both groups in the early morning on an empty stomach and centrifuged at 2,000 x g for 5 min. Serum was collected and stored at -80°C (AU5800 automatic biochemistry analyzer; Beckman Coulter). Enzyme-linked immunosorbent assay (ELISA) was used to detect the expression levels of S-100β, CysC and NF-κB in the samples of the experimental and control groups. The kit was purchased from Wuhan Boster Biological Technology Co., Ltd. Specific experimental methods were carried out in accordance with the manufacturer's instructions.

Observation indexes. Comparison of baseline data between the two groups was as follows: i) Comparison of the expression levels of S-100β, CysC and NF-κB between the two groups. ii) Comparison of the different degree of nervous functional defects of groups and S-100β, CysC and NF-κB levels. iii) Comparison of serum S-100β, CysC and NF-κB levels in patients with different infarct size. iv) Comparison of S-100β, CysC and NF-κB levels in ACI patients with different prognosis. v) ROC curve analysis of serum S-100β, CysC and NF-κB levels for diagnosis of ACI.

Statistical methods. In the present study, SPSS 20.0 software (Beijing Bizinsight Information Technology Co., Ltd.) was used for statistical analysis. The enumeration data were assessed by chi-square test. The measurement data were expressed as the mean number ± standard deviation. A Student's t-test was used to compare the two groups. One-way analysis of variance was used for comparison of multiple groups, such as groups with different levels of neurological deficits and groups with different infarct size. Bonferroni test was the post hoc test used with ANOVA. The S-100β, CysC and NF-κB levels, and the value of prognosis in the diagnosis of ACI were assessed by the receiver operating characteristic (ROC) curve. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Comparison of baseline data between the two groups. There was no significant difference in baseline data such as age and BMI between the two groups (all $P>0.05$; Table I).

Comparison of serum S-100β, CysC and NF-κB levels between the two groups. The serum S-100β, CysC and NF-κB levels of patients in the experimental group were significantly higher than those in the control group. The difference was statistically significant (all $P<0.05$; Table II).

Comparison of the groups with different degree of nervous functional defects and S-100β, CysC and NF-κB levels. The serum S-100β, CysC and NF-κB levels of patients with different degree of nervous functional defects were

Table I. Comparison of baseline data between the two groups.

Factors	Experimental group (n=120)	Control group (n=90)	t/χ^2	P-value
Age, years	62.25±2.18	62.36±2.07	0.370	0.712
BMI/kgm^2	26.58±2.36	26.14±2.72	1.359	0.176
Sex				
Male	68 (56.67)	53 (58.89)		
Female	52 (43.33)	37 (41.11)	0.104	0.747
Hypertension				
Yes	88 (73.33)	68 (75.56)		
No	32 (26.67)	22 (24.44)	0.133	0.715
Diabetes mellitus				
Yes	65 (54.17)	48 (53.33)		
No	55 (45.83)	42 (46.67)	0.014	0.905
Hyperlipidemia				
Yes	77 (64.17)	58 (64.44)		
No	43 (35.83)	32 (35.56)	0.002	0.967
Smoking				
Yes	62 (51.67)	50 (55.56)		
No	58 (48.33)	40 (44.44)	0.313	0.576
Drinking				
Yes	69 (57.50)	53 (58.89)		
No	51 (42.50)	37 (41.11)	0.041	0.840

BMI, body mass index.

Table II. Comparison of serum S-100β, CysC and NF-κB levels between the two groups.

Factors	Experimental group (n=120)	Control group (n=90)	t	P-value
S-100β ($\rho/\mu g \cdot l^{-1}$)	1.185±0.15	0.923±0.24	9.70	<0.05
CysC (mg/l)	1.36±0.24	1.05±0.14	10.93	<0.05
NF-κB (pg/ml)	326.4±25.4	305.2±16.6	6.899	<0.05

S100β, S100 protein β; CysC, cystatin C; NF-κB, nuclear factor kappa B.

Table III. Comparison of different degree of nervous functional defects group and S-100β, CysC and NF-κB levels.

Grouping	Severe type infarction group (n=27)	Medium type infarction group (n=56)	Mild type infarction group (n=37)	F	P-value
S-100β ($\rho/\mu g \cdot l^{-1}$)	1.432±0.341[a]	0.747±0.243[b]	0.421±0.123	139.53	<0.05
CysC (mg/l)	1.73±0.21[a]	1.25±0.18[b]	1.17±0.16	85.455	<0.05
NF-κB (pg/ml)	435.3±32.8[a]	408.6±21.6[b]	376.3±18.6	49.550	<0.05

[a]P<0.05, compared with the medium and mild type infarction groups. [b]P<0.05, compared with the mild type infarction group. S100β, S100 protein β; CysC, cystatin C; NF-κB, nuclear factor kappa B.

compared, and the differences were statistically significant (all P<0.05). The levels of serum S-100β, CysC and NF-κB in the severe and medium type infarction groups were significantly higher than those in the mild type infarction group (all P<0.05). The serum S-100β, CysC and NF-κB levels of patients in the severe type infarction group were higher than those in the medium type infarction group (P<0.05; Table III).

Table IV. Comparison of serum S-100β, CysC and NF-κB levels in patients with different infarct size.

Grouping	Large size infarction group (n=23)	Medium size infarction group (n=58)	Small size infarction group (n=39)	F	P-value
S-100β (ρ/μg·l^{-1})	1.278±0.256[a]	0.821±0.223[b]	0.435±0.103	130.5	<0.05
CysC (mg/l)	1.56±0.21[a]	1.35±0.17[b]	1.07±0.15	63.39	<0.05
NF-κB (pg/ml)	424.3±30.3[a]	403.2±21.4[b]	368.3±16.4	53.15	<0.05

[a]P<0.05, compared with the medium and small size infarction group. [b]P<0.05, compared with the small size infarction group. S100β, S100 protein β; CysC, cystatin C; NF-κB, nuclear factor kappa B.

Table V. Comparison of S-100β, CysC and NF-κB levels in ACI patients with different prognosis.

Grouping	Worsening group (n=36)	Non-worsening group (n=84)	t	P-value
S-100β (ρ/μg·l^{-1})	1.473±0.347	0.445±0.142	23.10	<0.001
CysC (mg/l)	1.36±0.24	1.21±0.37	2.236	0.027
NF-κB (pg/ml)	432.7±23.5	385.4±26.1	9.364	<0.001

ACI, acute cerebral infarction; S100β, S100 protein β; CysC, cystatin C; NF-κB, nuclear factor kappa B.

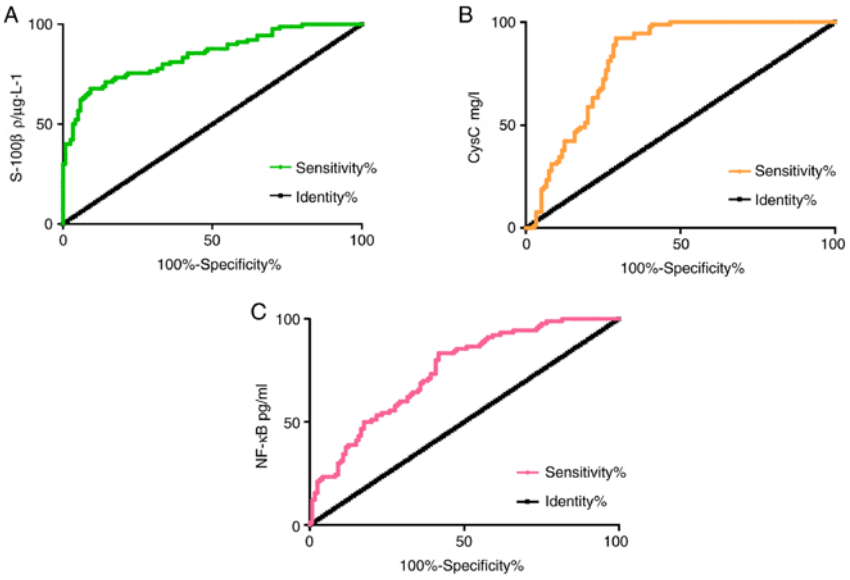

Figure 1. ROC curve of S-100β, CysC and NF-κB levels for diagnosis value of ACI. (A) The diagnostic sensitivity of S-100β to ACI was 67.78%. The specificity was 90.08%. The AUC was 0.845. The 95% CI was 0.791-0.899. The critical value was 0.985 ρ/μg·l^{-1}. (B) The diagnostic sensitivity of CysC to ACI was 92.22%. The specificity was 70.00%. The AUC was 0.823. The 95% CI was 0.765-0.879. The critical value was 1.193 mg/l. (C) The diagnostic sensitivity of NF-κB to ACI was 83.33%. The specificity was 57.50%. The AUC was 0.745. The 95% CI was 0.679-0.810. The critical value was 317.7 pg/ml. ROC, receiver operating characteristic; S100β, S100 protein β; CysC, cystatin C; NF-κB, nuclear factor kappa B; ACI, acute cerebral infarction;

Comparison of serum S-100β, CysC and NF-κB levels in patients with different infarct size. The serum S-100β, CysC and NF-κB levels of patients with different infarct size were compared, and the differences were statistically significant (all P<0.05). The serum S-100β, CysC and NF-κB levels in patients with large and medium size infarction were significantly higher than those in the small size infarction group (all P<0.05). The serum S-100β, CysC and NF-κB levels of patients in the large size infarction group were higher than those in the medium size infarction group (P<0.05; Table IV).

Comparison of S-100β, CysC and NF-κB levels in ACI patients with different prognosis. Serum S-100β, CysC and NF-κB levels in patients of the worsening group were significantly higher than those in the non-worsening group. The difference was statistically significant (all P<0.05; Table V).

ROC curve analysis of serum S-100β, CysC and NF-κB levels for diagnosis value of ACI. The diagnostic sensitivity, specificity and AUC of S-100β to ACI were 67.78, 90.08 and 0.845%, respectively. The 95% CI was 0.791-0.899, and the

critical value was 0.985 ρ/μg·l^{-1}. The diagnostic sensitivity, specificity and AUC of CysC to ACI were 92.22, 70.00 and 0.823%, respectively. The 95% CI was 0.765-0.879, and the critical value was 1.193 mg/l. The diagnostic sensitivity, specificity and AUC of NF-κB to ACI was 83.33, 57.50 and 0.745%, respectively. The 95% CI was 0.679-0.810, and the critical value was 317.7 pg/ml (Fig. 1)

Discussion

ACI, a common cerebrovascular disease, has a great impact on the health and quality of life of patients (21). There are nuermous clinical methods and standards for the diagnosis of ACI, but there are some shortcomings. According to the level value of some related markers, the doctor can assess the condition of the patient and carry out treatment (22). Therefore, the search for serum markers for diagnosis of ACI has a certain influence on the treatment and prognosis of patients (23).

The expression of S-100β, CysC and NF-κB factors in ACI patients was investigated in the present study. First, the serum S-100β, CysC and NF-κB levels in the experimental group were higher than those in the control group. It was revealed that the serum S-100β, CysC and NF-κB levels in ACI patients were higher than those in healthy subjects. The level of detection factors is conducive to the diagnosis of diseases. Studies (24,25) have revealed that after the occurrence of atherosclerosis in cerebral infarction, inflammation and nociceptive stimuli lead to an increased secretion of protease and serum S-100β levels. CysC plays an important role in the progression and occurrence of cardiovascular disease and systemic inflammatory response and atherosclerosis. In the case of ischemia, CysC is released in large quantities (26). It has been reported that CysC can protect the brain against ischemic brain injury, and exogenous CysC exerts neuroprotective effects by reducing infarct volume (27). The high expression of NF-κB can induce the aggravation of inflammatory response and disease (28). This is consistent with the present research results.

Then serum S-100β, CysC and NF-κB levels of patients with different degree of nervous functional defects, different infarct size, and different prognosis were compared. The results revealed that the levels of serum S-100β, CysC and NF-κB in severe and medium type infarction groups were significantly higher than those in the mild type infarction group. The serum S-100β, CysC and NF-κB levels of patients in the severe type infarction group were higher than those in the medium type infarction group in different degree of nervous functional defects. The serum S-100β, CysC and NF-κB levels in patients with large and medium size infarction were significantly higher than those in the small size infarction group. The serum S-100β, CysC and NF-κB levels in the large size infarction group were higher than those in the medium size infarction group in different infarct size. Serum S-100β, CysC and NF-κB levels in the worsening group were significantly higher than those in the non-worsening group in different prognosis patients. According to the results, it is speculated that the increased levels of S-100β, CysC and NF-κB can be used as ideal indices for the diagnosis of cerebral infarction and clinical indices to diagnose the disease. In other words, the higher the S-100β, CysC and NF-κB levels, the larger the size of cerebral infarction, the more serious the clinical degree of nervous functional defects. Studies have shown that (29,30) serum S-100β levels in patients of acute cerebral infarction are closely related to the size of focal volume and the severity of the clinical condition. High levels of S100-β protein can lead to further damage of nervous functional of patients. Related research (31) have shown that the difference in NF-κB response in ACI patients at different periods is closely related to the progression of the disease. Abnormal increase of the CysC level is closely related to the occurrence and progression of cerebral infarction and other cerebrovascular diseases (32,33), consistent with our research results. Then, in order to further clarify the diagnostic value of serum S-100β, CysC and NF-κB levels for ACI, a prediction analysis was conducted. ROC is a common method for evaluating medical diagnostic efficacy. The research results revealed that the diagnostic AUC of CysC to ACI was 0.823, and the diagnostic AUC of NF-κB to ACI was 0.745. S-100β, CysC and NF-κB have high diagnostic values for ACI. Therefore, it is considered that the detection of serum S-100β, CysC, NF-κB levels has a positive effect on the diagnosis and treatment of ACI diseases.

In summary, higher levels of S-100β, CysC and NF-κB expression value can be detected in ACI patients. With the progression of the disease degree and the enlargement of the lesion area, the level of the three markers are increased. This reveals that the three biomarkers are important for the treatment and prognosis. However, the present study still has some limitations. The diagnostic significance of the three combined indices for ACI disease was not detected, thus, this will be addressed in follow-up experiments. The present study focuses on the effect of markers on ACI, therefore, only ROC curves of the three factors were produced for the diagnostic value of the disease. Other effects of markers will be further studied in the future.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

ZL conceived and designed the study and drafted the manuscript. ZL and ZX collected, analyzed, interpreted the experimental data, and revised the manuscript critically for important intellectual content. Both authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Xuzhou Central Hospital (Xuzhou, China). Signed written informed consents were obtained from the patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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