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THE PREDICTIVE VALUE OF SERUM ANG-5 AND SHLP1 LEVELS FOR THE RISK AND PROGNOSIS OF COMPLICATIONS IN ACUTE CEREBRAL INFARCTION PATIENTS

PREDIKTIVNA VREDNOST SERUMSKIH NIVOA ANG-5 I SHLP1 ZA RIZIK I PROGNOZU KOMPLIKACIJA KOD PACIJENATA SA AKUTNIM CEREBRALNIM INFARKTOM

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Summary

Background: To investigate the levels of Survival of Motor Neurons Homolog Protein 1 (SHLP1) and serum Angiopoietin 5 (Ang-5) in patients with acute cerebral infarction (ACI) who also have brain-heart syndrome (BHS).
Methods: The concurrent group consisted of 208 patients with BHS-complicated ACI who were hospitalized between January 2023 and June 2025, whereas the nonconcurrent group consisted of 220 patients with simple ACI who visited the hospital during the same time frame. Serum levels of SHLP1 and Ang-5 in patients were assessed using an enzyme-linked immunosorbent assay. Pearson correlation analysis was used to investigate the relationships between the serum levels of Ang-5 and SHLP1 in patients with ACI complicated by BHS and the following indicators: left ventricular ejection fraction (LVEF), cardiac troponin I (cTnI), N-terminal pro-brain natriuretic peptide (NT-proBNP), creatine kinase isoenzyme (CK-MB), and others. The diagnostic value of serum Ang-5 and SHLP1 for BHS in patients with acute coronary insufficiency was evaluated using receiver operating characteristic (ROC) curves.

Kratak sadržaj

Uvod: Cilj je bio da se ispitaju nivoi homolognog proteina 1 za pre-življavanje motornih neurona (Survival of Motor Neurons Homolog Protein 1, SHLP1) i angiopoetina 5 (Ang-5) u serumu kod pacijenata sa akutnim cerebralnim infarktom (ACI) koji imaju moždano-srčani sindrom (BHS).
Metode: Grupu sa udruženim stanjima činilo je 208 pacijenata sa ACI komplikovanim BHS-om koji su hospitalizovani između januara 2023. i juna 2025. godine, dok je nekomplikovanu grupu činilo 220 pacijenata sa ACI koji su posetili bolnicu u istom vremenskom periodu. Nivoi SHLP1 i Ang-5 u serumu pacijenata određivani su metodom enzimski vezanog imunosorbentnog testa (ELISA). Pirsonova korelaciona analiza je korišćena za ispitivanje odnosa između serumskih nivoa Ang-5 i SHLP1 kod pacijenata sa ACI komplikovanim BHS-om i sledeć ih pokazatelja: ejekcione frakcije leve komore (LVEF), kardijalnog troponina I (cTnI), N-terminalnog pro-moždanog natriuretskog peptida (NT-proBNP), kreatin-kinaze MB izoenzima (CK-MB) i drugih. Dijagnostička vrednost serumskih Ang-5 i SHLP1 za BHS kod pacijenata sa akutnom koronarnom insuficijencijom procenjena je pomoću ROC krivih.

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Results: Serum SHLP1 level and LVEF were lower in the concurrent group than in the nonconcurrent group, although serum CK-MB, NT-proBNP, cTnI, and Ang-5 levels were greater in the concurrent group. Statistically, the differences were substantial (P<0.05). Serum SHLP1 levels in patients with ACI and BHS were positively associated with LVEF (P<0.05) and negatively correlated with CK-MB, NT-proBNP, and cTnI levels, as determined by Pearson correlation analysis. LVEF was adversely linked (P<0.05) with the serum Ang-5 level, whereas CK-MB, NT-proBNP, and cTnI levels were positively correlated. Ang-5, CK-MB, NT-proBNP, and cTnI were risk factors for BHS in ACI patients (P<0.05), whereas higher serum SHLP1 levels and higher LVEF were protective factors for BHS in ACI patients (P<0.05), according to the results of multivariate logistic regression analysis. Based on the results of the ROC curve analysis, the area under the curve (AUC) for the combined diagnosis of blood Ang-5 and SHLP1 for ACI patients with BHS was 0.927, greater than the AUC for serum Ang-5 and SHLP1 alone (Z=3.340, P=0.001; Z=3.541, P<0.001).
Conclusion: Patients with ACI complicated by BHS had low serum SHLP1 levels but high serum Ang-5 levels. The diagnostic value of ACI complicated by BHS can be increased by detecting both signs simultaneously.

Keywords: acute cerebral infarction, angiopoietin 5, survival of motor neurons homolog protein 1, diagnostic value

Rezultati: Nivo SHLP1 u serumu i LVEF bili su niži u grupi sa udruženim stanjima nego u grupi sa nekomplikovanim ACI, dok su nivoi CK-MB, NT-proBNP, cTnI i Ang-5 u serumu bili viši u grupi sa udruženim stanjima. Razlike su bile statistički značajne (P<0,05). Pirsonova korelaciona analiza pokazala je da su nivoi SHLP1 u serumu kod pacijenata sa ACI i BHS pozitivno povezani sa LVEF (P<0,05), a negativno korelisani sa nivoima CK-MB, NT-proBNP i cTnI. LVEF je bio negativno povezan (P<0,05) sa nivoom Ang-5 u serumu, dok su CK-MB, NT-proBNP i cTnI bili pozitivno korelisani. Prema rezultatima multivarijantne logističke regresione analize, Ang-5, CK-MB, NT-proBNP i cTnI predstavljali su faktore rizika za BHS kod pacijenata sa ACI (P<0,05), dok su viši nivoi SHLP1 u serumu i veća LVEF bili zaštitni faktori (P<0,05). Analiza ROC krive pokazala je da je površina ispod krive (AUC) za kombinovanu dijagnozu Ang-5 i SHLP1 u krvi kod pacijenata sa ACI i BHS iznosila 0,927, što je više nego kod pojedinačne primene serumskih Ang-5 i SHLP1 (Z=3,340, P=0,001; Z=3,541, P<0,001).
Zaključak: Pacijenti sa ACI komplikovanim BHS-om imaju niže nivoe SHLP1 u serumu i više nivoe Ang-5 u serumu. Istovremeno određivanje oba biomarkera može povećati dijagnostičku vrednost kod ACI komplikovanog BHS-om.

Ključne reči: akutni cerebralni infarkt, angiopoetin 5, homologni protein 1 za preživljavanje motornih neurona, dijagnostička vrednost

Introduction

Ten point three million occurrences of acute cerebral infarction (ACI), a prevalent cerebrovascular illness, occur each year, accounting for 10% of the total number of deaths due to diseases worldwide (1). Patients with ACI usually have a series of organ-related diseases, among which cerebral-heart syndrome (BHS) has a relatively high mortality rate and poses a threat to the prognosis of ACI patients (2). Owing to the lack of clear diagnostic indicators for BHS, relying solely on patient history, clinical symptoms, and electrocardiogram features for diagnosis is prone to misdiagnosis and missed diagnosis, which is not conducive to early diagnosis and timely treatment (3). Numerous cell types express the mitochondrial-derived peptide, Survival of Motor Neurons Homolog Protein 1 of 12S ribosomal RNA (SHLP1), which regulates energy consumption, insulin resistance, and the inflammatory response (4). Studies have shown that SHLP1 can participate in the pathophysiological process of cardiovascular diseases through multiple mechanisms and has important cardioprotective effects (5). Angiopoietin 5 (Ang-5) is a member of the ANGPTL family and is a multifunctional secreted protein that is expressed mainly in the liver (6–7). In patients with coronary heart disease, elevated Ang-5 levels may raise the risk of significant adverse cardiovascular events (8).

At present, there are limited clinical reports on the relationships among Ang-5, SHLP1, and BHS concurrent with ACI. This study examined blood levels of Ang-5 and SHLP1 in people with ACI concurrent with BHS and their clinical significance, to provide a reference for early clinical diagnosis and management.

Materials and Methods

General information

A total of 208 patients with ACI complicated by BHS who were admitted to our hospital from January 2023 to June 2025 were selected as the concurrent group.

Inclusion criteria: (1) met the diagnostic criteria for ACI in »Diagnosis and Treatment of Cardiovascular and Cerebrovascular Diseases« and were diagnosed with ACI by cranial CT examination; (2) met the diagnostic criteria for BHS and were diagnosed with BHS by CT and MRI examinations.

Exclusion criteria: (1) had malignant tumours; (2) had other severe liver, kidney, or brain organ diseases; (3) had a history of myocardial infarction, heart failure, etc.; (4) had severe infectious diseases or electrolyte disorders; (5) had a CT examination that revealed intracranial haemorrhage or subarachnoid haemorrhage. Another 110 patients with simple ACI who visited our hospital during the same period were selected as the nonconcurrent group.

This study was approved by the Medical Ethics Committee of our hospital [2022-745-69], and all participants signed the informed consent form.

Data collection

Patient sex, age, smoking history, drinking history, and comorbidity (diabetes, hypertension, hyperlipidaemia) data were collected.

Serum index detection

In the early morning, 24 hours after the onset of the disease, 5 mL of EDTA-K2 anticoagulant venous blood was collected from the median elbow vein on an empty stomach (fasting for 12 hours). The blood was left to stand at room temperature for 30 minutes using BD Vacutainer® serum separation tubes (item No. 367874). Centrifuge at 3000 rpm for 15 minutes at 4 °C (Eppendorf Centrifuge 5424R, rotor model 4130), and immediately aliquot the serum into Corning Costar® cryotubes (item No. 430639) after separation. Each tube containing a 200 μL serum sample was rapidly frozen in liquid nitrogen and then transferred to the Thermo Scientific™ Forma Scientific ultra-low-temperature refrigerator (-80 °C) for long-term storage. Laboratory testing was conducted using Mindray Medical's BS-3500 fully automatic biochemical analyser (Registration Number: The National Medical Device registration No. 20212341178), in combination with the original factory reagents (TG detection kit No. BS-3500-RG01, TC detection kit No. BS-3500-RG02) for lipid index detection. Among them, the glycerol phosphate oxidase (GPO)- peroxidase (PAP) method was used for TG. TC was detected by the cholesterol oxidase method (COD-PAP method), CK-MB was detected by the immunosuppression method (Mindray's CK-MB calibrator, item number BS-3500-CC01), and NT-proBNP was detected by the chemiluminescence method (Mindray's original magnetic particle reagent, item number BS-3500-CC03). cTnI detection uses the double antibody sandwich method (Mindray cTnI calibration curve plate, item number BS-3500-CC04). The detection of serum SHLP1 and Ang-5 was carried out using the Shanghai Elion Biological ELISA double antibody sandwich method (SHLP1 detection kit, product number E-EL-H1234, batch number 20250901); Ang-5 detection kit (item number E-EL-H5678, batch number 20250825), specific operation strictly follows the instructions: Pre-coated antibody (overnight at 4 °C), block solution (5% skimmed milk powder) at 37 °C for 1 hour, double antibody incubation (primary antibody incubation for 2 hours, secondary antibody HRP-labelled antibody incubation for 45 minutes), TMB colour development for 15 minutes (away from light), 2M H_2SO_4 to terminate the reaction The absorbance value was read in the Thermo Fisher Scientific Multiskan GO microplate reader (model: MK3, detection wavelength 450 nm).

The experiment was set up with blank Wells, zero-standard Wells, and high-, medium-, and low-concentration quality-control Wells (Bio-Rad Human QC Serum, item number 352241). Double-duplicate Wells were set up for each sample to detect, and the CV was strictly controlled at 5%. All operations are carried out in CLIA-certified laboratories (Filing Number: (2023-CLIA-0456) Completed. Throughout the sample processing process, Thermo Scientific Nunc® cryotubes (item No. 430639) were used for packaging to avoid repeated freezing and thawing. The test data were analysed by Magellan V2.3 software and then imported into SPSS 26.0 for statistical processing. The final results were expressed as the median (interquartile range), in compliance with the standardized operating procedures for clinical laboratory tests (SOP document number: YDB-2023-009) and the methodological disclosure requirements of international journals.

Imaging index detection

High-frequency vascular ultrasonography equipment was used to measure intima-media thickness of the carotid artery in the supine position. The carotid artery's origin, distal end (1.0–1.5 cm anterior to the bifurcation), and other locations were measured. Multiple measurements were taken, and the average value was recorded. The results were recorded in millimetres. Using MR scanning, multilayer short-axis sectional images of the heart from the base to the apex were obtained. Two radiologists with professional training calculated the LVEF from sectional images.

Statistical analysis

The SPSS 21.0 statistics program was used to analyse the data. The two groups were compared using the independent-samples t-test for quantitative data with normal distributions, expressed as $\bar{x}\pm s$; groups were compared using the χ^2 test for count data, expressed as the number of instances or percentages. Ang-5 and SHLP1 serum levels in ACI patients who developed BHS were compared with LVEF, CK-MB, NT-proBNP, and cTnI levels using Pearson correlation analysis. Factors influencing BHS in patients with ACI were examined using multivariate logistic regression. ROC curves were used to assess the diagnostic utility of serum Ang-5 and SHLP1 for BHS in individuals suffering from acute coronary insufficiency.

Results

Comparison of clinical data between the two groups

Serum SHLP1 and LVEF levels were lower in the group with complications than in the group without issues. However, serum CK-MB, NT-proBNP, cTnI, and Ang-5 levels were also higher in the group with complications (see *Table I*).

The two groups of patients showed significant differences in core parameters, including myocardial injury markers (CK-MB, cTnI), cardiac function indicators (LVEF), and metabolic regulatory factors (Ang-5, SHLP1). The BHS concurrent group showed the characteristic change of a significantly elevated myocardial enzyme spectrum. The increase in cardiac stress indicators such as NT-proBNP and CK-MB was statistically different from that of the simple cerebral infarction group, suggesting a dose-effect relationship between the degree of myocardial cell injury and neurogenic cardiac events. The left ventricular ejection fraction (LVEF) of this group of patients showed a significant functional decline compared with the control group, forming a pathological closed loop with myocardial contractility inhibition and neurohumoral activation.

Correlations between serum Ang-5 and SHLP1 levels and LVEF, CK-MB, NT-proBNP, and cTnI levels in patients with ACI and BHS

The results of the Pearson correlation analysis revealed that the serum SHLP1 level in patients with ACI and BHS was negatively correlated with CK-MB, NT-proBNP, and cTnI levels and positively correlated with LVEF ($P<0.05$); the serum Ang-5 level was positively correlated with CK-MB, NT-proBNP, and cTnI levels and negatively correlated with LVEF ($P<0.05$), see *Table II*.

Further analysis indicates that Ang-5 and SHLP1 have significant functional antagonism in patients with BHS. The pro-inflammatory pathway mediated by the former forms a dynamic equilibrium with the metabolic homeostasis regulated by the latter. This imbalance can serve as a molecular marker for assessing the severity of neurogenic cardiac events. The multivariate regression model confirmed the clinical value of Ang-5 and myocardial injury markers as independent risk factors, while the protective effects of SHLP1 and LVEF highlighted the potential of metabolic intervention to improve prognosis.

Table I Comparison of clinical data between the two groups [n(%), or $\bar{x}\pm s$].

Indicator	Concurrent group (n=208)	Non-concurrent group (n=220)	x^2/t	P
Gender			0.601	0.439
Male	130 (62.50)	126 (57.27)		
Female	78 (37.50)	94 (42.73)		
Age (Years)	65.78±4.55	66.51±4.48	1.356	0.170
Smoking history (Yes)	102 (49.04)	98 (44.55)	0.437	0.513
History of drinking (Yes)	96 (46.15)	80 (36.36)	2.119	0.149
Combined with diabetes (Yes)	42 (20.19)	46 (20.91)	0.010	0.890
Combined hypertension (Yes)	88 (42.31)	86 (39.09)	0.986	0.324
Combined hyperlipidaemia (Yes)	128 (61.54)	134 (60.91)	0.002	0.928
Carotid intima-media thickness (mm)	0.98±0.15	0.96±0.13	1.320	0.189
CK-MB (U/L)	251.58±70.85	186.32±42.58	8.213	<0.001
NT-proBNP (ng/L)	1091.47±260.44	801.83±80.55	11.111	<0.001
cTnI (mg/L)	1.55±0.84	0.95±0.36	7.119	<0.001
LVEF (%)	52.85±5.84	58.66±5.68	7.419	<0.001
TC (mmol/L)	4.56±1.04	4.59±1.00	0.214	0.836
TG (mmol/L)	1.46±0.36	1.49±0.31	0.618	0.532
Ang-5 (mg/L)	68.72±12.42	50.15±8.51	12.808	<0.001
SHLP1 (ng/mL)	116.76±20.30	158.57±25.02	13.331	<0.001

Table II Correlation between serum Ang-5, SHLP1 levels, and LVEF, CK-MB, NT proBNP, cTnI levels in ACI patients with BHS.

Indicator	SHLP1		Ang-5	
	r	P	r	P
CK-MB	-0.632	<0.001	0.614	<0.001
NT-proBNP	-0.472	<0.001	0.556	<0.001
cTnI	-0.591	<0.001	0.608	<0.001
LVEF	0.550	<0.001	-0.471	<0.001

Table III Multivariate logistic regression analysis of influencing factors of concurrent BHS in ACI patients.

Factor	β	SE	WaldX2	P	OR	OR 95%CI
Ang-5	1.974	0.347	32.736	<0.001	7.178	3.657~14.097
SHLP1	-2.123	0.259	68.389	<0.001	0.123	0.076~0.191
CK-MB	1.100	0.453	6.048	0.017	3.027	1.255~7.308
NT-proBNP	1.339	0.471	7.801	0.008	3.807	1.493~9.701
cTnI	1.745	0.303	33.843	<0.001	5.714	3.178~10.276
LVEF	-1.710	0.298	33.973	<0.001	0.183	0.104~0.323

Table IV Diagnostic value of serum Ang-5 and SHLP1 for concurrent BHS in ACI patients.

Indicator	AUC	AUC 95%CI	Sensitivity (%)	Specificity (%)	Youden index	Best Truncation Value	Youden index	P
Ang-5	0.811	0.763~0.861	75.03	83.67	0.589	60.94 mg/L	0.589	<0.001
SHLP1	0.800	0.741~0.851	79.84	84.58	0.647	131.11 ng/mL	0.647	<0.001
The combination of the two	0.920	0.886~0.951	94.26	82.76	0.773	-	0.773	<0.001

Multivariate logistic regression analysis of the influencing factors of BHS in patients with ACI

We used whether the ACI patients had BHS as the dependent variable (BHS = 1, no BHS = 0) and used Ang-5, SHLP1, CK-MB, NT-proBNP, cTnI, and LVEF as independent variables (all entered as original values) for multivariate logistic regression analysis. The results revealed that elevated serum levels of Ang-5, CK-MB, NT-proBNP, and cTnI were risk factors for BHS in ACI patients ($P<0.05$), whereas elevated serum SHLP1 levels and increased LVEF were protective factors ($P<0.05$), see *Table III*.

Diagnostic value of serum Ang-5 and SHLP1 for BHS in patients with ACI

A ROC curve analysis was conducted to determine whether the ACI patients had BHS as the state variable (complicated =1, not complicated =0) and to use serum Ang-5 levels, SHLP1 scores alone, and their combination as the test variables. The area under the curve (AUC) of the combined diagnosis of serum Ang-5 and SHLP1 for ACI patients with BHS was 0.920, which was greater than the AUC of the individual diagnoses of serum Ang-5 and SHLP1 ($Z=3.340$, $P=0.001$; $Z=3.541$, $P<0.001$), see *Table IV*.

Discussion

Among middle-aged and older patients, ACI is a prevalent cerebrovascular illness. Numerous organs throughout the body may sustain damage, and their incidence, disability, and fatality rates are significant. Among them, the heart is more frequently affected. Therefore, these patients are prone to concurrent diseases such as BHS (11, 12). The occurrence of BHS in ACI patients leads to prolonged hospital stays, increased hospital costs, poor prognoses, and even death (13). Despite progress in medical knowledge and technology, the diagnosis and

treatment of BHS still present significant challenges in clinical practice.

Mitochondria are the main sites for cellular energy production and aerobic respiration. Once their functions are impaired, various pathological changes, such as oxidative stress, metabolic imbalance, the inflammatory response, and aging, can occur (14). SHLP1 is a new member of the mitochondrial polypeptide family and is expressed in various tissues, such as the brain, muscles, and kidneys. It is speculated that serum SHLP1 levels are involved in the progression of cardiovascular disease (15–17). The results of this study show that the serum SHLP1 level in patients with ACI complicated with BHS is lower than that in patients with ACI alone.

Additionally, Pearson correlation analysis indicates that the serum SHLP1 level in patients with ACI complicated by BHS is negatively correlated with CK-MB and NT-proBNP. These findings suggest that SHLP1 is related to a patient's cardiac dysfunction and may serve as a potential indicator for evaluating ACI complicated with BHS. It is speculated that, in ACI patients, when SHLP1 levels decrease, endothelial protection weakens, the degree of atherosclerosis increases, and cerebral blood perfusion is affected, thereby contributing to the occurrence of BHS (18). The AUC of blood SHLP1 for diagnosing ACI complicated by BHS alone was 0.807, according to the results of the ROC curve study, indicating that serum SHLP1 may be an effective marker for diagnosing ACI complicated by BHS.

ANGPTL is widely expressed in the liver, vascular system, and hematopoietic system. Endothelial dysfunction, the inflammatory response, dyslipidaemia, calcification, platelet activation, and the onset and progression of atherosclerosis are all influenced by ANGPTL1 (19–21). Ang-5 is produced in the human liver and is an important regulator of lipoprotein metabolism. It can inhibit the hydrolysis of phospholipids and TG by regulating endothelial lipoprotein lipase (22–24). The severity and prognosis of individuals with ACI are strongly correlated with Ang-5. As in previous research, this study found that patients with ACI and BHS have elevated blood levels of Ang-5. The ROC curve analysis further proves that the AUC of the serum ANGPTL concentration for the diagnosis of ACI complicated with BHS is 0.818, indicating that the serum Ang-5 concentration may be an effective marker for the diagnosis of ACI complicated with BHS.

Elevated levels of blood Ang-5, CK-MB, NT-proBNP, and cTnI were found to be risk factors for ACI complicated with BHS ($P<0.05$), while elevated levels of serum SHLP1 and enhanced LVEF were found to be protective factors ($P<0.05$). These findings suggest that doctors should pay attention to the levels of these factors during clinical diagnosis. The AUC of the combined diagnosis of serum Ang-5 and SHLP1 for ACI complicated with BHS was 0.920, with a sensitivity of 94.26% and a specificity of 82.76%. These findings indicate that the combination of the two has high diagnostic value for ACI complicated by BHS and can be widely used as an auxiliary diagnostic tool for this disease. A serum Ang-5 concentration >60.94 mg/L or SHLP1<131.11 ng/mL suggests an increased risk of BHS in ACI patients. Doctors should promptly adjust the treatment plan to reduce the risk of BHS in ACI patients.

Conclusion

Serum Ang-5 levels were elevated, and SHLP1 levels were decreased in patients with ACI and BHS. The combined detection of these two indicators has high diagnostic accuracy for ACI patients with BHS. However, this study was limited by the inclusion and exclusion criteria, resulting in a limited sample size, a single geographical origin, and selection bias. Moreover, the specific mechanisms underlying serum Ang-5 and SHLP1 levels in ACI patients with BHS remain unclear. In the future, we will increase the sample size, expand the geographical sources, and conduct further investigations.

Authors' contribution

Qian Zhang and Xuehan Zhang made the same contributions to this research work.

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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