Neurology Asia 2023; 28(3) : 541 – 551

Serum galectin-3 as a potential predictive biomarker Is associated with post-stroke depression

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Abstract

Objective: As an inflammatory mediator, serum galectin-3 is involved in a variety of biological processes, including fibrosis, angiogenesis, apoptosis and immune activation, as well as in the physiological and pathological processes of multiple nervous system diseases. The aim of this study was to investigate the relationship between serum galectin-3 and post-stroke depression in acute ischemic stroke (AIS) patients. *Methods:* Baseline data of patients with AIS admitted to the Department of Neurology, First Affiliated Hospital, Shihezi University School of Medicine from October 2021 to May 2022 were continuously collected. The general data of the patients were collected and serum galectin-3 levels were measured. Hamilton Depression Scale was used to evaluate the occurrence of post-stroke depression. *Results:* The level of serum galectin-3 was increased in AIS patients with post-stroke depression. The prevalence of post-stroke depression increased with the increase of serum galectin-3 level, suggesting that serum galectin-3 was associated with post-stroke depression. The findings from the ROC curve showed that the area under the curve of serum galectin-3 as a possible biomarker for diagnosing post-stroke depression in AIS patients was 0.719. The sensitivity and specificity were 78.1% and 65.2%, respectively. Multivariate logistic regression analysis showed that serum galectin-3 level remained to be a predictor of post-stroke depression.
Conclusions: Elevated serum galectin-3 levels are linked to a higher risk of post-stroke depression. Serum galectin-3 may be a promising biomarker for clinical monitoring of post-stroke depression.

Keywords: Acute ischemic stroke, galectin–3, post-stroke depression

INTRODUCTION

Stroke is the leading cause of death and disability among Chinese adults. Global burden of disease (GBD) data shows that the incidence of ischemic stroke is increasing year by year[1-2], and post-stroke anxiety and depression are common complications of a stroke. According to previous reports, 29% to 36% of stroke patients experience depression, and the severity of the residual symptoms or physical disability was significantly related to depression.[3-4] Post-stroke depression (PSD) may hinder rehabilitation by its effect on physical and cognitive function and may also increase the risk of death. As such, counseling for post-stroke depression is essential because rehabilitation in this critical period is crucial to the recovery of neurological function. Therefore, research into biomarkers for predicting PSD is of importance.

Recent studies have found that galectin-3, an inflammatory mediator derived from microglia participates in the pathophysiological process of multiple neurological diseases.[5,6] Studies have shown that galectin-3 can be used as a prognostic marker of heart failure. High galectin-3 level is a predictive biomarker of thrombosis in cardioembolic stroke[7,8] and can also be used as an inflammatory biomarker in the formation and development of atherosclerosis.[9,10] However, the relationship between galectin-3 and PSD remains unknown. Previous studies have shown that high galectin-3 levels may increase the risk of depression and anxiety in patients with diabetes and cardiovascular diseases.[11] This study aimed to investigate whether galectin-3 may be a biomarker for predicting depression after acute ischemic stroke and to provide a reference for early clinical intervention and prevention of depression after ischemic stroke.

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Date of Submission: 26 October 2022; Date of Acceptance: 18 April 2023

https://doi.org/10.54029/2023szm

METHODS

Study population

A total of 98 consecutive patients with acute ischemic stroke (AIS) treated in the Department of Neurology, The First Affiliated Hospital of Shihezi University from October 2021 to May 2022 were selected as AIS group. The inclusion criteria were: (1) AIS diagnosis was consistent with the WHO standards.[12] (2) Time of first onset was ≤24 hours. (3) Serum galectin-3 level measured. (4) Complete clinical data available. (5) No previous history of depression and related depression diagnosis. (6) Has signed written consent and were willing to cooperate with the relevant blood sampling and complete the Hamilton Depression Scale, NIHSS score, and MRS scale.

A total of 62 healthy volunteers were recruited in the control group. The control were recruited from the staffs of the First Affiliated Hospital of Shihezi University. The control were healthy with normal Head CT and MRI and no previous history of depression.

The study protocol complied with the requirements of the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Shihezi University (KJX-2022-007-01).

Baseline characteristics

The information collected include general information of subjects; age, gender, education level, hypertension, diabetes, arrhythmia, hyperlipidemia, TOAST classification[13], plaque formation (divided into no-plaque, stable plaque, and unstable plaque), infarct volume, current smoking, current drinking and treatment methods, the National Institute of Health Stroke Scale (NIHSS)[14] scores and the modified Rankin Scale (MRS) score on the seventh day of admission. Biochemical indexes: Total cholesterol (TC), triacylglycerol (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), fasting blood glucose (FBG), creatinine, uric acid, cystatin C, white blood cell count, lymphocyte count, monocyte count, neutrophil count.

Blood samples test

Fasting peripheral venous blood was collected from all AIS patients within 24 hours after admission and healthy volunteers within the morning of the medical examination. Subsequently, the blood samples were centrifugated at 3000 r/min for 10 minutes, and the supernatant was placed in the refrigerator at -80°C for unified storage. The concentration of serum galectin-3 was detected by enzyme-linked immunosorbent assay (ELISA) and based on previous research reports and instructions. A kit from ABCAM in the UK was used, with an in-batch variation of 3.4% and an intercluster variation of 1.6%.

Subgroups

All enrolled AIS patients and volunteers underwent a carotid ultrasound examination. Carotid ultrasound is a non-invasive examination, has been listed as a routine item of health examination, and can be large-scale screening. The American Heart Association recommended carotid ultrasound screening for asymptomatic adults to cardiovascular and cerebrovascular disease.[15] The results of extensive data studies suggest that carotid artery plaque formation tends to be younger, and the detection rate of carotid artery plaque increases significantly with age.[16] Two-dimensional ultrasound can directly observe the location and size of the plaque, measure the carotid intima-media, and accurately judge the internal echo of plaque, blood flow velocity through the plaque, and resistance index. Unstable plaques have a greater risk of thrombosis and are prone to rapid progression. Unstable plaques are more likely to break off and cause blood clots than stable plaques. The echogenic characteristics of unstable plaques were used by ultrasound to assess plaque stability. Groups according to the results of carotid ultrasound: (1) no-plaque; (2) stable plaque; (3) unstable plaque.

All enrolled AIS patients underwent head CT or MRI scans within 24 hours of onset. Experienced radiologists completed the volume of cerebral infarction assessments and were blind to the patient's baseline characteristics.[17] AIS patients were divided into three subgroups according to the volume of cerebral infarction[18]: (1) Large infarction group (infarct volume >3 cm^3); (2) Middle infarct group (infarct volume 1.5-3 cm^3); (3) Small infarct group (infarct volume <1.5 cm^3).

All patients enrolled in AIS received a head CT scan within 24 hours of onset, and more than two professional radiologists issued infarction site reports according to the images. Group of infarct sites[19]: (1) Group A included one or several regions in the frontal lobe, temporal lobe, parietal lobe, and occipital lobe; (2) Group B consists of the thalamus, basal ganglia, corpus callosum, and one or several regions in the lateral ventricle. (3)

Group C includes cerebellum and/or brainstem; (4) Group D involved at least two regions in the above three groups.

All patients enrolled in AIS were assessed by the National Institutes of Health Stroke Scale (NIHSS) on the first day after admission.[20] According to the NIHSS score, AIS patients were divided into a mild neurological impairment group (NIHSS score ≤3 points) and a moderate to severe neurological impairment group (NIHSS score >3 points).

All patients enrolled in AIS received different treatments after admission. The patients with cerebrovascular examinations were classified into stroke etiology groups (TOAST classification). They were screened according to the inclusion and exclusion criteria into the large-artery atherosclerosis group (n=58) and small vessel occlusion group (n=39). Large-artery atherosclerosis type: The patient showed significant (>50%) cerebrovascular imaging stenosis or branch occlusion of major cerebral or cortical arteries, cortical or cerebellar lesions with a diameter greater than 1.5 cm on head CT or MRI, and cerebral stem or subcortical hemisphere infarction. Small vessel occlusion type: head CT or magnetic resonance examination was normal, or the infarction was less than 1.5 cm in diameter.[21]

Treatment methods: Give priority to improving cerebral blood circulation, the early recovery of blood flow, promoting recanalization, reduce brain tissue hypoxia injury. Intravenous thrombolytic-bridging intravascular interventional therapy is the first choice within the treatment time window of patients with acute vascular occlusive stroke. Currently, there are the following treatment methods[22]: (1) No perfusion therapy; (2) Intravenous thrombolysis - Endovascular interventional bridging therapy; (3) Endovascular treatment.

All enrolled AIS patients were scored on the MRS scale[23] on the 7th day after admission. According to the MRS score, AIS patients were divided into a good functional outcome group (score <2 points) and a poor functional outcome group (score ≥2 points).

Hamilton Depression Scale (HAMD) score

HAMD[24] was used to evaluate PSD in AIS patients on the seventh day after admission. The score of the HAMD scale can better reflect the severity of depressive symptoms, and it is often used in clinical diagnosis and classification of depression. According to the HAMD score, AIS patients were categorized into the post-stroke non-depression subgroup (HAMD score <7) and the post-stroke depression subgroup (HAMD score ≥7). According to the HAMD score, AIS patients were categorized into two subgroups: The post-stroke depression subgroup (32 cases) and the post-stroke non-depression subgroup (66 points).

Statistical analysis

Statistical analyses were conducted using the software package SPSS 26.0 (IBM Corporation, Armonk, NY). In the research, continuous variables conforming to normal distribution were articulated as mean ± standard deviation, and the comparison between constant variables that follow the normal distribution was made utilizing Student's t-test. Continuous variables with non-normal distribution were articulated as median(quartiles), and the comparison between constant variables with asymmetric distribution was created using the Mann-Whitney U test. Categorical variables were expressed as relative numbers, x^2 test was utilized to examine the differences between categorical variables. Pearson correlation analysis was used to analyze the correlation between two continuous variables. The sensitivity and the specificity of serum galectin-3 levels in the diagnosis of post-stroke depression were evaluated utilizing receiver-operating characteristic (ROC) curve analysis. Calculate the point that maximizes (Sensitivity + Specificity-1) as the cut-off value. Multivariate logistic regression analysis of the link between serum galectin-3 levels and PSD. 0.05 is used as the threshold to determine whether the difference is significant.

RESULTS

Comparison of general information and galectin-3 level between the AIS group and control group

In the end, our prospective cohort analysis included 98 patients with AIS and 62 healthy volunteers as control. We recorded the following baseline characteristics: age, gender, current smoking, and drinking. We compared the baseline characteristics of the two groups, and the results showed no statistical significance (P>0.05). There was no significant difference in the biochemical indexes of TC, TG, LDL, HDL, creatinine, uric acid, cystatin C, monocyte count and LMR between the AIS group and control group at admission (P>0.05). The levels of FBG, white blood cell count, neutrophil count, GLR, PLR and

serum Galectin-3 in the AIS group were higher than those in the control group. The lymphocyte count at admission and PWR were lower than those in the control group (P<0.05), as shown in Table 1.

Relationship between the prevalence of post-stroke depression and serum galectin-3 levels

According to the quartile of serum Galectin-3 levels, the detection rate of PSD is illustrated in Table 2. The results showed a linear relationship between PSD and the quartile of baseline serum galectin-3 levels in AIS patients: the detection rate of PSD increased with the increase of serum galectin-3 levels ($p < 0.001$).

Comparison of general information and galectin-3 levels between the post-stroke depression subgroup and the post-stroke non-depression subgroup

Seven days after the onset of AIS, 98 patients were included in our prospective cohort analysis. Among them, 32 AIS patients developed PSD, with an incidence rate of 32.65%. We compared the above baseline characteristics and biochemical parameters of the two cohorts, and the following clinical data showed no statistical significance: gender, education level, the incidence of hypertension, diabetes, arrhythmia, hyperlipidemia, plaque formation, infarct volume, current smoking, and drinking; TC, TG, LDL, HDL, FBG, creatinine, uric acid, cystatin, white blood cell count, monocyte count ($p > 0.05$). However, age, TOAST classification, treatment

Table 1: General data of AIS group and control group

Clinical Data	Control Group (n=62)	AIS Group (n=98)	Test Statistics	P values
Age, years	60.4 ± 9.9	63.1 ± 12.5	1.605[a]	0.111
Gender, male, n%	39 (62.9)	70 (71.4)	0.334[b]	0.563
Current smoking, n%	24 (38.7)	35 (35.4)	0.433[b]	0.510
Current drinking, n%	17 (27.4)	19 (19.2)	1.915[b]	0.166
Plaque formation, n%			14.443[b]	0.001*
No-plaque	18 (29.0)	8 (8.1)		
Stable plaque	12 (19.4)	35 (35.4)		
Unstable plaque	32 (51.6)	61 (61.6)		
TC, mmol/L	4.1 (1.5)	4.4 (1.5)	-1.189[c]	0.234
TG, mmol/L	1.5 ± 0.8	1.5 ± 1.0	0.300[a]	0.764
LDL, mmol/L	2.6 (1.4)	2.9 (1.3)	-1.606[c]	0.108
HDL, mmol/L	1.1 (0.2)	1.0 (0.3)	-1.560[c]	0.119
FBG, mmol/L	5.7±1.6	8.3±4.7	4.739[a]	<0.001*
Creatinine, μmoI/L	64.6 (16.7)	63.9 (21.9)	-0.655[c]	0.513
Uric Acid, μmoI/L	289.3 (105.0)	298.0 (132.0)	-0.375[c]	0.708
Cystatin C, mg/L	1.0±0.2	1.0±0.4	0.316[a]	0.753
White blood cell count, 10^9/L	6.6±2.0	8.0±2.9	5.577[a]	<0.001*
Lymphocyte count, 10^9/L	2.0 (0.8)	1.6 (1.1)	-2.757[c]	0.006*
Monocyte count, 10^9/L	0.5 (0.2)	0.4 (0.4)	-0.060[c]	0.952
Neutrophil count, 10^9/L	4.0±2.0	5.7±2.8	6.242[a]	<0.001*
LMR, %	3.6 (2.8)	3.7 (2.9)	-1.633[c]	0.102
GLR, %	2.2±1.3	4.4±3.1	6.293[a]	<0.001*
PWR, %	36.4 (15.0)	29.0 (14.1)	-3.759[c]	<0.001*
PLR, %	119.5 (52.2)	147.3 (89.9)	-3.239[c]	0.001*
Galectin-3, ng/mL	2 006.3±58.7	2 371.6±74.0	35.099[a]	<0.001*

Abbreviations: AIS: Acute Ischemic Stroke; TC: Total cholesterol, TG: Triacylglycerol, LCL: Low-density lipoprotein, HDL: High-density lipoprotein, FBG: Fasting Blood Glucose, LMR:Lymphocyte-to-Monocyte Ratio, GLR:Neutrophil-to-Lymphocyte ratio, PWR:Platelet-to-White blood cell ratio, PLR:Platelet-to-Lymphocyte Ratio; [a] represents T value, [b] represents x^2 value, [c] represents U value, *P<0.05.

Table 2: Relationship between the detection rate of post-stroke depression and serum galectin-3 levels

Variable	Serum Galectin-3 levels				P for trend
	Q1=2368.48	Q2=2411.33	Q3=2454.18	Q4=2497.03	
Post-stroke depression,n(%)	2 (8.16)	6 (24.49)	12 (48.98)	13 (53.06)	0.014

method, site of infarction, MRS score, NIHSS score, the severity of neurological impairment, lymphocyte count, neutrophil count, and Serum galectin-3 is associated with PSD (P<0.05). The serum galectin-3 levels of AIS patients were 2367.5(142.6)μg/L and 2411.3(42.9)μg/L in the non-depressed group and depressed group, respectively. Compared with the non-depression subgroup, the serum galectin-3 level in the PSD subgroup was significantly higher, and the difference was significant ($p < 0.001$), suggesting that the elevated serum galectin-3 level was associated with PSD. Table 3 summarizes the baseline features of patients with AIS.

Logistic regression analysis for the association of galectin-3 with post-stroke depression

Univariate analysis was used to analyze statistically significant differences as independent variables, including age (measured value), infarct site in group A and group D, different treatment methods (0= general treatment, 1= non-general treatment), TOAST classification (0= small artery occlusion, 1= large atherosclerosis), prognosis (0= good functional outcome, 1= poor functional outcome, The serum levels of Neutrophil count, LMR, GLR, PWR, PLR and serum galectin-3 (measured values) were analyzed by stepwise logistic regression analysis. The results showed that poor functional outcome (MRS score≥2 score) and elevated serum galectin-3 level were risk factors for PSD (OR>1, P<0.05), as shown in Table 4.

ROC analysis of serum galectin-3 in the post-stroke depression diagnosis

ROC curve analysis was used to assess the diagnostic value of serum galectin-3 as a potential marker. The area under the curve (AUC) of serum galectin-3 in AIS patients was 0.719[95%CI(0.618,0.819)], while the diagnostic sensitivity was 78.1%, and the specificity was 65.2%. The results of the ROC analysis are shown in Figure 1.

In ROC analysis, we found that the threshold point of serum galectin-3 level for diagnosing post-stroke depression was 2385.33 ng/ml. Using this cut-off point, we subsequently analyzed the link between serum galectin-3 levels and PSD in bivariate analysis. The results showed that AIS patients with serum galectin-3 levels > 2385.33 ng/mL were more likely to develop PSD than those with galectin-3 levels below 2385.33 ng/mL (OR = 1.015, P =0.011).

DISCUSSION

Previous studies shows that galectin-3, an inflammatory mediator derived from microglia, plays an essential role in innate and acquired immunity. One of the characteristic features of microglial activation after stroke is a marked increase in proliferation, peaking 48 – 72h after initial ischemic injury.[25] In the adult brain, galectin-3 is crucial for resident microglia activation and proliferation in response to ischemic insult and plays pivotal roles in fine-tuning microglia morphology and phenotype.[26] Following brain injury, it triggers the anti-inflammatory properties of microglia by promoting a pro-inflammatory phenotype by activating Toll-like receptor 4(TLR4) and downstream inflammatory targets, and it also acts as a triggering receptor expressed on myeloid cells 2 (TREM2) ligand of microglia.[27,28] In addition, galectin-3 stimulates the expression of various inflammatory and chemokines and is a core modulator of critical processes in acute and chronic inflammatory environments. It participates in the pathophysiology of various neurological diseases by regulating apoptotic neutrophils, clearing neutrophils, attracting monocytes/macrophages to accumulate in lesions, binding to integrins on the cell surface, and disrupting the blood-brain barrier.[29]

This study examined the difference in serum galectin-3 levels between the AIS and the control groups. The results of the study showed that serum galectin-3 levels of AIS patients were higher as opposed to the control group. Previous studies have shown that serum galectin-3 level can be used as an emerging biomarker to evaluate the

Table 3: Baseline features of patients with AIS

Clinical Data	Post-stroke Non-depression group	Post-stroke depression group	Test Statistics	P values
Age, years	57.0 (22.0)	67.5 (22.0)	-1.990[a]	0.047*
Gender, male, n%	47 (71.2)	20 (62.5)	0.756[b]	0.384
Education level, n%			2.160[b]	0.142
Junior high school below	19	14		
Junior high school and above	47	18		
Hypertension, n%	54 (81.8)	24 (75.0)	0.617[b]	0.432
Diabetes, n%	25 (37.9)	12 (37.5)	0.001[b]	0.971
Arrhythmia, n%	17 (25.8)	12 (37.5)	1.426[b]	0.232
Hyperlipidemia, n%	29 (43.9)	13 (40.6)	0.058[b]	0.809
Current smoking, n%	25 (37.9)	9 (28.1)	0.905[b]	0.341
Current drinking, n%	13 (19.7)	5 (15.6)	0.238[b]	0.625
Plaque formation, n%			0.778[b]	0.704
No-plaque	4 (6.1)	3 (9.4)		
Stable plaque	25 (37.9)	10 (31.3)		
Unstable plaque	37 (56.1)	19 (59.4)		
The volume of cerebral infarction, n%			5.692[b]	0.058
Large infarct volume	35 (53.0)	9 (28.1)		
Middle infarct volume	17 (25.8)	11 (34.4)		
Small infarct volume	14 (21.2)	12 (37.5)		
Site of infarction,n%				
Group A	27 (40.9)	21 (65.6)	5.268[b]	0.022*
Group B	48 (72.7)	26 (81.3)	0.847[b]	0.358
Group C	13 (19.7)	4 (12.5)	0.779[b]	0.378
Group D	14 (21.2)	16 (50.0)	8.408[b]	0.004*
Treatment Methods, n%			12.372[b]	0.001*
No perfusion therapy	49 (74.2)	12 (37.5)		
IV+IA	12 (18.2)	13 (40.6)		
IA	5 (7.6)	7 (21.9)		
TOAST classification, n %			6.369[b]	0.012*
Large-artery atherosclerosis	34 (51.5)	25 (78.1)		
Small vessel occlusion	32 (48.5)	7 (21.9)		
MRS score, n%			12.775[b]	<0.001*
MRS score<2 score	51 (77.3)	13 (40.6)		
MRS score≥2 score	15 (22.7)	19 (59.4)		
NIHSS score	2.3±1.7	3.6±1.9	-3.548[c]	0.001*
The severity of neurological impairment				
NIHSS score ≤3 points	31 (47.0)	8 (25.0)	4.342[b]	0.037*
NIHSS score > 3 points	35 (53.0)	24 (75.0)		
TC, mmol/L	4.4 (2.1)	4.3 (2.2)	-0.427[a]	0.669
TG, mmol/L	1.4 (0.7)	1.1 (0.8)	-1.878[a]	0.060
LDL, mmol/L	2.9 (2.0)	2.9 (1.7)	-0.648[a]	0.517
HDL, mmol/L	0.9 (0.4)	1.0 (0.2)	-0.125[a]	0.900
FBG, mmol/L	7.1±2.9	9.2±4.6	-0.009[c]	0.993
Creatinine, μmoI/L	55.9 (25.2)	63.6 (26.9)	-0.365[a]	0.715

Uric Acid, μmoI/L	309.0 (187.0)	277.0 (113.0)	-1.162[a]	0.245
Cystatin C, mg/L	0.9 (0.3)	1.0 (0.3)	-0.988[a]	0.323
White blood cell count, 10^9/L	7.2 (2.4)	7.7 (3.2)	-1.209[a]	0.227
Lymphocyte count, 10^9/L	1.6 (1.3)	1.6 (0.5)	-2.858[a]	0.004*
Monocyte count, 10^9/L	0.5±0.3	0.6±0.4	0.366[c]	0.715
Neutrophil count, 10^9/L	4.7 (1.5)	5.4 (3.6)	-2.339[a]	0.019*
LMR, %	4.0 (2.8)	2.8 (3.2)	-1.975[a]	0.048*
GLR, %	3.1 (4.0)	3.6 (4.0)	-3.381[a]	0.001*
PWR, %	34.6 (12.5)	24.8 (14.4)	-2.635[a]	0.008*
PLR, %	146.7 (85.4)	156.1 (104)	-2.106[a]	0.035*
Galectin-3, ng/mL	2367.5 (142.6)	2411.3 (42.9)	-3.496[a]	<0.001*

Abbreviations: Group A: one or several regions in the frontal lobe, temporal lobe, parietal lobe, and occipital lobe; Group B: the thalamus, basal ganglia, corpus callosum, and one or several regions in the lateral ventricle; Group C: cerebellum and/or brainstem; Group D: at least two regions in the above three groups. TOAST: Trial of ORG 10172 in Acute Stroke Treatment; MRS: Modified Rankin Scale; NHISS: National Institute of Health Stroke Scale. TC: Total cholesterol, TG: Triacylglycerol, LCL: Low-density lipoprotein, HDL: High-density lipoprotein, FBG: Fasting Blood Glucose, LMR:Lymphocyte-to-Monocyte Ratio, GLR:Neutrophil-to-Lymphocyte ratio, PWR:Platelet-to-White blood cell ratio, PLR:Platelet-to-Lymphocyte Ratio. [a] represents U value, [b] represents x^2 value, [c] represents T value. *P<0.05.

prognosis of cerebrovascular diseases.[30] This study showed that elevated serum galectin-3 was associated with ischemic stroke, consistent with previous findings. Serum galectin-3 levels are upregulated in response to inflammatory stimuli and promote the release of relevant inflammatory factors and chemokines, which are involved in the activation of niacinamide adenine dinucleotide phosphate (NADPH) and the release of superoxide ions, further aggravating ischemic tissue injury and neurological impairment. It plays an essential role in oxidative stress and interferes with the occurrence and development of cerebrovascular diseases.

This study investigated the relationship between serum galectin-3 levels and PSD. The results showed that the prevalence of PSD increased with increasing serum galectin-3 levels(P<0.001). The findings also showed that serum galectin-3 levels were higher in patients in the PSD group than in patients in the poststroke non-depression group (P<0.05). Nevertheless, the relationship between galectin-3 and PSD is still unknown. Up to now, it has been shown that depression in type 1 diabetes was associated with high levels of circulating galectin-3[31], and higher galectin-3 levels are independently associated

Table 4: Multivariate Logistic regression analysis of Post-stroke depression

Clinical Data	P values	OR	95%CI
Age, years	0.126	1.045	0.988-1.105
Group A, n	0.365	0.538	0.141-2.053
Group D, n	0.278	0.472	0.121-1.833
Treatment Methods, n	0.023	0.184	0.043-0.792
Large-artery atherosclerosis, n	0.092	3.459	0.818-14.623
MRS score≥2 score, n	0.015*	0.191	0.050-0.727
Neutrophil count, 10^9/L	0.449	0.817	0.483-1.380
LMR, %	0.929	0983	0.680-1.423
GLR, %	0.907	1.052	0.448-2.473
PWR, %	0.271	0.918	0.789-1.069
PLR, %	0.676	1.005	0.980-1.031
Galectin-3, ng/mL	0.019*	1.013	1.002-1.024

Abbreviations: Group A: one or several regions in the frontal lobe, temporal lobe, parietal lobe, and occipital lobe; Group D: at least two regions in the above three groups. MRS: Modified Rankin Scale. LMR:Lymphocyte-to-Monocyte Ratio, GLR:Neutrophil-to-Lymphocyte ratio, PWR:Platelet-to-White blood cell ratio, PLR:Platelet-to-Lymphocyte Ratio. [a] represents U value, [b] represents x^2 value, [c] represents T value. *P<0.05.

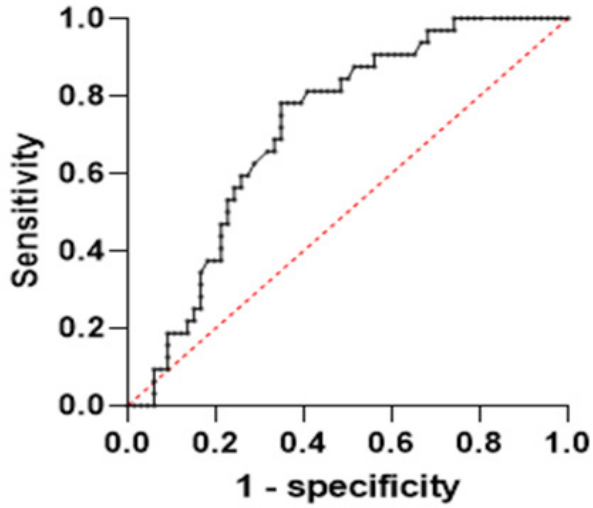

Figure 1: ROC curve for the accuracy of serum galectin-3 levels to diagnose post-stroke depression. The AUC of serum galectin-3 levels on post-stroke depression was 0.719 with the 95% CI 0.618–0.819. The sensitivity and specificity for serum galectin-3 levels on post-stroke depression were 78.1% and 65.2%, respectively. Abbreviations: ROC: receiver-operating characteristic; AUC: area under the curve; CI: confidence interval.

with lower anxiety in patients with risk factors for heart failure, suggesting that galectin-3 may be involved in the development of depression after stroke.[32] Therefore, to evaluate the accuracy of serum galectin-3 levels in the diagnosis of PSD, we conducted ROC analysis and found that serum galectin-3 levels have high sensitivity and specificity for the diagnosis of post-stroke depression. To further determine the link between PSD and serum galectin-3 levels, we performed multivariate logistic regression analysis. After removing confounding factors, we found that serum galectin-3 could serve as an independent predictor and a crucial clinical biomarker of PSD.

Currently, the pathogenesis of PSD is not fully understood, but factors such as dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, exacerbation of inflammation, neurotransmitter shifts, and abnormalities in neurotrophic responses are considered. Evidence from previous studies suggests that some parts of the innate immune system may be activated in response to environmental psychosocial stress or anticipated danger.[33] Several studies have shown that elevated baseline levels of sympathetic nerve activity and disturbances in the HPA axis trigger elevated levels of immunoglobulin-3bp in patients with mood disorders.[34] Disorders of the immune system involving monocytes and macrophages contribute to the development of atherosclerosis and cardiovascular disease. Galectin-3 binding protein (galectin-3 BP) is a macrophage scavenger receptor that, when activated, induces a variety of proinflammatory cytokines involved in the course of the acute inflammatory response. Matrix metalloproteinase-9 (MMP-9) is one of the most well-described proteases in the CNS, targeting galectin-3 for cleavage. Galectin-3 is also a positive downstream regulator of MMP-9 expression.[35] Levels of MMP-9 are elevated in the brains of patients with bipolar depression during depressive episodes, monophasic major depression, and Alzheimer's disease, and MMP-9 is also thought to play an important role in synaptic trafficking and the regulation of glutamate receptors such as N-methyl-D-aspartate receptors. This is inextricably linked to the pathogenesis of depressive symptoms.

The results of this study suggest that serum galectin-3 may be an important clinical biomarker for predicting the development of PSD and further exploring the factors that influence the development of PSD in patients with AIS.[36] Previous studies have shown that advanced age, degree of atherosclerosis, multiple treatment methods, increased inflammatory indicators, neurological impairment, poor functional outcome, lesion locations, and other factors can affect PSD. The Hamilton Depression Scale used in this study included physical discomfort, which may lead to an overestimation of the severity of emotional problems in stroke patients. Old age is an unmodifiable risk factor. Neurons in elderly patients will gradually decline, and the body's

ability to repair and regenerate will decrease progressively.

Intravenous thrombolysis and endovascular therapy may make them more aware of the risk of irreversible neurological sequelae and stroke recurrence, thus increasing the risk of PSD. After all, intravenous thrombolysis or intravascular therapy as a treatment for cerebral infarction has certain risks. However, studies have shown that PSD may be associated with dysfunctional connectivity between different regions of the dynamic network (prefrontal cortex, amygdala, insular gyrus, internal capsule, striatum, hippocampus, and anterior cingulate gyrus). The severity of depressive symptoms was associated with infarcted areas, asymptomatic infarcts, and subcortical small-vessel disease (characterized by lacunar, white-matter damage, and cerebral microhemorrhages). The distance between the brain injury area and the frontal pole was associated with dysfunction of the brain's default mode network (DMN). Multivariate logistic regression analysis showed poor functional outcome (MRS score≥2) and elevated serum galectin-3 levels were risk factors for post-stroke depression ($P<0.05$). Stroke severity was identified as a vital factor for PSD because it influenced the degree of disability and independence of the patient, which remain important risk factors for the prevention of PSD. Poor functional prognosis and severe neurological impairment can lead to disability and affect daily social life.

There are several aspects of this study that need improvement. Firstly, as a prospective case-control study, the sample size of this study was small due to time and sample size limitations. Therefore, first of all, we need to expand the sample size, and we also need research from different regions and nationalities to support our conclusions; Secondly, we did not follow up and dynamically monitor serum galectin-3 levels and patients' mood changes; Finally, we did not conduct further intervention experiments in animal and cell models. Nonetheless, our research verified the association between serum galectin-3 levels and PSD for the first time.

In conclusion, the main finding of this study was that serum galectin-3 levels were associated with PSD in patients with AIS. The prevalence of PSD increased with the increase of serum galectin-3 levels. Serum galectin-3 levels were significantly higher in the PSD group of AIS patients than in the post-stroke non-depression group. The accuracy of serum galectin-3 levels as a biomarker for the diagnosis of PSD was improved. Logistic regression results indicate that serum galectin-3 levels may be a predictor of the onset of the PSD group. If the link between serum galectin-3 level and the PSD group is confirmed, targeted galectin-3 therapy is expected to improve the prognosis of AIS patients with high galectin-3 levels. It can control the incidence of PSD by reducing the serum galectin-3 levels, which may be valuable for the early intervention of the PSD. Our current research further expands our understanding of the involvement of galectin-3 in PSD.

DISCLOSURE

Financial support: This study has received funding by Bingtuan Guiding Science and Technology Program(2022ZD072), Shihezi City Financial Science and Technology Plan Project(2023BX01-3), Science and Technology Project of the First Affiliated Hospital of School of Medicine, Shihezi University(GP202110).

Conflict of interest: None

Data availability: The data utilized which corroborated this study's conclusions are accessible upon request from the corresponding author.

REFERENCES

1. Xu Y, Wang K, Wang Q, *et al*. The antioxidant enzyme PON1: a potential prognostic predictor of acute ischemic stroke. *Oxid Med Cell Longev* 2021; 2021:6677118. DOI:10.1155/2021/6677111.
2. US Preventive Services Task Force, Davidson KW, Barry MJ, *et al*. Screening for prediabetes and type 2 diabetes in children and adolescents: US Preventive Services Task Force recommendation statement. *JAMA* 2022; 25(01):368-401. DOI:10.1001/jama.2022.14543.
3. Kernan WN, Viera AJ, Billinger SA, *et al*. Primary care of adult patients after stroke: A scientific statement from the American Heart Association/American Stroke Association. *Stroke* 2021; 52(09):558-71. DOI:10.1161/STR.0000000000000382.
4. Leung A, Shirvalkar P, Chen R, *et al*. Transcranial magnetic stimulation for pain, headache, and comorbid depression: INS-NANS Expert Consensus Panel Review and Recommendation. *Neuromodulation* 2020; 23(3):70-94. DOI:10.1111/ner.13094.
5. Gao ZY, Liu ZN, Wang R, *et al*. Galectin-3 Is a potential mediator for atherosclerosis. *J Immunol Res* 2020;14(2): 5284728. DOI: 10.1155/2020/5284728.
6. Venkatraman A, Hardas S, Patel N, *et al*. Galectin-3: an emerging biomarker in stroke and cerebrovascular diseases. *Eur J Neurol* 2018; 25(2):238-46. DOI:10.1111/ene.13496.

7. Andrade JG, Aguilar M, Atzema C, *et al*. The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation. *Can J Cardiol* 2020; 36(12):1847-948. DOI:10.1016/j.cjca.2020.09.001.
8. Vlachou F, Varela A, Stathopoulou K, *et al*. Galectin-3 interferes with tissue repair and promotes cardiac dysfunction and comorbidities in a genetic heart failure model. *Cell Mol Life Sci* 2022;79(5):250. DOI:10.1007/S00018-022-04266-6.
9. Wu JH, Zhang LS, Neplioueva I, *et al*. Drebrin attenuates atherosclerosis by limiting smooth muscle cell transdifferentiation. *Cardiovasc Res* 2021; 118(3):772-84. DOI:10.1093/CVR/CVAB156.
10. Oyenuga A, Folsom AR, Fashanu O, *et al*. Plasma galectin-3 and sonographic measures of carotid atherosclerosis in the atherosclerosis risk in communities study. *Angiology* 2019; 70(1):47-55. DOI:10.1177/0003319718780772.
11. García RJ, Boza SA, Espinosa OAM, *et al*. Galectin-3,a rising star in modulating microglia activation under conditions of neurodegeneration. *Cell Death Dis* 2022; 13(7):628-39. DOI:10.1038/S41419-022-05058-3.
12. Liu LP, Chen WQ, Zhou HY, *et al*. Chinese Stroke Association guidelines for clinical management of cerebrovascular disorders: executive summary and 2019 update of clinical management of ischaemic cerebrovascular diseases. *Stroke Vasc Neurol* 2020 06;5(2):159-76. DOI:10.1136/svn-2020-000378.
13. Robben D, Boers AMM, Marqieromg HA, *et al*. Prediction of final infarct volume from native CT perfusion and treatment parameters using deep learning. *Med Image Anal* 2020; 59(C):101589. DOI:10.1016/j.media.2019.101589.
14. Tung YJ, Huang CT, Lin WC, *et al*. Longer length of post-acute care stay causes greater functional improvements in poststroke patients. *Medicine* 2021 6(02):100-26. DOI:10.1097/MD.0000000000026564.
15. Zhang J, Li J, Chen WR, Meng XY, Hu WL. Clinical analysis of the relationship between vascular cognitive impairment and infarction locations and white matter lesions at early stages of acute cerebral infarction. *Chinese J Stroke* 2013; 8(06):459-63. DOI:10.3969/j.issn.1673-5765.2013.06.011.
16. Tung YJ, Huang CT, Lin WC, *et al*. Longer length of post-acute care stay causes greater functional improvements in post-stroke patients. *Medicine* 2021; 6(02):100-26. DOI:10.1097/MD.0000000000026564.
17. Goyal N, Tsivgoulis G, Malhotra K, *et al*. Medical management vs mechanical thrombectomy for mild strokes: An international multicenter study and systematic review and meta-analysis. *JAMA Neurol* 2019; 77(1):16-24. DOI:10.1001/jamaneurol.2019.3112.
18. Jaroonpipatkul C, Onwanna J, Tunvirachaisakul C, *et al*. Depressive symptoms due to stroke are strongly predicted by the volume and location of the cerebral infarction, white matter hyperintensities, hypertension, and age: A precision nomothetic psychiatry analysis. *J Affect Disord* 2022; 309:141-50. DOI:10.1016/J.JAD.2022.04.041.
19. Chiorescu RM, Mocan M, Inceu AI, Buda AP, Blendea D, Vlaicu SI. Vulnerable atherosclerotic plaque: Is there a molecular signature? *Int J Mol Sci* 2022; 23(21):13648. DOI:10.3390/IJMS232113638.
20. Chinese Society of Health Management, Chinese Society of Ultrasound Medicine, Chinese Society of Cardiovascular Disease, Editorial Board of Chinese Journal of Health Management. Expert consensus on screening and management of risk factors for cardiovascular diseases in Chinese medical examination population. Chinese J Health Management 2015; 9(6):398-412.
21. Simonsen SA, West AS, Heiberg AV, Wolfram F, Jennum PJ, Iversen HK. Is the TOAST classification suitable for use in personalized medicine in ischemic stroke? *J Pers Med* 2022;12(3):496-6. DOI: 10.3390/JPM12030496.
22. Chinese Society of Neurology, Chinese Stroke Society, Neurovascular Intervention Group of Chinese Society of Neurology. Chinese guidelines for the endovascular treatment of acute ischemic stroke 2022. Chinese J Neurol 2022; 55(06):565-80.
23. Diederichsen SZ, Frederiksen KS, Xing LY, *et al*. Severity and etiology of incident stroke in patients screened for atrial fibrillation vs usual care and the impact of prior stroke: A post hoc analysis of the LOOP randomized clinical trial. *JAMA Neurol* 2022; 29(8);15-23. DOI: 10.1001/JAMANEUROL.2022.3031.
24. Hu JJ, Wang LY, Fan KL, *et al*. The association between systemic inflammatory markers and post-stroke depression: A prospective stroke cohort. Clin Interv Aging 2021; 16:1231-9. DOI:10.2147/CIA.S314131.
25. Soares LC, Al-Dalahmah O, Hillis J, *et al*. Novel galectin-3 roles in neurogenesis, inflammation and neurological diseases. *Cells* 2021; 10(11):3023-47. DOI:10.3390/CELLS10113047.
26. Zhu BL, Hu AY, Huang GQ, *et al*. Association between obesity and post-stroke anxiety in patients with acute ischemic stroke. *Front Nutr* 2021; 8:749958-749966. DOI: 10.3389/FNUT.2021.749958.
27. Zhong CK, Lu Z, Che BZ, *et al*. Choline pathway nutrients and metabolites and cognitive impairment after acute ischemic stroke. *Stroke* 2021; 52(3):887-95. DOI: 10.1161/STROKEAHA.120.031903.
28. Gao ZY, Liu ZN, Wang R, *et al*. Galectin-3 is a potential mediator for atherosclerosis. *J Immunol Res* 2020;14(2): 5284728. DOI: 10.1155/2020/5284728.
29. Boziki M, Polyzos SA, Deretzi G, *et al*. A potential impact of Helicobacter pylori-related Galectin-3 in neurodegeneration. *Neurochem Int* 2018; 17 (02):113. DOI: 10.1016/j.neuint.2017.12.003.
30. Gabr M, Rehman AU, Chen HF. Quinoline-pyrazole scaffold as a novel ligand of galectin-3 and suppressor of TREM2 signaling. *ACS Med Chem Lett* 2020; 11(9):1759-65. DOI:10.1021/acsmedchemlett.0c00330.
31. Melin EO, Dereke J, Thunander M, Hillman M. Depression in type 1 diabetes was associated with high levels of circulating Galectin-3. *Endocr Connect* 2018; 7(6): 819-28. DOI:10.1530/EC-18-0108.
32. Melin EO, Dereke J, Hillman M. Galectin-3,

metalloproteinase-2 and cardiovascular disease were independently associated with metalloproteinase-14 in patients with type 1 diabetes: a cross sectional study. *Diabetol Metab Syndr* 2021; 13(1):118-27. DOI:10.1186/S13098-021-00727-3.

33. Rahimian R, Béland LC, Sato S, *et al*. Microglia-derived galectin-3 in neuroinflammation; a bittersweet ligand? *Medicinal Res Rev* 2021,41(4): 2582-9. DOI:10.1002/MED.21784.
34. Bergman MA, Vissers CThWM, Collard RM, *et al*. The effect of alexithymia on attentional bias toward emotional stimuli in depression: an eye-tracking study. *Front Psychiatry* 2021; 11:569946. DOI: 10.3389/FPSYT.2020.569946.
35. Rybakowski JK, Remlinger-Molenda A, Czech-Kucharska A, Wojcicka M, Michalak M, Losy J. Increased serum matrix metalloproteinase-9 (MMP-9) levels in young patients during bipolar depression. *J Affect Disord* 2013; 146(2): 286-9. DOI:10.1016/j.jad.2012.07.019.
36. Lalancette-Hébert M, Swarup V, Beaulieu JM, *et al*. Galectin-3 is required for resident microglia activation and proliferation in response to ischemic injury. *J Neurosci* 2012; 25(7):10383-95. DOI:10.1523/JNEUROSCI.1498-12.2012.