Neurol Ther (2025) 14:949–964
https://doi.org/10.1007/s40120-025-00729-7

ORIGINAL RESEARCH

U-Shaped Relationship of Serum Albumin and Neurological Functional Outcomes After Acute Ischemic Stroke: A Prospective Cohort Study

Yuan Zhu · Gang Xue · Shufan Xu · Qi Qin · Peian Liu · Lianhong Ji · Huimin Wu · Minghua Wu · Zhuyuan Fang

Received: January 6, 2025 / Accepted: March 6, 2025 / Published online: April 16, 2025

ABSTRACT

Introduction: Several studies indicate that individuals with acute ischemic stroke (AIS) who have low levels of serum albumin (SA) have a dismal prognosis. However, intravenously administering albumin 25% at a dose of 2 g/kg did not lead to improved outcomes for patients with AIS after 90 days. Our objective was to examine the possible correlation between SA levels and stroke outcomes in a prospective cohort investigation.

Methods: The research included a total of 5111 participants diagnosed with AIS. The correlation between SA level and modified Rankin Scale (mRS) scores 90 days after onset was examined via univariate and multivariate logistic analyses. The relationships were examined employing restricted cubic splines. An investigation was conducted to ascertain the connection between SA levels and neurological functional results by employing mediation analysis, with the mediation impact of low-density lipoprotein (LDL) taken into account. In addition, the subgroup analyses were performed using the logistic regression.

Results: The connection between levels of SA and neurological functional outcomes following AIS exhibited a U-shaped pattern. The likelihood of a negative result dropped significantly with an elevation in SA (per g/L: OR (odds ratio) 0.88; 95% CI (confidence interval) 0.847–0.913) among individuals with SA levels below 42.2 g/L. Conversely, the likelihood of a negative outcome rose with an increase in SA (per g/L: OR 1.033, 95% CI 1.009–1.058) among people with SA levels of 42.2 g/L or above. Comparable findings were seen for mortality outcomes. A mediation study revealed that LDL had a mediating function in the statistical connection between SA levels and neurological functional outcomes, accounting for 12.3% of the connection. No significant interactions were seen in any of the groupings.

Y. Zhu · S. Xu · Q. Qin · P. Liu · L. Ji · H. Wu · M. Wu (✉)
Department of Neurology, Affiliated Hospital of Nanjing University of Chinese Medicine, Jiangsu Province Hospital of Chinese Medicine, Nanjing, China
e-mail: yfy0069@njucm.edu.cn

Y. Zhu
Department of Medicine, Physiology and Biophysics, UC Irvine Diabetes Center, University of California Irvine (UCI), California, Irvine, USA

G. Xue
Yangzhou Hospital of Traditional Chinese Medicine, Yangzhou, China

Z. Fang (✉)
Department of Cardiology, Affiliated Hospital of Nanjing University of Chinese Medicine, Jiangsu Province Hospital of Chinese Medicine, Nanjing, China
e-mail: fangzhuyuan@njucm.edu.cn

Conclusion: Among patients with AIS, there was a U-shaped relationship between SA levels at admission and the likelihood of poor outcomes, which was partially mediated by LDL.

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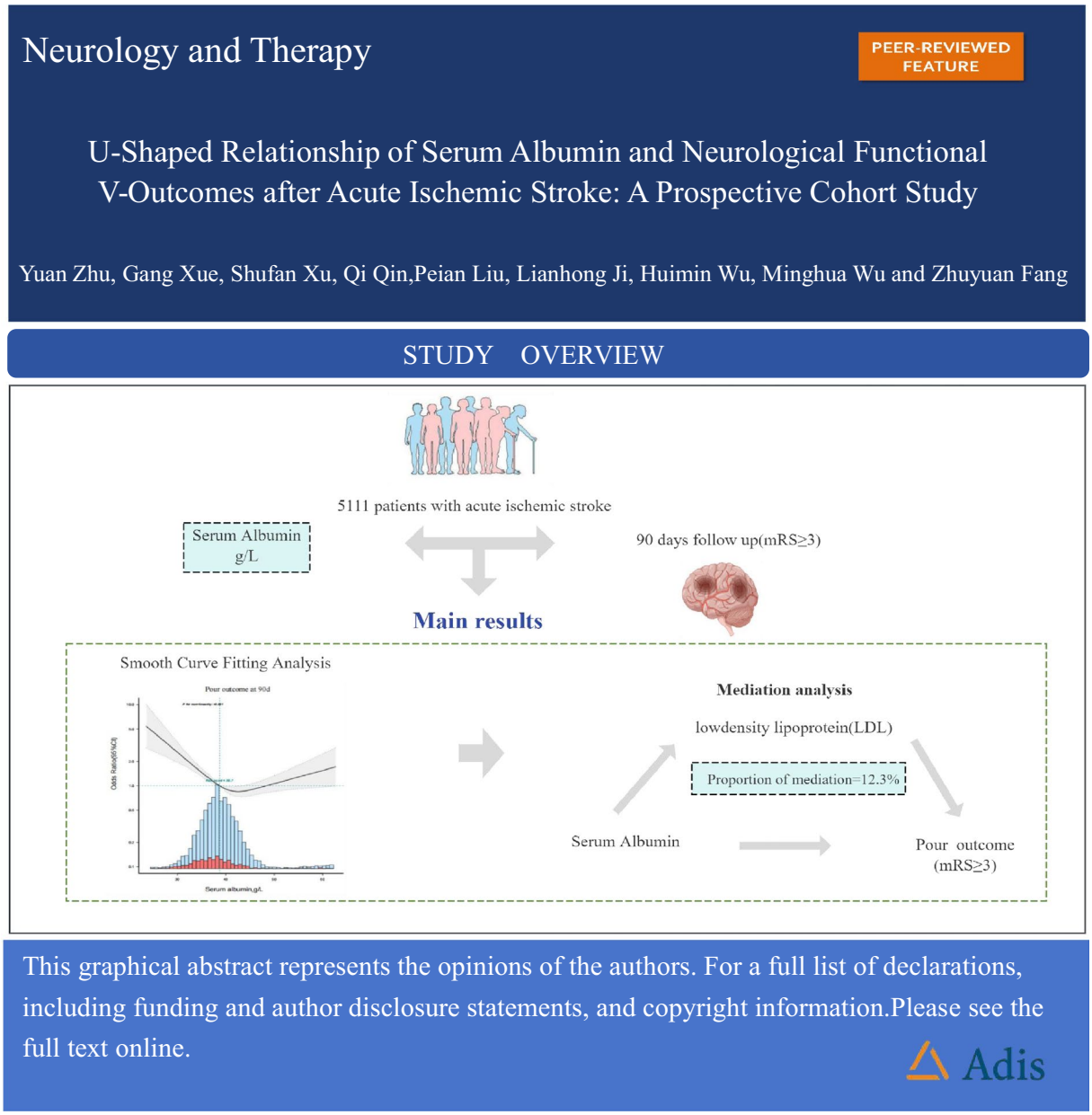

Keywords: Serum albumin; AIS; Neurological functional outcome; Metabolism

Key Summary Points

Why carry out this study?

Previous albumin supplementation treatments have not demonstrated benefits for patients with acute ischemic stroke (AIS).

What was learned from this study?

We found a U-shaped correlation between serum albumin (SA) levels and neurological functional result among patients with AIS.

By threshold effect analysis, we identified a specific turning point (SA: around 40 g/L).

A mediation study revealed that low-density lipoprotein (LDL) had a mediating function in the statistical connection between SA levels and neurological functional outcomes.

SA may potentially be targeted for intervention in AIS.

DIGITAL FEATURES

This article is published with digital features, including a Graphical Abstract, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.28547924.

INTRODUCTION

Stroke is linked to a high occurrence of illness, disability, death, and recurrence. Consequently, it has a significant impact on both public health and overall well-being. Stroke is the primary factor leading to death among the Chinese population [1]. Understanding detailed mechanisms underlying acute stroke, especially according to its different stroke subtypes, may lead to the development of effective therapeutic strategies for the improvement of functional recovery from neuronal injury [2].

Albumin, the predominant serum protein, is predominantly synthesized in the liver and controlled by many physiological systems [3, 4]. Extensive research has revealed an adverse connection between serum albumin (SA) levels and the neurological functional outcome of stroke [3, 5]. The findings from the Albumin in Acute Stroke (ALIAS) studies indicated that intravenously administering albumin 25% at a dosage of 2 g/kg did not lead to any improvement in outcomes after 90 days [6]. The first stage of the ALIAS trial, which had 424 participants, was halted when it was found that the albumin group had a significantly greater 90-day death rate (20.8%) compared to the control group (13.4%) (relative risk (RR) 1.55, 95% confidence interval (CI) 1.01–2.39) [7]. Consequently, administering albumin during the acute stage of ischemic stroke does not decrease patient mortality. The apparent contradiction between the compelling fundamental facts and the lack of success in translating them into positive patient outcomes is very perplexing. Further research is required to investigate the possible connection between SA levels and the neurological functional findings of stroke.

SA serves as a widely employed benchmark clinical test, acting as a biomarker to evaluate nutritional and inflammatory disorders, such as overnutrition and malnutrition [8, 9]. In contrast, elevated SA levels were shown to be favorably associated with lipid profiles, metabolic syndrome, and hyperglycemia [10–12]. A prior investigation identified a U-shaped correlation between SA levels and brachial-ankle pulse-wave velocity (PWV) [13]. Currently, extensive research has started investigating the U-shaped correlation between SA levels and illnesses. A well-documented connection has been observed between SA levels and the development of chronic kidney disease (CKD) in persons with hypertension (HTN), which follows a U-shaped pattern [14]. The correlation between SA levels and the neurological functional outcome of stroke may not follow a straight line, and previous studies have lacked sufficient statistical power to evaluate non-linear associations [3, 5].

The objective of this research was to ascertain the SA levels throughout the first stage of ischemic stroke and to investigate the possible link between SA levels and neurological functional outcomes.

METHODS

Study Design and Participants

This research obtained data from the Stroke Center of Jiangsu Province Hospital of Chinese Medicine over the period from January 2017 to July 2023. A group of 6343 individuals with ischemic stroke were included in an observational cohort. Participants were considered eligible for inclusion in the final analysis if they satisfied the following set of criteria: (1) Must be a minimum of 18 years old; (2) Must have been diagnosed with acute ischemic stroke (AIS) on the basis of the criteria defined by the World Health Organization, and the presence of stroke lesion confirmed by brain magnetic resonance imaging; (3) Must have been admitted to hospital within 48 h of the beginning of symptoms. The criteria for exclusion were as follows: (1) Insufficient data on SA levels; (2) Patients with severe systemic disorders or a life expectancy of less than 90 days, such as advanced stages of heart failure or cancers; (3) modified Rankin Scale (mRS) score [15] greater than 2 prior to the onset of the study, to avoid confounding the assessment of poor neurological outcomes at 90 days; (4) Participants who were not followed up for 90 days after the onset of the study; (5) Patients who received thrombolysis or mechanical thrombectomy, as these treatment modalities are often associated with better outcomes. After removing patients who did not satisfy the specified criteria for inclusion, a comprehensive analysis was conducted on a total of 5111 individuals (Fig. 1). Out of these patients, 3361 (65.8%) were male.

This study received ethical approval from the Ethics Committee of the Affiliated Hospital of Nanjing University of Chinese Medicine (2017NL-012-01). All patients or their legal representatives consented to participate in this study and consented for publication. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. All authors have agreed to participate in the study and the publication of this study.

Demographic and Clinical Assessment

On the first day of admission, the demographic characteristics (age and gender), presence of vascular risk factors including history of smoking and drinking, body mass index (BMI), diabetes mellitus (DM), hypertension (HTN), atrial fibrillation (AF), hyperlipidemia (HLD), and coronary heart disease (CHD), medical history (use of antiplatelets, antihypertensives, and antidiabetics), and laboratory data of patients were collected. The laboratory data included measurements of C-reactive protein (CRP), triglyceride (TG) levels, total cholesterol (TC), high-density lipoprotein (HDL) levels, low-density lipoprotein (LDL), glycated hemoglobin (HbA1c), and platelet (PLT) counts. An AU-5400 automated analyzer (Olympus, Tokyo, Japan) was used to test laboratory parameters, including SA levels. HTN is characterized by a blood pressure reading of 140/90 mmHg or above or by the current use of medication to reduce blood pressure. DM is distinguished by the following criteria: a fasting blood glucose level of 126 mg/dL or higher, a positive result on a 75-g oral glucose tolerance test, or the current administration of oral hypoglycemic drugs or insulin for the purpose of controlling blood glucose levels. Those who were either currently smokers or had stopped within the last 6 months were deemed as smokers. Alcohol usage was related to current drinking habits or cessation within the past 6 months. Acute ischemic stroke (AIS) is characterized by the abrupt appearance of acute neurological impairments, which are validated using brain computed tomography or magnetic resonance imaging. Patients with AIS are promptly hospitalized within 48 h of symptom onset. The degree of neurological impairment was evaluated upon admission using the National Institutes of Health Stroke Scale (NIHSS) score [16]. Stroke subtypes

were classified according to the Trial of Org 10 172 in acute stroke treatment (TOAST) criteria [17].

Outcome Definition

Neurological functional outcome was evaluated by measuring the mRS score 90 days after the symptoms began [15, 18]. Prospective clinical information about the outcome following discharge was collected by normal clinic visits or telephone interviews with patients or their caretakers 90 days following the qualifying event. We classified the functional result depending on the mRS score. Functional independence, indicated by an mRS score of 0–2, was considered a favorable result [19], and the primary outcome was defined as the presence of moderate-to-severe impairment or mortality, indicated by an mRS score ≥ 3, which included the occurrence of either recurrent AIS or intracranial bleeding.

Statistical Analysis

The multiple imputation approach was utilized to address missing covariate values, aiming to enhance statistical efficiency and minimize bias resulting from the removal of certain variables. The percentage of missing values for each variable category is below 10%. Additionally, sensitivity studies were conducted utilizing a complete-case approach. The data appears as the mean ± standard deviation (SD) or the median (interquartile range) for continuous variables. Categorical variables are expressed as frequencies or proportions. Logistic regression models were employed to ascertain the connections between albumin levels and neurological functional outcomes. Both unadjusted and multivariable-adjusted models were employed. The selection of components for adjustments was based on their clinical significance and the variables that showed a p value of < 0.05 in the univariate analysis (Table 1). The multivariate-adjusted models were controlled for various factors, including age, gender, smoking, alcohol consumption, BMI, HTN, DM, HLD, TOAST classification, NIHSS score at admission, CRP, TG, TC, LDL, and PLT at admission. Furthermore, we used the technique of smooth curve fitting, namely the cubic spline smoothing, to determine whether there was a non-linear relationship between albumin levels and neurological functional results or mortality. If a non-linear relationship was found, a two-piecewise linear regression model was employed to ascertain the threshold effect and identify the point of change in direction between two straight lines (using a recursive technique). Mediation analysis was deployed to ascertain the connection between SA levels and negative outcomes, specifically focusing on the role of LDL. The bias-corrected bootstrap approach was applied using a sample size of 5111 to establish confidence intervals at the 95% level. A large indirect impact was seen when the confidence interval did not include zero. In addition, the subgroup analyses were conducted using the logistic regression model, and the interactions between subgroups were assessed using likelihood ratio tests. The R Statistical Software (http://www.R-project.org, The R Foundation) and Free Statistics analytic platform were used for all studies. A significance level of $P < 0.05$, using a two-tailed test, was deemed statistically significant in all analyses.

RESULTS

Baseline Characteristics of Study Subjects

The 5111 patients who satisfied the inclusion criteria were included in this research. On the basis of the criterion of poor outcomes, 775 patients (15.2%) had poor results within 3 months after AIS. Out of these 775 patients, 71 died (43 deaths were attributed to neurological diseases and 28 to other causes), 21 had a recurrence of stroke, 9 suffered from symptomatic cerebral bleeding, while the rest remained incapacitated. The baseline characteristics of the patients involved in the study were categorized on the basis of their SA level tertiles (Table 1). In summary, the

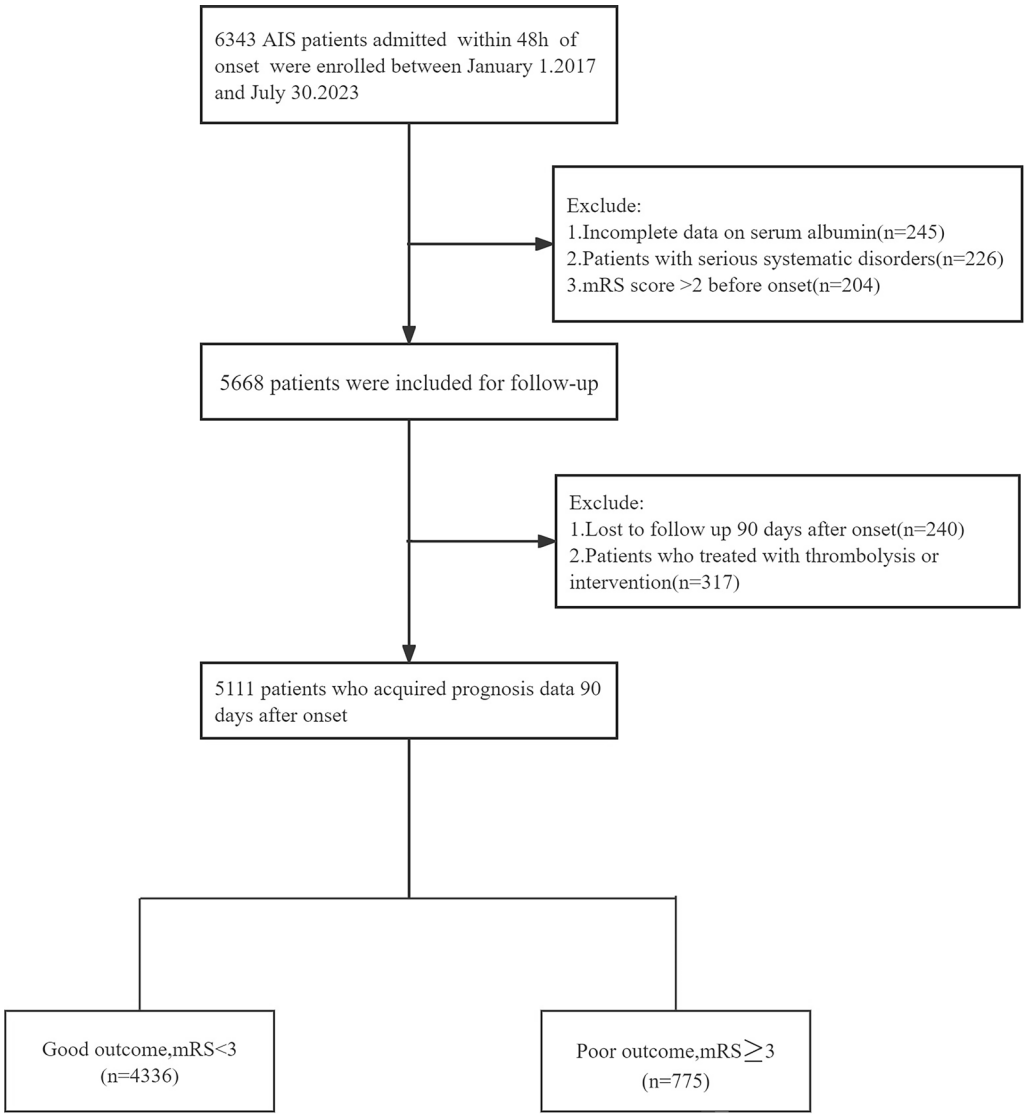

Fig. 1 Flowchart for patient selection. *AIS* acute ischemic stroke, *mRS* modified Rankin Scale

average age of the 5111 patients with AIS who participated in the study was 68.6 years, with an SD of 11.9 years. Out of these patients, 3361 (65.8%) were male. The average concentration of SA was 39.3 g/L, with a SD of 5.9 g/L. Patients with greater SA levels had a greater likelihood of experiencing higher BMI, HTN, and HLD in comparison to those with low SA levels. Younger individuals with lower levels of CRP and greater levels of admission blood pressure (BP), TC, TG, LDL, and PLT had higher SA levels.

Association Between SA and Clinical Outcome

Out of the 5111 individuals who had AIS, 775 individuals had poor outcomes, and 71 individuals died. In general, there was a U-shaped connection between SA levels and neurological functional outcome/death (Fig. 2). During the study of the threshold effect, it was revealed that there was a significant reduction in the likelihood of poor neurological functional outcome with each elevation of SA by 1 g/L (OR 0.88,

95% CI 0.847–0.913) in individuals whose SA levels were below 42.2 g/L. Conversely, in participants with SA levels of 42.2 g/L or higher, there was a significant rise in the risk of poor neurological functional outcome with each increase of SA by 1 g/L (OR 1.033, 95% CI 1.009–1.058) (Table 2). The study thoroughly examined the U-shaped connection between SA levels and the chance of a poor outcomes using multiple logistic regression techniques in a multivariable logistic regression analysis. We propose to estimate the clinical outcomes of patients 90 days after experiencing a stroke, with a total of 71 fatalities observed. Nevertheless, a distinct U-shaped pattern persists in the connection between SA levels and mortality within 90 days following the commencement (Fig. 2, Table 2). Additional research will be undertaken using extended observation periods to delve deeper into this subject. When SA levels were divided into sextiles, participants in sextile 1 (≤ 34.8 g/L) had a significantly greater risk of poor results compared to those in sextile 5 (40.4–42.7 g/L) (OR 2.89, 95% CI 2.21–3.77). Similarly, individuals in sextile 6 (≥ 42.8 g/L) had a greater risk of poor outcomes (OR 1.43, 95% CI 1.03–1.98) (Fig. 3). In addition, further adjustments were made for age, gender, smoking, alcohol consumption, BMI, HTN, DM, HLD, TOAST classification, NIHSS score at admission, CRP, TG levels, TC, LDL, and PLT at admission. However, these adjustments did not significantly alter the outcomes. The mortality outcome also showed a U-shaped relationship with SA levels (Table 2, Fig. 3).

Levels of Low-density Lipoprotein (LDL) with Varying SA Levels

The LDL levels of each group of SA level tertiles were compared (Fig. 4). The observations revealed that LDL was positively correlated with SA levels.

Mediation Analysis

Figure 5 illustrates the proportional impact of LDL in mediating the connection between SA and negative outcomes at 90 days in the mediation models. It shows the combined, direct, and indirect impacts. The mediation hypothesis was confirmed through bootstrapping analysis, which showed significant relative indirect effects for poor outcomes (indirect effect = 0.012, 95% CI 0.0031–0.0248; direct effect = 0.085, 95% CI 0.0066–0.236). This indicates that LDL possessed a mediating effect on the statistical link between SA and poor outcomes at 90 days, accounting for 12.3% of the association.

Stratified Analyses by Potential Effect Modifier

We performed further exploration subgroup studies to ascertain the connection between SA levels and the poor outcomes in two separate patient groups, categorized on the basis of the crucial threshold of 39.8 g/L of SA (Fig. 6). No significant interactions were seen in any of the subgroups, encompassing gender, age, smoking, drinking, HTN, and DM. All p values for the interactions were > 0.05.

DISCUSSION

The results of this observational, large, single-center cohort study demonstrated that SA levels below around 40 g/L were negatively correlated with poor neurological functional outcomes, whereas SA levels above 40 g/L showed a positive correlation with poor neurological functional outcomes. After adjustment for age, gender, smoking, alcohol consumption, BMI, HTN, DM, HLD, TOAST classification, NIHSS score at admission, CRP, TG, TC, LDL, and PLT at admission, we found a U-shaped correlation between SA levels and neurological functional result. Additionally, by threshold effect analysis, we identified a specific turning point (SA: around 40 g/L).

Albumin is a protein that has a molecular weight of 69 kDa, making up almost 50% of the total content of serum in the body. The liver synthesizes and releases around 10–15 g of albumin into the circulatory space on a daily basis [20]. Insulin, amino acid consumption, and low colloid osmotic pressure all promote

Table 1 Demographics and clinical characteristics of patients with AIS according to serum albumin tertiles

Variables	Total ($n = 5111$)	Q1 ($n = 1694$)	Q2 ($n = 1683$)	Q3 ($n = 1734$)	*P* value
Serum albumin, g/L	39.3 ± 5.9	34.2 ± 2.9	38.7 ± 0.9	44.9 ± 6.0	< 0.001
Age, years	68.6 ± 11.9	72.1 ± 11.4	68.1 ± 11.4	65.6 ± 12.0	< 0.001
Gender, *n* (%)					0.197
Male	3361 (65.8)	1091 (64.4)	1103 (65.5)	1167 (67.3)	
Female	1750 (34.2)	603 (35.6)	580 (34.5)	567 (32.7)	
Smoking, *n* (%)					0.004
No	3589 (70.2)	1238 (73.1)	1171 (69.6)	1180 (68.1)	
Yes	1522 (29.8)	456 (26.9)	512 (30.4)	554 (31.9)	
Alcohol consumption, *n* (%)					< 0.001
No	4073 (79.7)	1408 (83.1)	1316 (78.2)	1349 (77.8)	
Yes	1038 (20.3)	286 (16.9)	367 (21.8)	385 (22.2)	
BMI, kg/m^2	22.2 ± 9.6	20.3 ± 8.9	22.5 ± 12.0	23.4 ± 6.2	< 0.001
HTN, *n* (%)					0.024
No	1162 (22.7)	413 (24.4)	392 (23.3)	357 (20.6)	
Yes	3949 (77.3)	1281 (75.6)	1291 (76.7)	1377 (79.4)	
DM, *n* (%)					0.175
No	3117 (61.0)	1062 (62.7)	1021 (60.7)	1034 (59.6)	
Yes	1994 (39.0)	632 (37.3)	662 (39.3)	700 (40.4)	
AF, *n* (%)					0.059
No	4879 (95.5)	1610 (95)	1597 (94.9)	1672 (96.4)	
Yes	232 (4.5)	84 (5)	86 (5.1)	62 (3.6)	
CHD, *n* (%)					0.024
No	4818 (94.3)	1588 (93.7)	1574 (93.5)	1656 (95.5)	
Yes	293 (5.7)	106 (6.3)	109 (6.5)	78 (4.5)	
HLD, *n* (%)					< 0.001
No	4779 (93.5)	1629 (96.2)	1555 (92.4)	1597 (92.1)	
Yes	332 (6.5)	65 (3.8)	128 (7.6)	137 (7.9)	
Antihypertensive treatment, *n* (%)					< 0.001
No	1456 (28.5)	564 (33.3)	466 (27.7)	428 (24.7)	
Yes	3655 (71.5)	1130 (66.7)	1217 (72.3)	1306 (75.3)	
Antidiabetic treatment, *n* (%)					0.334
No	3286 (64.3)	1120 (66.1)	1065 (63.3)	1101 (63.5)	

Table 1 continued

Variables	Total ($n = 5111$)	Q1 ($n = 1694$)	Q2 ($n = 1683$)	Q3 ($n = 1734$)	*P* value
Yes	1825 (35.7)	574 (33.8)	618 (36.7)	633 (36.5)	
Antiplatelet use, *n* (%)					0.499
No	429 (8.4)	158 (9.3)	131 (7.8)	142 (8.2)	
Yes	4682 (91.6)	1536 (90.7)	1552 (92.2)	1592 (91.8)	
TOAST classification, *n* (%)					0.015
SAO, *n* (%)	2747 (53.7)	865 (51.1)	903 (53.7)	979 (56.5)	
LAA, *n* (%)	2031 (39.7)	705 (41.6)	662 (39.3)	664 (38.3)	
CE, *n* (%)	268 (5.2)	107 (6.3)	91 (5.4)	70 (4)	
Other causes, *n* (%)	40 (0.8)	12 (0.7)	16 (1)	12 (0.7)	
Unclassified, *n* (%)	25 (0.5)	5 (0.3)	11 (0.7)	9 (0.5)	
NIHSS score at enrollment	3.5 ± 4.1	4.2 ± 4.7	3.2 ± 3.9	3.2 ± 3.5	< 0.001
mRS score at enrollment	2.2 ± 1.3	2.5 ± 1.4	2.1 ± 1.3	2.0 ± 1.3	< 0.001
Admission SBP, mmHg	142.9 ± 21.2	141.7 ± 21.0	142.8 ± 21.6	143.9 ± 20.9	0.222
Admission DBP, mmHg	84.0 ± 13.5	81.2 ± 14.1	84.1 ± 12.8	86.3 ± 13.4	< 0.001
CRP, mg/L	8.3 ± 19.8	14.9 ± 28.4	5.3 ± 11.2	5.1 ± 14.5	< 0.001
TG, mmol/L	1.6 ± 1.2	1.4 ± 0.9	1.7 ± 1.3	1.7 ± 1.4	< 0.001
TC, mmol/L	4.3 ± 1.1	4.1 ± 1.1	4.3 ± 1.0	4.5 ± 1.2	< 0.001
LDL, mmol/L	2.7 ± 0.9	2.5 ± 0.9	2.7 ± 0.9	2.8 ± 0.9	< 0.001
HDL, mmol/L	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.3 ± 0.3	0.018
HbA1c,%	6.9 ± 1.7	6.9 ± 1.7	6.9 ± 1.7	6.9 ± 1.6	0.863
PLT, 10^9/L	199.4 ± 70.0	193.5 ± 75.6	197.0 ± 63.0	207.5 ± 70.4	< 0.001

Data are reported as mean ± standard deviation (SD)

BMI body mass index, *HTN* hypertension, *DM* diabetes mellitus, *AF* atrial fibrillation, *CHD* coronary heart disease, *HLD* hyperlipidemia, *TOAST* Trial of Org 10 172 in acute stroke treatment, *SAO* small artery occlusion, *LAA* large artery atherosclerosis, *CE* cardioembolism, *NIHSS* National Institutes of Health Stroke Scale, *mRS* modified Rankin Scale, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *CRP* C-reactive protein, *TG* triglycerides, *TC* total cholesterol, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *PLT* platelet, *HbA1c* hemoglobin

the production of albumin [21]. Factors that reduce albumin synthesis include elevated colloid osmotic pressure, starvation, inflammation, diabetes, liver illness, and sepsis [14]. The processes behind albumin breakdown remain little elucidated. However, it is believed to mostly take place in the skin, muscles, liver, and kidneys. Prior observational epidemiological research has shown inverse and linear associations between low levels of SA and negative health outcomes, such as death, CHD, and stroke [3, 5, 21]. Zhou et al. [3] found that decreased levels of SA are indicative of a worse prognosis in individuals suffering from AIS or transient ischemia attack. However, the paper shows that the link between SA and poor functional outcomes of stroke at 3 months is not a simple linear one. Additionally, the fitted curve only includes data for SA

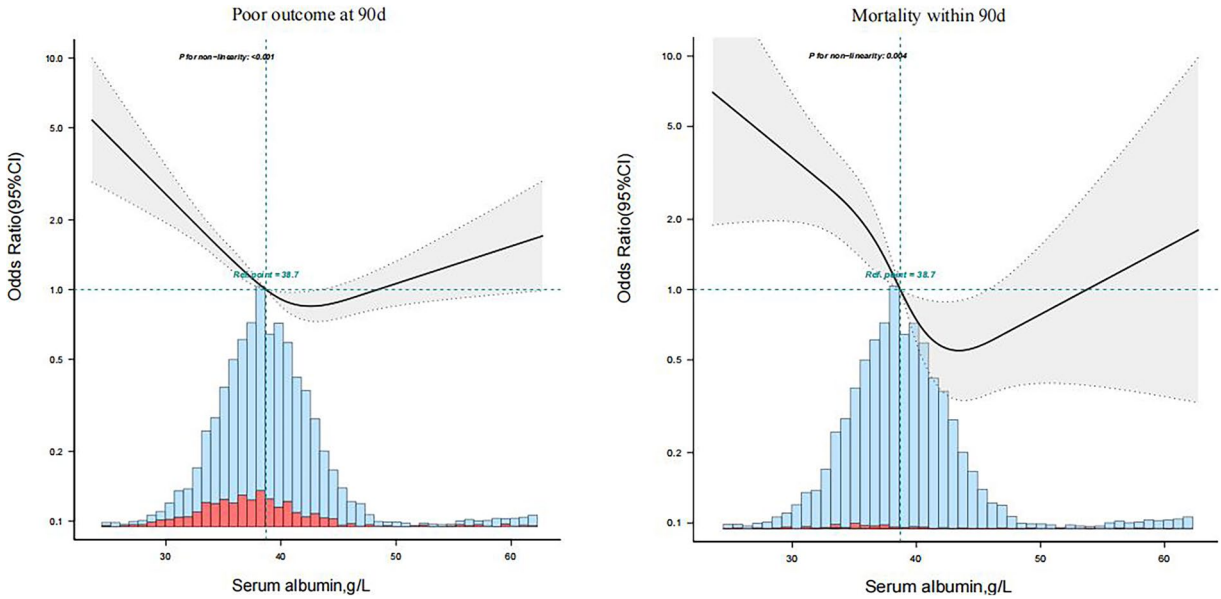

Fig. 2 Connection between serum albumin levels and clinical outcome based on the smooth curve fitting analysis. *CI* confidence interval

levels below 46 g/L. Babu et al. [5] found that ischemic stroke has a substantial detrimental outcome when accompanied by low levels of albumin. Nevertheless, the research suffered from a limited sample size and did not conduct statistical curve fitting, leaving the possibility of non-linear connections open.

Elevated SA levels have traditionally been linked with favorable outcomes in stroke. Nevertheless, intravenously administering albumin 25% at a dosage of 2 g/kg did not result in a better outcome after 90 days. Instead, it was linked to greater incidences of intracerebral hemorrhage and pulmonary edema [6]. Recently, there has been a growing body of research investigating the U-shaped correlation between albumin levels and the onset of several illnesses [14]. Hence, the correlation between SA and clinical outcomes in stroke may possess a greater degree of intricacy, necessitating a reassessment of the putative link.

Several investigations have shown a correlation between low SA levels and poor stroke prognosis. The significance of low SA levels in stroke mostly pertains to malnutrition and inflammation [3]. The specific mechanisms via which elevated SA levels may contribute to a worse functional outcome after a stroke are still unknown. High SA level is linked to overnutrition [22] and insulin resistance [23]. Insulin has the potential to enhance the process of albumin gene transcription and mRNA synthesis in a way that is directly proportional to the dosage [14]. Furthermore, Kim and Kang [8] suggested that the raised SA levels may be a result of elevated synthesis of albumin as a compensatory mechanism in response to reduced antioxidant activity of albumin in a condition of insulin resistance. Furthermore, several investigations have reported a favorable connection between elevated SA levels and metabolic syndrome [12, 24], greater lipid levels [25, 26], blood pressure [27], platelets [28], and BMI [29]. In our present investigation, elevated SA levels were shown to be linked with higher levels of BMI, BP, TG, TC, LDL, PLT, and a greater incidence of HTN and HLD at the beginning of the research (Table 1). In addition, the mediation studies showed that LDL has a limited role in mediating the connection between SA and stroke prognosis during 90 days of follow-up in patients with AIS. HLD or metabolic syndrome can lead to endothelial

Table 2 Serum albumin threshold effects on clinical outcomes: two-piecewise regression analyses

Serum albumin (g/L)	Crude models		Serum albumin (g/L)	Model I		Serum albumin (g/L)	Model II		Serum albumin (g/L)	Model III	
	OR (95% CI)	*P* value		OR (95% CI)	*P* value		OR (95% CI)	*P* value		OR (95% CI)	*P* value
Poor outcome at 90 days											
< 42.2	0.89 (0.867–0.913)	< 0.001	< 40.5	0.939 (0.916–0.964)	< 0.001	< 40.5	0.894 (0.866–0.923)	< 0.001	< 39.8	0.88 (0.847–0.913)	< 0.001
≥ 42.2	1.034 (1.007–1.062)	0.0144	≥ 40.5	1.06 (1.004–1.118)	0.0352	≥ 40.5	1.026 (1.001–1.051)	0.0387	≥ 39.8	1.033 (1.009–1.058)	0.007
Mortality within 90 days											
< 41.5	0.896 (0.869–0.925)	< 0.001	< 43.2	0.86 (0.805–0.918)	< 0.001	< 43.2	0.858 (0.8–0.919)	< 0.001	< 42.3	0.881 (0.814–0.953)	0.0015
≥ 41.5	1.025 (1.001–1.049)	0.0446	≥ 43.2	1.03 (0.915–1.16)	0.6226	≥ 43.2	1.07 (0.957–1.197)	0.2331	≥ 42.3	1.102 (0.973–1.249)	0.127

The crude models represented the univariate analysis

Model I: adjusted for gender and age

Model II: adjusted for covariables in model I, plus smoking, alcohol consumption, BMI, hypertension, diabetes mellitus, hyperlipidemia, TOAST classification, and NIHSS score at admission

Model III: adjusted for covariables in model II, plus CRP, TG, TC, LDL, and PLT

OR odds ratio, *CI* confidence interval, *BMI* body mass index, *TOAST* Trial of Org 10 172 in acute stroke treatment, *NIHSS* National Institutes of Health Stroke Scale, *CRP* C-reactive protein, *TG* triglyceride, *TC* total cholesterol, *LDL* low-density lipoprotein, *PLT* platelet

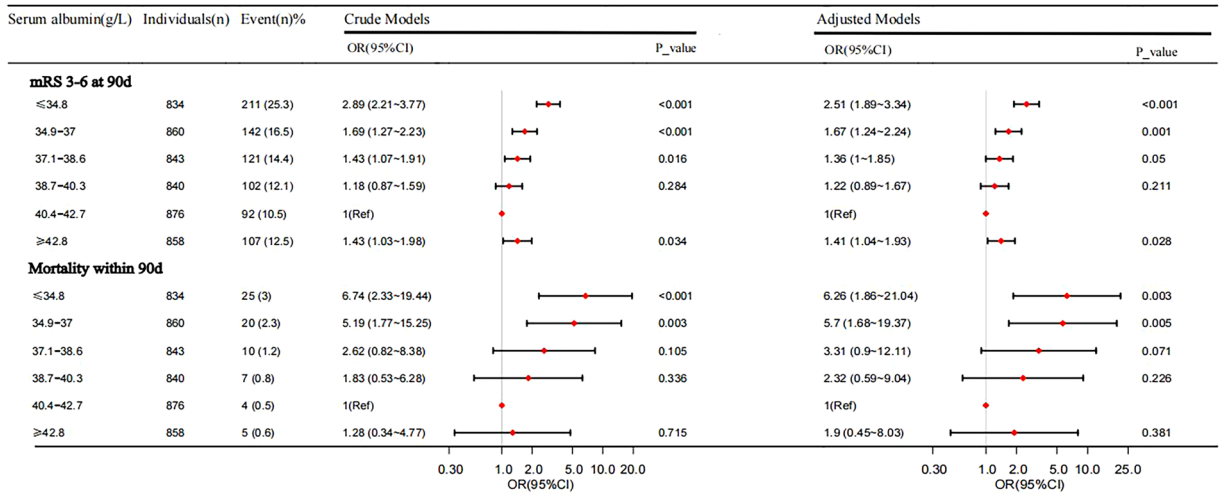

Fig. 3 Effect of serum albumin sextiles on clinical outcomes.*OR* odds ratio, *CI* confidence interval

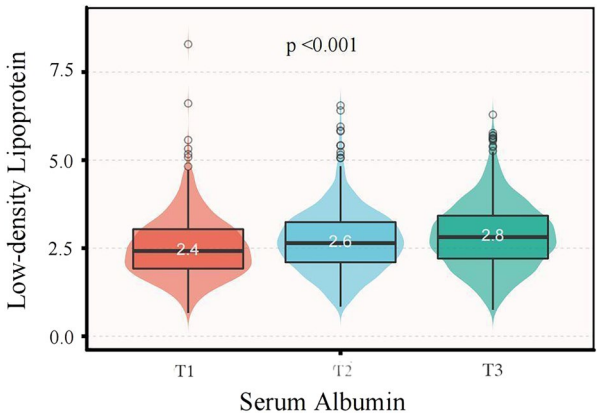

Fig. 4 Violin plot of serum albumin tertiles and LDL levels. *LDL* low-density lipoprotein

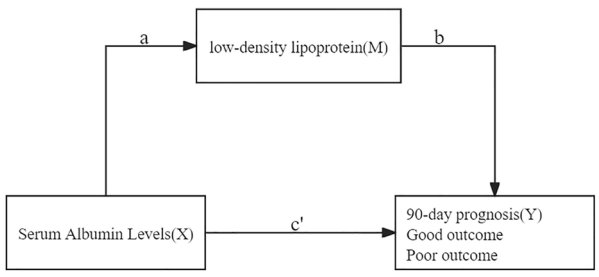

Fig. 5 Hypothetical causal pathway model for patients with ischemic stroke: total, direct, and indirect effects. *LDL* low-density lipoprotein

dysfunction, characterized by an elevation in vasoconstrictor molecules, upregulation of adhesion molecules, and a reduction in vasodilator molecules. This condition also promotes hemostasis alterations, resulting in a prothrombotic state with elevated concentrations of fibrinogen, plasminogen activator inhibitor-1, and platelet activation/aggregation [30]. Additional investigation is required to clarify the relationship between SA and lipids. Overall, our research suggests that there may be a cause-and-effect relationship between SA levels and neurological functional outcomes following AIS. We have found a U-shaped relationship between SA and poor functional outcome, which is biologically plausible, as explained earlier. Additionally, our analyses have shown a strong association that is not influenced by other factors, as demonstrated by the multiple regression and stratified analyses. However, more research is required to validate our findings.

However, the present study has several potential limitations that cannot be overlooked. First, this study was based on single-center prospective data, but a large sample size was included to minimize the risk of selection bias. Second, this study did not further differentiate whether patients received albumin treatment. However, the use of albumin treatment is not a standard treatment for AIS at present. Therefore, the

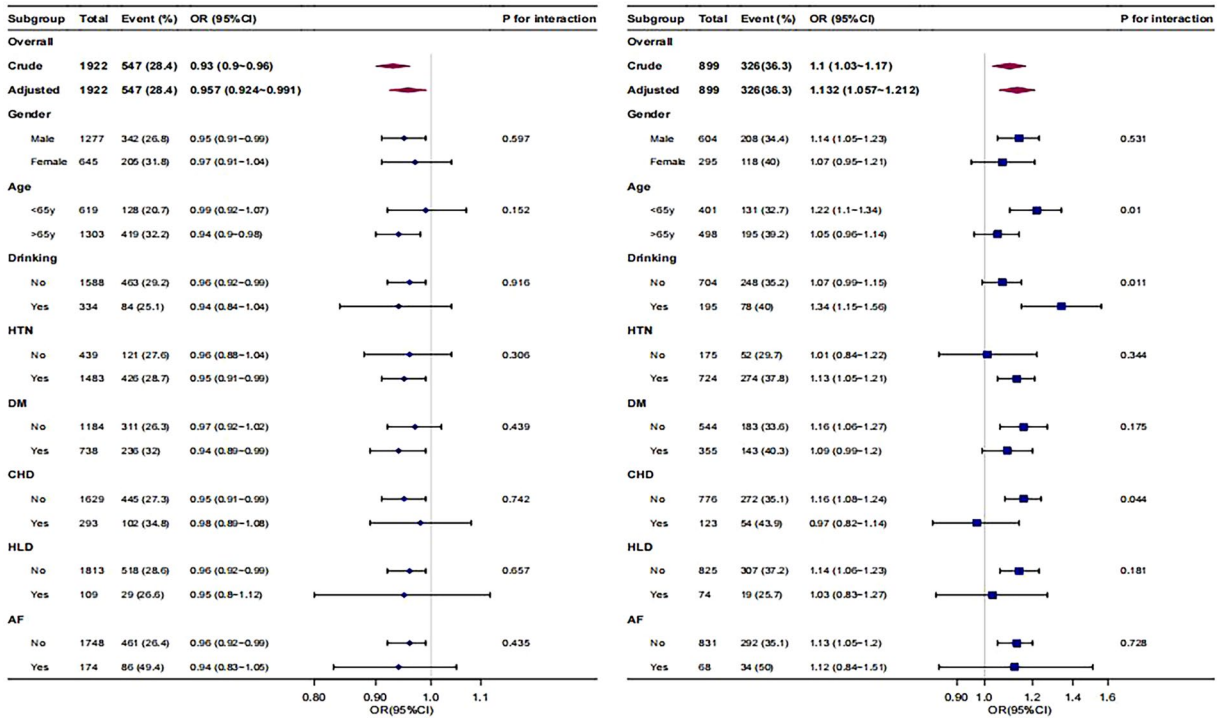

Fig. 6 Stratified analysis for poor outcome and serum albumin levels in subgroups divided by 39.8 g/L. *HTN* hypertension, *DM* diabetes mellitus, *CHD* coronary heart disease, *HLD* hyperlipidemia, *AF* atrial fibrillation, *OR* odds ratio, *CI* confidence interval

number of patients treated with albumin is very small, and it is only administered to patients with extremely poor overall nutritional status. Furthermore, the albumin levels measured in this study were obtained from blood samples collected upon admission and were thus not influenced by any albumin treatment administered during hospitalization. Third, because our study only conducted follow-ups for 3 months after onset, the number of deaths recorded was relatively low. Although a U-shaped connection between SA and mortality outcomes has been observed, longer follow-up periods would be meaningful. Fourth, this study only assessed the SA levels of patients upon admission. Increasing the frequency of SA-level assessments would provide a more precise evaluation of the progression of AIS. Fifth, the findings of our study indicate that there is a U-shaped relationship between SA levels and the likelihood of poor outcomes, which reaches a critical point at around 40 g/L. This cutoff point is based on findings from our single-center study and requires validation through larger sample sizes and multicenter studies. Sixth, we categorized patients on the basis of whether they were current smokers/drinkers or had a history of smoking/drinking cessation, but there is no quantitative data of smoking and alcohol consumption. In future we plan to conduct a study on the relationship between SA and AIS including differentiating between various infarct locations, extending the follow-up period, categorizing different causes of death, and quantitatively assessing smoking and alcohol consumption to enhance the accuracy and reliability of our findings. Given the observational nature of our work, we are unable to exclude the potential for residual or unmeasured confounding and so cannot make definitive conclusions about direct causation. Further evidence from Mendelian randomization studies, clinical trials, and mechanistic research is required to authenticate our results.

CONCLUSION

The findings of our study indicate that there is a U-shaped relationship between SA levels at admission and the likelihood of poor outcomes in patients with AIS. This relationship reaches a critical point at around 40 g/L. The findings of our study suggested that SA may potentially be targeted for intervention in AIS.

ACKNOWLEDGEMENTS

This publication was made possible by support from the Department of Neurology at Jiangsu Province Hospital of Chinese Medicine.

Author Contributions. Yuan Zhu primarily contributed to the study design, conducted data analysis, interpreted the results, and prepared the paper. Gang Xue, Peian Liu and Qi Qin mostly participated in the collection and analysis of data. Shufan Xu and Huimin Wu mostly participated in data collecting. Lianhong Ji primarily contributed to data analysis and the drafting of the text. Zhuyuan Fang and Minghua Wu primarily contributed to the study's design, data analysis, and publication writing. The authors reviewed and endorsed the final paper. Dr Minghua Wu and Zhuyuan Fang take full responsibility for the integrity of the data presented in this manuscript.

Funding. This research received funding from multiple sources. Zhuyuan Fang acknowledges support from the Leading Talents of Traditional Chinese Medicine of Jiangsu Province [SLJ0201] and the Peak Academic Talent Project of Jiangsu Province Hospital of Chinese Medicine [y2021rc01]. Minghua Wu received support from the National Natural Science Foundation of China (Grant No. 82274428, 81973794), Jiangsu Province Administration of Chinese Medicine (ZT202102), and the Project of National Clinical Research Base of Traditional Chinese Medicine in Jiangsu Province, China [JD2023SZ]. Funding for the creation and publication of the Graphical Abstract and the Rapid Service Fee were from the same sources as the manuscript.

Data Availability. The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of Interest. All the authors, Yuan Zhu, Gang Xue, Shufan Xu, Qi Qin, Peian Liu, Lianhong Ji, Huimin Wu, Minghua Wu and Zhuyuan Fang, declare that they have no competing interests. Yuan Zhu no longer studies at the Department of Medicine, Physiology and Biophysics, UC Irvine Diabetes Center, University of California Irvine (UCI),California, Irvine, USA.

Ethical Approval. This study received ethical approval from the Ethics Committee of the Affiliated Hospital of Nanjing University of Chinese Medicine (2017NL-012-01). All patients or their legal representatives consented to participate in this study and consented for publication. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. All authors have agreed to participate in the study and the publication of this study.

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