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The relationship between blood uric acid, serum lipoprotein(a) and the severity of neurological damage in patients with acute arteriolar occlusive cerebral infarction combined with type 2 diabetes mellitus and the therapeutic effect of ligustrazine

Yue Yu[1], Chengshi Zhang[1], Ziyu Jiang[1], Lingwei Kong[2], Xiujie Zhang[1], Yu Xiao[1] and Dongxia Wang[1]*

[1]Department of Neurology, The First Affiliated Hospital of Qiqihar Medical University, Qiqihar, Heilongjiang, China
[2]Department of Gastroenterology, The First Affiliated Hospital of Qiqihar Medical University, Qiqihar, Heilongjiang, China

Abstract: **Background**: This study aimed to investigate the relationship between blood uric acid (UA), serum lipoprotein(a) [Lp(a)], and the severity of neurological damage in patients with acute penetrating artery occlusive cerebral infarction combined with type 2 diabetes mellitus (T2DM). **Objectives**: To evaluate the role of UA and Lp(a) levels as independent risk factors for neurological damage severity and poor prognosis, and to observe the therapeutic effect of tanshinone. **Methods**: Clinical data of patients were analyzed to compare differences in indicators between the mild and moderate groups, as well as between groups with good and poor prognosis. **Results**: Patients in the moderate infarction group showed significantly higher levels of UA, Lp(a), and other biochemical markers, along with higher rates of unhealthy lifestyle habits and comorbidities. UA, Lp(a), and infarct diameter were independent risk factors for poor prognosis. Their combined prediction model demonstrated good sensitivity and specificity. Pre-treatment UA and Lp(a) levels were significantly positively correlated with pre-treatment NIHSS scores and post-treatment mRS scores, respectively. **Conclusion**: In patients with acute penetrating artery occlusive cerebral infarction combined with T2DM, blood uric acid and serum Lp(a) levels are associated with the severity of neurological damage and serve as independent risk factors for poor prognosis.

Keywords: Acute small artery occlusion type of cerebral infarction; Ligustrazine; Neurological impairment; Serum lipoprotein(a); Type 2 Diabetes mellitus; Uric Acid

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INTRODUCTION

Among ischemic strokes, acute small artery occlusion type of cerebral infarction (SAO) is an important subtype (Shi *et al.*, 2025), accounting for 20%-30% of all cerebral infarction cases (Uezato *et al.*, 2024). Its pathological characteristics primarily involve lacunar infarction caused by occlusion of perforating arteries with diameters ranging from 100 to 400 μm (Tang *et al*., 2024b). Against the backdrop of the increasing global prevalence of diabetes, the comorbidity of type 2 diabetes mellitus (T2DM) and SAO has become increasingly prominent. Relevant studies indicate that compared to non-diabetic patients, individuals with T2DM have a significantly elevated risk of SAO-2 to 4 times higher (Kitagawa *et al.*, 2024) and experience more severe neurological impairment, with a disability rate as high as 38.6% (Foschi *et al.*, 2024). However, the molecular mechanisms underlying neurological damage in patients with SAO and T2DM remain largely unknown, and there is a lack of effective biomarkers to guide individualized clinical treatment. As the end product of purine metabolism (Liu *et al.*, 2021), uric acid (UA) exhibits antioxidant properties within the physiological concentration range and is considered beneficial to human health. However, elevated UA levels are not only closely associated with insulin resistance but can also promote reactive oxygen species production by activating NADPH oxidase (Zang *et al.*, 2023), thereby exacerbating endothelial inflammatory responses. A large-scale cohort study showed that patients with hyperuricemia had a 1.89-fold increased risk of acute cerebral infarction (95% CI 1.34-2.65) (Wang *et al.*, 2020). Serum lipoprotein (a)[Lp(a)], as an independent cardiovascular risk factor, is a special form of low-density lipoprotein (LDL) particles. High levels of Lp(a) are considered to be an independent risk factor for cardiovascular disease, mainly by promoting the formation and development of atherosclerotic plaques. Although there are relatively few studies on the relation of Lp(a) with ischemic stroke, existing data suggest that Lp(a) may be indirectly involved in acute arteriolar occlusive stroke by accelerating the progression of atherosclerosis (Ran *et al.*, 2020). Abnormal serum UA levels can aggravate microvascular complications in patients with T2DM by modulating pathways such as oxidative stress and inflammatory responses (Niu *et al.*, 2024). Notably, among the T2DM population, the chronic inflammatory state resulting from long-term poor glycemic control may further amplify the adverse effects of Lp(a) on vascular

**Corresponding author:* e-mail: dengkaozhan40@163.com

health. Both serum UA and serum Lp(a) levels are closely associated with the pathogenesis of various cardiovascular diseases (Lin and Lin, 2024). However, their role in patients with acute small artery occlusive stroke combined by T2DM, as well as their impact on the severity of neurological impairment, have not yet been fully elucidated.

The assessment and intervention of neurological damage is the core issue in the treatment of SAO (Sasahara *et al.*, 2024). The National Institutes of Health Stroke Scale (NIHSS) is closely related to infarct volume ($r=0.63$, $P<0.01$) and long-term prognosis (Qu *et al.*, 2024). However, SAO patients often present with "clinical symptom-imaging mismatch" (Ma *et al.*, 2024) due to their small lesions, resulting in insufficient sensitivity of the traditional assessment system. Ligustrazine has been widely used in treating cardiovascular and cerebrovascular diseases. Numerous experimental studies have confirmed that ligustrazine possesses multiple pharmacological activities, including vasodilation, improvement blood circulation, inhibition of platelet aggregation, and attenuation of oxidative stress damage. Its therapeutic potential in patients with acute small artery occlusive cerebral infarction complicated by T2DM has attracted widespread attention. Considering the potential role of serum UA and Lp(a) in these patients, it is particularly important to explore whether ligustrazine can improve the patient's neurological function damage by regulating the levels or effects of these two biomarkers. Animal experiments have found that ligustrazine can inhibit UA production by downregulating the XO/ROS/NLRP3 pathway and improve lipid metabolism disorders by regulating the PPARγ/LXRα pathway, suggesting that it may have a "dual-target" regulatory effect (Cao *et al.*, 2024). However, whether these mechanisms can be translated into actual benefits in clinical treatment still needs further verification. Therefore, in-depth exploration of the relationship between blood UA, serum Lp(a) and neurological damage in patients with acute arteriolar occlusive cerebral infarction and T2DM and evaluation of the therapeutic effect of ligustrazine in this context, will reveal the pathophysiological mechanism of such diseases and provide new ideas for finding more effective intervention strategies.

MATERIALS AND METHODS

General data

A retrospective study was conducted on 100 patients with acute arteriolar occlusive cerebral infarction and T2DM who were hospitalized in the Department of Neurology of our hospital. The case group: (1) aged 18 years and above; (2) initially diagnosed with SAO and the diagnosis was confirmed by imaging examination (Arboix *et al.*, 2005); (3) TOAST classification (Chen *et al.*, 2012) belongs to the arteriolar occlusive type: sudden illness, clinical symptoms including unconsciousness, pure paresthesia, motor dysfunction or language disorder, etc., history of diabetes or hypertension as support, head CT or MRI showing infarction with a diameter of less than 15 mm in the normal or deep perforating blood supply area; (4) completed at least 7 hours of nocturnal multi-channel sleep apnea monitoring; (5) complete clinical data of the patients, including color ultrasound of neck vessels, blood lipid level, blood UA concentration, blood homocysteine content and other related test data. Age- and sex-matched T2DM patients hospitalized during the same period were selected and all completed blood lipid, blood UA, homocysteine, neck vascular ultrasound and head CT/MRI examinations.

Diagnosis of T2DM was based on the guidelines (Chinese Elderly Type 2 Diabetes *et al.*, 2022): ① The patient has clinical symptoms of diabetes, specifically polydipsia, polyphagia, polyuria and unexplained weight loss and the venous plasma glucose level at any time point reaches or exceeds 11.1 mmol/L; or in fasting state, venous plasma glucose more than 7.0 mmol/L; ② The patient presents no obvious symptoms but has diabetes risk factors. Diagnosis requires a 75g oral glucose tolerance test (OGTT), confirmed by a 2-hour post-load blood glucose level reaching or exceeding 11.1 mmol/L; ③ Other factors that may cause elevated blood sugar need to be excluded.

Inclusion criteria: (1) meeting the diagnostic requirements (Liu *et al.*, 2023); (2) requiring admission to hospital within 7 days after cerebral infarction onset; (3) diagnosed with type 2 diabetes before admission or during hospitalization; (4) imaging examination confirmed the presence of new infarction foci; (5) intracranial vascular examination confirmed small artery occlusive cerebral infarction; (6) complete clinical data, high patient cooperation and compliance with the principle of informed consent. *Exclusion criteria*: (1) Patients with previous immune or blood system diseases; (2) Patients with severe organic diseases such as liver and kidney diseases or infectious diseases; (3) Patients with chronic obstructive pulmonary disease or ischemic heart disease; (4) Patients with mental illness, malignant tumors or impaired cognitive function; (5) Patients who have undergone surgery or are currently relying on ventilators and other equipment for treatment; (6) Patients who are unable to undergo MRI examinations; (7) Patients with missing clinical information; (8) Patients with abnormally elevated blood sugar due to other diseases or factors other than diabetes; (9) Patients with a history of using drugs such as hormones or immunosuppressants before enrollment; (10) Patients with a history of cerebral hemorrhage; (11) Patients who have recently used diuretics.

Methods

General clinical data

The baseline information and clinical comorbidity data were systematically collected. Among them: smoking behavior is defined as long-term regular smoking, which

requires an average daily smoking of ≥10 cigarettes and a continuous smoking period of more than 12 months; excessive drinking is defined as a weekly pure alcohol intake of ≥500 grams and a continuous drinking history of more than 1 year. Hypertension: The judgment is based on Guidelines (Liu and Revision, 2019). The specific criteria are: the patient has been diagnosed with hypertension, or the results of three blood pressure measurements without the use of antihypertensive drugs all show that the systolic blood pressure is more than 140 mmHg and the diastolic blood pressure is more than 90 mmHg. History of diabetes: follow the relevant standards (Chinese Elderly Type 2 Diabetes *et al*., 2022): History of coronary heart disease: stable or unstable angina pectoris, acute myocardial infarction, determined by coronary angiography or combined with clinical practice. Carotid atherosclerosis: High-frequency ultrasound imaging is employed for diagnosis when the carotid intima-media thickness (IMT) measures ≥1.0 mm, accompanied by the presence of atherosclerotic plaques and vascular stenosis reaching ≥50%.

Collection of biochemical indicators

The biochemical test data of patients were collected comprehensively, including high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol (TC) levels, content, triglyceride (TG) concentration, very low-density lipoprotein (VLDL), blood homocysteine (Hcy) index, serum UA value and serum Lp(a) and other related indicators.

Detection method

Detection of serum UA and lipoprotein α levels: After fasting for 8 hours overnight, 5 mL of peripheral venous blood was collected. After anticoagulation, the blood sample was separated by a low-temperature high-speed centrifuge (the parameter was set to 3000 rpm for 10 minutes). After centrifugation, the serum layer sample was accurately removed and the serum UA concentration was determined by the uricase method. The detection process was completed by a fully automatic biochemical analyzer and a matching diagnostic kit. The serum UA reference value (Richette *et al.*, 2020) was set to 420 μmol/L or less for men and 357 μmol/L or less for women. Exceeding this level is hyperuricemia. Lp(a)>300mg/dL is a high-risk value.

Treatment methods

Standardized treatment is given according to the relevant schemes: Ligusirizine injection (trade name: Ligusirizine injection; national medicine standard H11022110; Beijing Saisheng Pharmaceutical LTD; specification 1ml: 100 units), a single dose of 200U and after fully mixing with 250mL of 0.9% sodium chloride injection, it is administered by intravenous drip once a day. Simultaneously implement osmotic intracranial pressure reduction therapy to control intracranial pressure, dynamic blood pressure monitoring combined with individualized antihypertensive plan and other multi-dimensional symptomatic treatment. Chuanxiongzine injection (National Medicine Standard H22026448; Shanxi Kangyi Pharmaceutical LTD; specification 2ml: 40mg) was given, with a single dose of 80mg. After being fully mixed with 250mL of 5% glucose injection, it was intravenously dripped and administered twice a day.

Severity and prognosis assessment

Within 24 hours after admission, the standard requirements of the NIHSS were strictly followed and a comprehensive assessment was completed. The NIHSS scale covers consciousness, comprehension, language expression, muscle strength, etc. Among them, NIHSS score <5 points indicates mild neurological impairment and NIHSS score ≥5 points indicates moderate to severe neurological impairment.

The modified Rankin Scale (mRS) was used to systematically evaluate neurological functional outcomes at 30 days after onset. The specific grading criteria are: 0 points for completely asymptomatic state, daily living ability is not affected; 1 point indicates that the patient has mild symptoms, but no obvious functional impairment and can smoothly carry out daily activities; 2 points indicate that the patient has mild disability, although he can independently complete some daily activities, but still needs some assistance; 3 points represent that the patient is in a moderately disabled state, needs the assistance of others to complete daily life and the walking ability is limited to a certain extent; 4 points indicate that the patient is severely disabled, needs to rely on others for daily life and cannot walk independently; 5 points indicate severe disability, requires continuous care and cannot walk independently and has communication barriers; 6 points indicate death. The mRS score greater than 2 points was used as the cutoff value and patients were further assigned into poor prognosis (score 3-6 points) and good prognosis group (score 0-2 points). The Cronbach's α coefficients measured by the scale were 0.796 and 0.781.

Quality control

All assessors have completed standardized training and proficiency testing in both the NIHSS and mRS to ensure scoring consistency. To further verify data reliability, experts periodically conduct random audits with secondary review of cases. Additionally, all assessment data are independently entered and cross-verified by two individuals using standardized documents. The equipment is regularly calibrated and maintained to ensure the accuracy of the assessment. The research team periodically reviews the integrity of the data and corrects any problems found in a timely manner.

Statistical analysis

SPSS 27.0 software was used for analysis. The correlation between mild cerebral infarction group and moderate cerebral infarction group and blood UA and lipoprotein a

index was analyzed by one-way ANOVA; one-way ANOVA between multiple groups was performed and the Bonferroni correction method was used for inter-group comparison; for quantitative data with skewed distribution or uneven variance, the median and interquartile range [M(QL, QU)] were used. Data were analyzed using Mann-Whitney U test or Kruskal-Wallis test. Bonferroni correction was used; the NIHSS score after treatment was used as the dependent variable and the significant index with $P<0.05$ was used as the independent variable by univariate analysis. Binary Logistic regression analysis was used to determine the risk factors. ROC curve analyzed the predictive value of UA and ApoA for the prognosis of patients with acute arteriolar occlusive cerebral infarction and T2DM and $a<0.05$ was the test standard.

RESULTS

Comparison of baseline data between moderate and mild groups

Comparison of general data between moderate and mild groups showed that the patients in moderate group were significantly older than mild group with higher proportion of males, smoking and drinking (Fig. 1A-1C). The average body mass index (BMI) value of moderate group was higher than mild group with increased blood lipid indicators, the TC, TG, VLDL and Hcy levels and lower HDL and LDL levels (Fig. 1B, 1D); Compared with mild neurological deficit group, serum UA level, lipoprotein (A) level and NIHSS score at admission in moderate group were significantly higher (Fig. 1E, 1G, 1H) without differences in infarction diameter (Fig. 1F).

Comparison of general data between good and poor prognosis groups

The average age of the good and poor groups was similar, both around 60 years old and the proportion of smoking, drinking, hypertension, hyperlipidemia, diabetes and coronary heart disease in the poor group was higher than in the good group, with a higher proportion of carotid atherosclerosis (Fig. 2A,2C). The average BMI of poor group was higher than that of the good group and the two groups had similar levels of TC, TG, VLDL, HDL and LDL and Hcy level in poor group was higher than that of the good group (Fig. 2B,2D). In addition, The concentration of apolipoprotein A1(ApoA) in poor prognosis group was significantly lower than that in good prognosis group(Fig. 2F). The UA concentration in the poor prognosis group was significantly higher than that in the good prognosis group, and the infarction diameter was larger, and the mRS score was significantly higher than that in the good prognosis group. (Figure 2E, 2G, 2H).

Relationship between prognosis and infarction site

The proportions of brainstem infarction, basal ganglia, corona radiata, cortex, thalamus, centrum semiovale and cerebellum in poor group were higher than in good group, but the difference in infarction proportion between the two groups was small (Fig. 3).

Analysis of risk factors for poor prognosis

The prognosis of patients with acute arteriolar occlusive cerebral infarction combined with T2DM was taken as the dependent variable (1=poor, 0=good) and the indicators with $P<0.05$ between the above groups were included. BMI, Hcy, ApoA and other real values were substituted as independent variables and included in the regression analysis in a full subset manner. Results BMI, Hcy, ApoA and carotid atherosclerosis were not risk factors for poor prognosis; multivariate analysis further confirmed that serum UA, Lp(a) and infarct diameter were independent risk factors, $P<0.05$. See (Fig. 4A-B). The AUC of the combination of the three was significantly greater than the diagnostic efficacy of the three alone for poor prognosis of patients ($Z=4.061$, $P=0.001$), (Fig. 4C). In order to clarify the risk-benefit of the obtained prediction model for the treatment effect of ligustrazine in patients, according to the ROC curve, it can be seen that the combined prediction efficiency is good, with an AUC of 0.887 (95%CI: 0.789~0.933), a sensitivity of 92.48% and a specificity of 93.06%, see (Fig. 4D); verified by the DCA curve, its risk-benefit was as high as 78.06%, which once again verified the good application value of the model for such patients with acute arteriolar occlusive cerebral infarction combined with T2DM, see (Fig. 4E).

Correlation between blood uric acid, lipoprotein (a) and NIHSS and mRS scores before and after treatment

Kendall and Pearson correlation analysis showed that blood UA and Lp (a) were significantly correlated with NIHSS and mRS scores before and after treatment. Blood UA was positively correlated with NIHSS and mRS scores before and after treatment ($r=0.97$, 0.91); Lp (a) was positively correlated with NIHSS before treatment and mRS scores after treatment ($r=0.98$, 0.92), $P<0.05$, see (Fig. 5).

DISCUSSION

The endothelial repair capacity of elderly patients is reduced (Chen *et al.*, 2024), microcirculatory disorders are aggravated and long-term T2DM metabolic disorders lead to accelerated lipid deposition in vascular walls, which aggravates ischemia-reperfusion injury in patients with acute arteriolar occlusive cerebral infarction combined with T2DM (Nariai *et al.*, 2023). The results showed significant differences in baseline characteristics and metabolic indicators between moderate and mild neurological impairment groups. The average age in moderate group was higher and the proportion of males, smoking and drinking was significantly increased, suggesting that aging, male gender and unhealthy lifestyle habits may synergistically aggravate the progression of arteriolar lesions. The analysis suggests that androgens may promote arteriosclerosis by upregulating inflammatory factors such as IL-6 and TNF-α, smoking may induce vasospasm through nicotine and acetaldehyde, a metabolite of ethanol, may directly damage the vascular

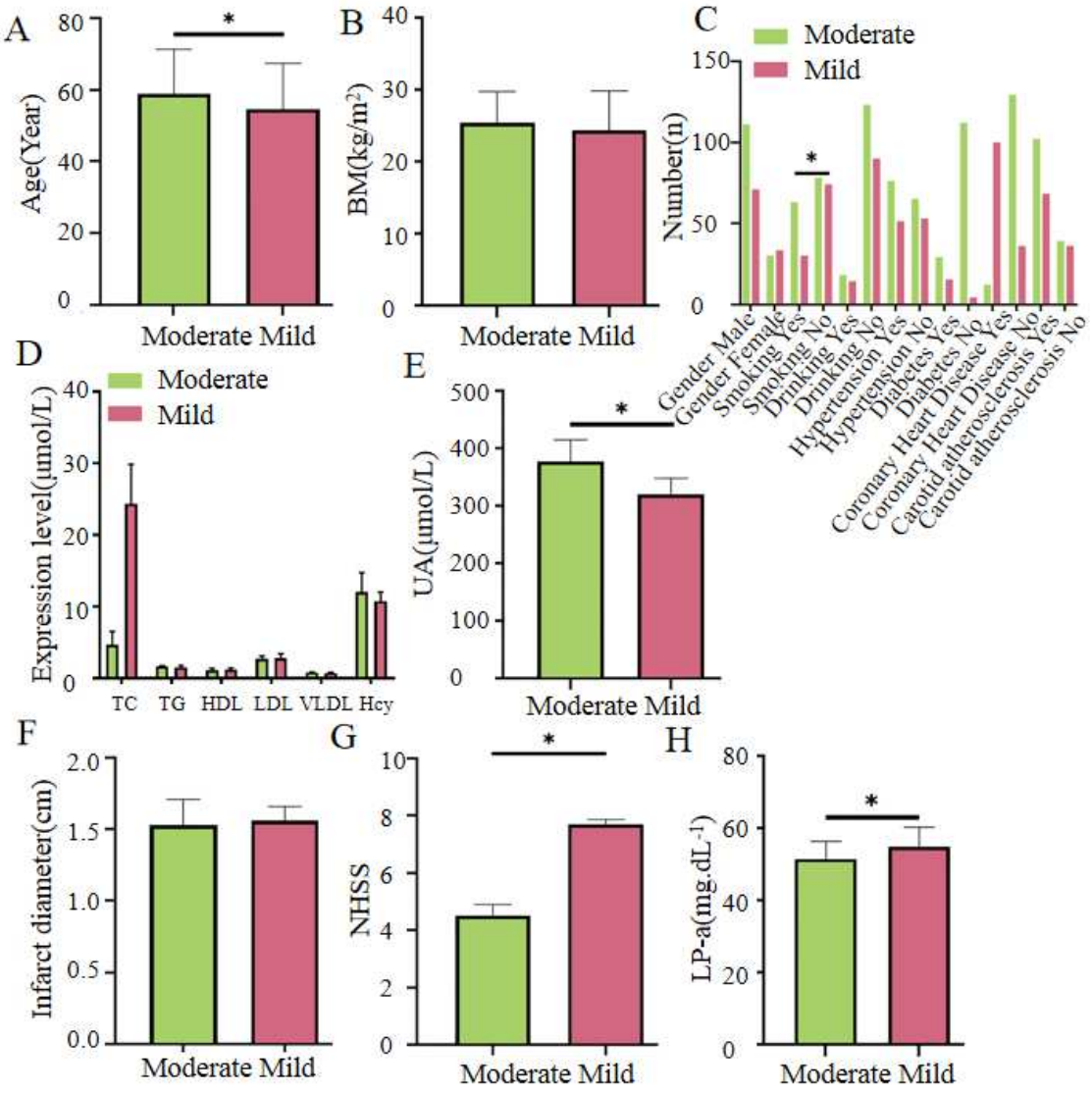

Fig. 1: Comparison of general data between moderate and mild groups.
(A). Age; (B).BMI; (C). Basic information and medical history; (D). Biochemical indicators; (E). UA level; (F). Infarction diameter; (G). NIHSS score; (H) Lp(a) level "*" P<0.05

endothelium and synergize with diabetes to increase the production of oxidized low-density lipoprotein (ox-LDL) (Khan *et al.*, 2025), accelerating arteriolar hyalinization.

Studies have found that UA has an antioxidant effect at a reasonable concentration (Giammanco *et al.*, 2025), but crystal deposition after supersaturation can activate the NLRP3 inflammasome (Tang *et al.*, 2024a). High UA aggravates insulin resistance by inhibiting the AMPK pathway, forming a vicious cycle of "metabolism-vascular damage". Therefore, UA in moderate group is higher than in mild group. This also suggests that clinically, characteristics such as age ≥ 65 years, male, smoking, obesity (BMI ≥ 28 kg/m²) and hyperuricemia (UA ≥ 420 μmol/L) may constitute high-risk warning indicators for neurological deterioration in patients with SAO and T2DM. Intensive monitoring and early intervention are required for such people.

Further analysis showed significantly higher BMI in moderate group than mild group, accompanied by increased TC, TG, VLDL and Hcy levels, while HDL decreased. This characteristic lipid profile may promote endothelial dysfunction through the dual mechanisms of lipotoxic effects and impaired anti-inflammatory function. It is worth noting that UA level in moderate group was increased and its excessive concentration (420 μmol/L) may aggravate the local inflammatory response by activating the NLRP3 inflammasome and form a vicious cycle with insulin resistance (Giammanco *et al*., 2025). Although there was no difference in the diameter of the infarct and mRS score between the two groups, the difference in NIHSS grade suggests that the relationship between the severity of neurological damage caused by arteriolar occlusion and the anatomical location of the lesions in key neural pathways, such as the basal ganglia,

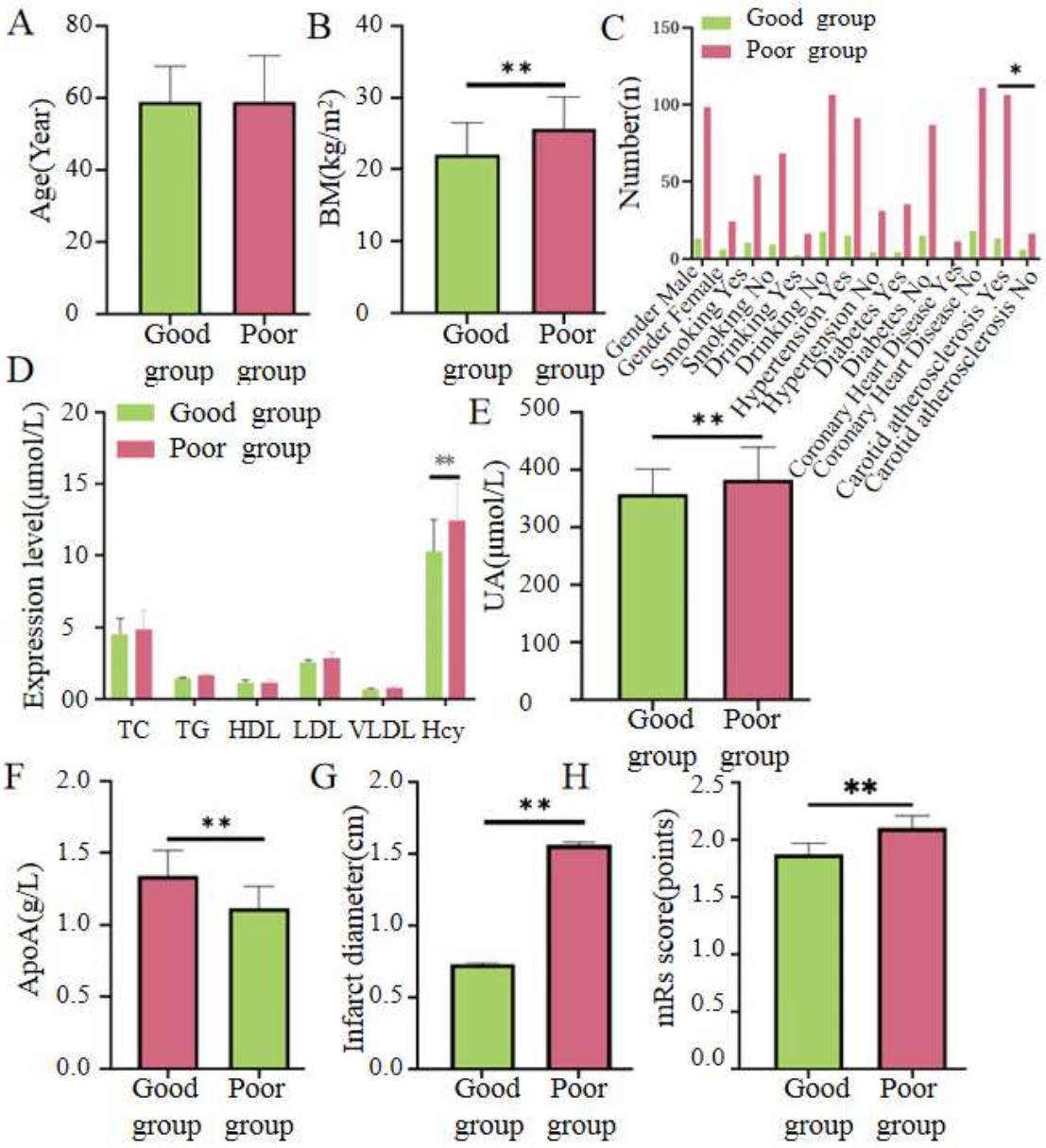

Fig. 2: Comparison of general data between good and poor groups.
(A). Age; (B). BMI; (C). Basic information and medical history; (D). Biochemical indicators; (E). UA level; (F). ApoA level; (G). Infarction diameter; (H). mRS score "**" P<0.01

may be more clinically significant than the simple infarct volume.

In this study, we divided and observed the therapeutic effect of ligustrazine. The analysis found that the proportion of smoking, drinking, hypertension, hyperlipidemia, diabetes and coronary heart disease in poor prognosis group was higher than in good group, indicating that unhealthy lifestyles, such as smoking and drinking, and the presence of multiple cardiovascular risk factors can aggravate the degree of neurological damage and affect prognosis. The proportion of carotid atherosclerosis was higher in the poor prognosis group than in the good prognosis group, suggesting that vascular lesions may be a significant contributing factor to unfavorable outcomes. The average BMI of poor group was higher than good group. Although the two groups were similar in TC, TG, VLDL, HDL and LDL levels, the concentration of Hcy in poor group was higher. It can be seen that obesity and its related metabolic disorders may be another important factor affecting the prognosis of patients. The increase in Hcy exacerbates vascular damage and inflammatory response and has an adverse effect on nervous system (Qin *et al.*, 2024).

The UA and Lp(a) concentrations and mRS scores of poor group were higher than good group, while the ApoA concentration was lower. Elevated serum UA levels are

generally associated with increased oxidative stress, which may further promote the progression of atherosclerosis (Li *et al.*, 2021b). ApoA, as the main protein component of high-density lipoprotein, its reduced concentration may reflect the weakening of cholesterol reverse transport capacity, which is not conducive to the repair of vascular walls (Li *et al.*, 2021a). In this study, in the logistic regression analysis, Lp(a), UA and infarct diameter were independent risk factors for poor prognosis, with OR=1.694, 95%CI (1.443~1.945). Long-term exposure to elevated Lp(a) levels in patients with acute small artery occlusive cerebral infarction and T2DM can accelerate the progression of coronary artery plaque volume. For every 1-fold increase in Lp(a) level, the cumulative percentage of plaque volume (PAV) increased by 0.694 times (Chandra *et al.*, 2025). In this process, high levels of UA can activate NADPH oxidase, thereby increasing the generation of reactive oxygen species (ROS), damaging vascular endothelial function and promoting the progression of atherosclerosis. The two work together to accelerate plaque progression and rupture risk, leading to more severe vascular occlusion and large-area cerebral infarction. In addition, the structures of apoA and plasminogen in Lp(a) are highly similar (Gaire *et al.*, 2019), which competitively inhibit fibrinolysis, leading to an increased risk of thrombosis and exacerbating the risk of worsening acute arteriolar occlusive cerebral infarction in patients. Lp(a) is a core target for residual cardiovascular risk (Averna and Cefalu, 2025) and its pathological mechanism and clinical intervention research are advancing rapidly. The structure of Lp(a) is similar to LDL, but it contains unique apoA, which makes it easier to deposit in the vascular endothelium. Its atherogenic effect is 5-6 times that of LDL, which also results in poor prognosis and repair effects for patients (Gaire *et al.*, 2020). About 20% to 30% of the world's population has elevated Lp(a) levels (50 mg/dL) and about 20% of the Chinese population exceeds 30 mg/dL (risk threshold) (Liu *et al.*, 2025).

In the study, the AUC for the combination of the three markers was significantly greater than that of any individual marker for predicting poor prognosis (Z=4.061, P=0.001), indicating excellent discriminative ability of the prediction mode. The DCA curve verified that its risk-benefit ratio was as high as 78.06%, which once again verified the good application value of the model for patients with acute arteriolar occlusive cerebral infarction and T2DM. It was very accurate for patients who benefited from ligustrazine treatment. The difference in mRS scores directly reflects the difference in neurological recovery after treatment. A higher score means a more severe degree of disability. The "cluster effect" of metabolic disorders in patients highlights the necessity of multi-target regulation, reflecting that the treatment of patients should also optimize UA-lowering therapy and homocysteine management (such as folic acid supplementation) on the basis of blood sugar control (Tang *et al*., 2024a) and improve lipid metabolism imbalance by adjusting the VLDL/HDL ratio; in addition, the separation of clinical symptoms and imaging evaluation suggests that a multidimensional evaluation system including biomarkers (such as UA, ApoA dynamic monitoring) and neurological function scales can be established in the clinic. The limitation of this study is that it did not include confounding factors such as the type of hypoglycemic drugs and blood pressure fluctuations.

In the future, prospective cohort studies are required to verify the temporal changes of UA and ApoA and explore the specific mechanism of Chinese medicine preparations, such as ligustrazine, regulating the metabolism-vascular axis through the XO/ROS/NLRP3 pathway to provide a more solid evidence basis for the formulation of individualized treatment plans. Further analysis of the infarction site in the study found that although the incidence of infarction in key functional areas such as the brainstem, basal ganglia, thalamus (motor conduction bundles, reticular activating system and limbic system nodes) and white matter fiber-dense areas such as the corona radiata and the semiovale center in poor prognosis group was slightly higher than good prognosis group, the difference in the proportion of infarction in each site between the two groups did not reach statistical significance.

This phenomenon may indicate that in the prognostic evaluation of acute arteriolar occlusive cerebral infarction combined with T2DM, the simple anatomical site distribution is not the core determinant of neurological function outcome. On the one hand, due to the "microanatomical heterogeneity" of the perforating artery supply area (Zhang *et al.*, 2024), even if such patients have infarction in the same part, the different degrees of microvascular lesions in diabetic patients and the difference in collateral circulation compensation capacity can lead to significant differentiation in clinical outcomes; and the interference effect of "silent infarction lesions" - some cortical or cerebellar infarctions are located in non-functional areas, which may be underestimated by the traditional prognostic evaluation system; metabolic disorders such as hyperglycemia and hyperuricemia can aggravate the destruction of the blood-brain barrier, making the key role of the metabolic-inflammatory microenvironment more significant in patients with the same volume of infarction lesions (Qin *et al*., 2024). This also warns that in clinical practice, we need to be vigilant about the limitations of "location determinism" and can adopt the "4P evaluation model" - that is, combining the location of the lesion (Position), metabolic parameters (Parameter), perfusion characteristics (Perfusion) and individualized repair potential (Potential) for comprehensive prediction, while paying attention to the neuroplasticity training of patients with infarction in key parts such as the brainstem, so as to break through the bottleneck of traditional anatomical prognosis prediction.

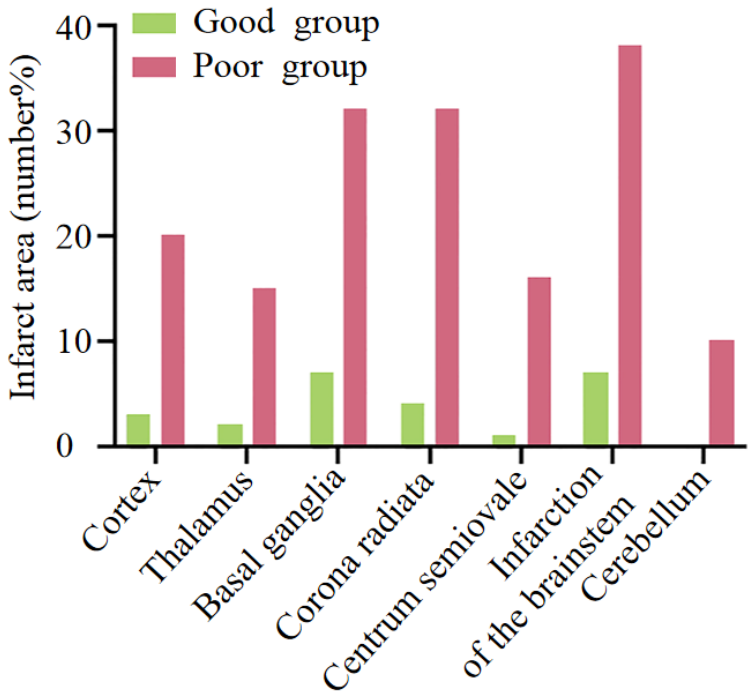

Fig. 3: Comparison of infarction sites between good and poor groups.

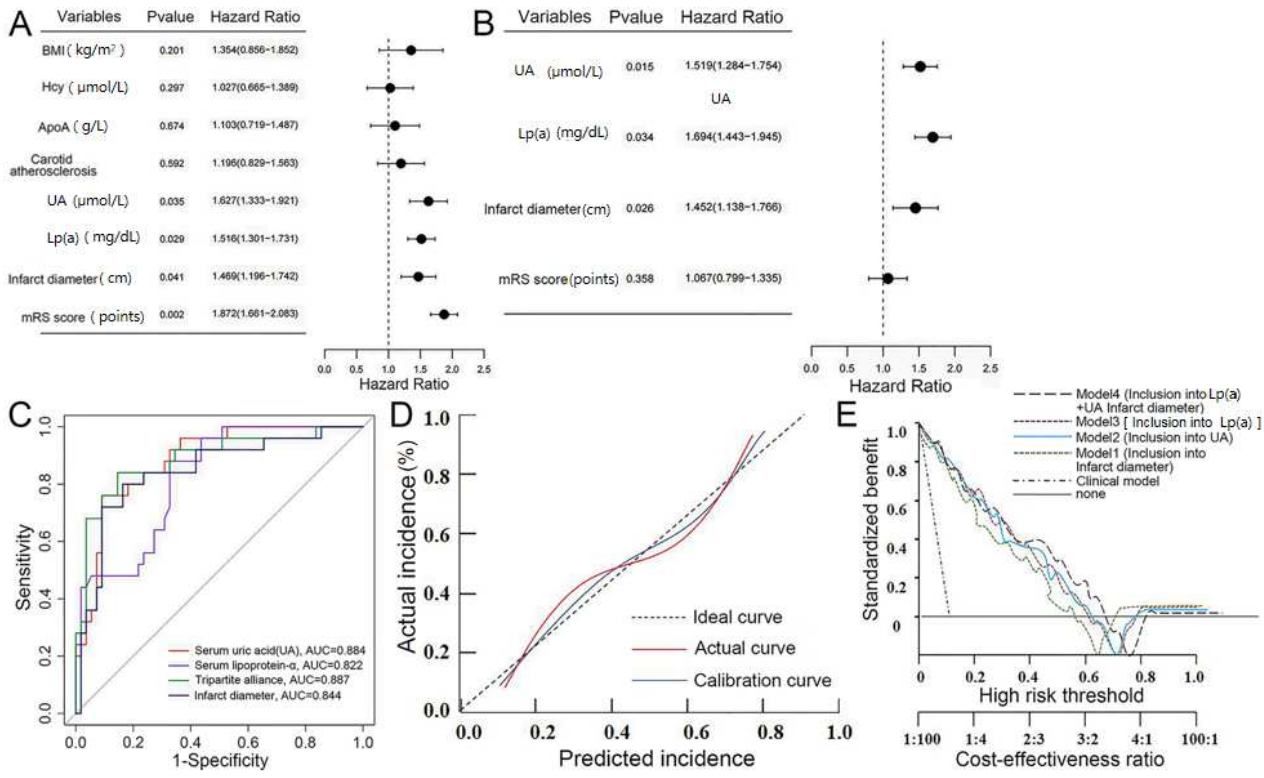

Fig. 4: Single and multi-factor logistic regression analysis and validation evaluation of model prediction efficiency.
(A): Logistic regression single factor forest plot; (B): Logistic regression multi-factor forest plot; (C): ROC analysis: (D): Calibration curve; (E): DCA evaluation of model benefit

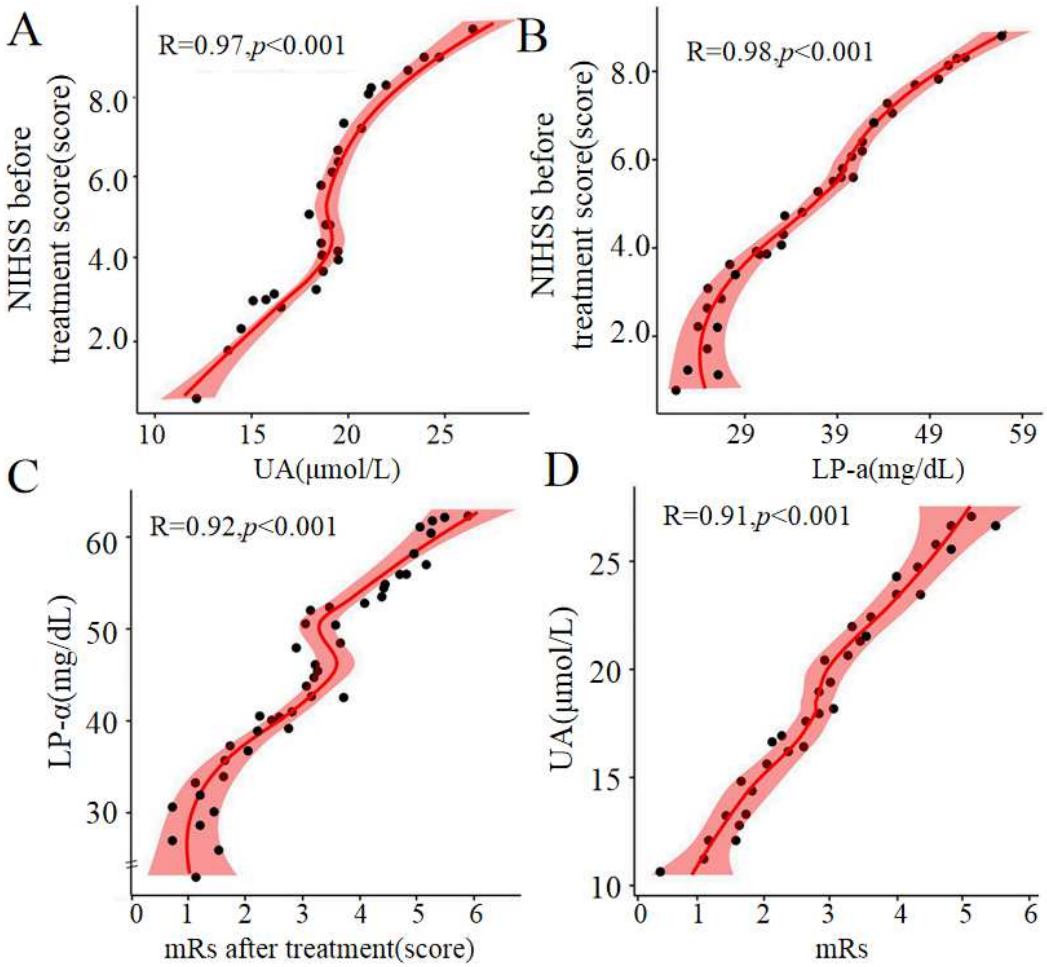

Fig. 5: Correlation analysis of serum uric acid, lipoprotein (a), NIHSS score before treatment and mRS score after treatment.
(A): Pearson correlation between serum uric acid and NIHSS before treatment; (B): Pearson correlation between Lp(a) and NIHSS before treatment; (C): Kendall correlation between serum uric acid and NIHSS before treatment; (D): Kendall correlation between Lp(a) and mRS score after treatment.

CONCLUSION

In summary, in patients with acute arteriolar occlusive cerebral infarction and T2DM, multiple metabolic disorders such as old age, male gender, smoking, obesity and hyperuricemia work together to increase the risk of neurological damage and poor prognosis. The prediction model established by combining multiple indicators showed good diagnostic efficacy and was able to accurately identify patients who responded better to ligustrazine treatment, emphasizing the importance of personalized treatment. In addition, although infarction in key anatomical sites has a certain impact on neurological function, the practice of simply relying on the location of infarction to assess prognosis has limitations; metabolic parameters (UA, lipoprotein a levels), perfusion characteristics and urinary infarction have a certain impact on neurological function. Factors such as symptoms and individualized repair potential are equally important, suggesting that clinicians need to focus on multi-target regulation, optimize patient management plans and improve prognosis.

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Not Applicable.

Authors' contributions
Yue Yu: Writing - original draft; Chengshi Zhang: Conceptualization Ziyu Jiang: Formal analysis; Lingwei Kong: Resources; Xiujie Zhang: Data curation; Yu Xiao: Supervision; Dongxia Wang: Writing - review & editing

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Data availability statement
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical approval

This study has been approved by the First Affiliated Hospital of Qiqihar Medical University (Ethical Review) under the approval number (Research) 07-01 (2024).

Conflict of interest

There are no conflicts to declare.

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