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Serum Irisin Levels are Inversely Correlated with Acute Ischaemic Stroke Incidence: Implications for Early Diagnosis in Southern China

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Objective: This study aimed to examine the correlation and prognostic value of serum irisin levels in acute ischaemic stroke (AIS) and the subsequent development of hemiplegia.

Methods: This study recruited participants from the Department of Neurology and Rehabilitation Medicine at Shunde Hospital, Southern Medical University. The Fugl–Meyer Assessment was used to assess functional impairment. Serum irisin levels were measured using the enzyme-linked immunosorbent assay method. Multivariate logistic regression was employed to explore the factors related to serum irisin levels and AIS.

Results: Serum irisin levels in the AIS group were significantly lower than those in the control group. However, no significant association was observed between serum irisin and stroke severity within the AIS cohort. Multivariate logistic regression analysis revealed an inverse correlation between serum irisin levels and AIS risk, indicating that it serves as a protective factor against AIS. The increase in serum irisin levels (adjusted odds ratio (OR) 0.938, 95% confidence interval [CI]: 0.899–0.977 per 100 pg/mL increment) was associated with a decreased risk of AIS. Analysis of the receiver operating characteristic curve confirmed the diagnostic value of serum irisin for AIS, with the area under the curve being 0.591 (95% CI: 0.522–0.659, $p = 0.012$).

Conclusion: Serum irisin levels were significantly lower in AIS and were identified as a protective factor, suggesting that serum irisin may have diagnostic value for AIS.

Keywords: irisin, acute ischaemic stroke, hemiplegia, risk factors, predictive value

Introduction

Stroke has recently emerged as the second leading cause of mortality and the third leading cause of disability worldwide, with ischaemic stroke accounting for 85% of all stroke incidents.[1] Despite a decrease in stroke incidence in high-income countries, it remains prevalent in low- and middle-income countries.[2,3] In China, between 1990 and 2019, a 106% increase in stroke incidence and a 32.3% rise in mortality rates were observed.[4–6] Ischaemic stroke is the predominant subtype, accounting for approximately 62.4–87% of total stroke occurrences.[1,7] Previous epidemiological studies have indicated significant geographical variations in stroke incidence, with distinct patterns observed across different regions of China. Southern China, in particular, has experienced a notable increase in stroke incidence rates, which may be attributed to a combination of factors, including regional lifestyle habits, environmental exposures and genetic predispositions. These variations underscore the importance of localised studies to better understand the specific risk factors

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and outcomes associated with stroke in these regions. Despite advancements in medical technology, including the development of intravenous thrombolytic therapy, intravascular interventional therapy and mechanical thrombectomy,[8–10] more than two-thirds of patients with ischaemic stroke continue to experience varying degrees of functional disability, with hemiplegia being the most common.[11] This significantly affects patients' quality of life and imposes a substantial burden on society.

Recent investigations have reported that serum irisin levels serve as a biomarker for the severity of neurological disorders.[12,13] Irisin is a myokine synthesised by skeletal muscle cells through the cleavage of fibronectin type III domain-containing protein 5 (FNDC5) following exercise,[14,15] and it can cross the blood–brain barrier.[16–20] This helps reduce neuroinflammation, improve neuronal function[19,21,22] and enhance the synthesis of brain-derived neurotrophic factor (BDNF), which augments cognitive function and provides neuroprotection against ischaemic injury.[23,24] The research conducted by the SHI team demonstrated a pronounced reduction in serum irisin levels in patients with Parkinson's disease. Additionally, serum irisin levels were shown to have an inverse relationship with the unified Parkinson's disease rating scale III scores and a direct correlation with the Montreal Cognitive Assessment scores.[25] This indicates an inverse association between motor symptoms and the severity of cognitive decline.[26] Irisin levels are a strong indicator of overall health. Diminished levels have been observed in patients with obesity, osteoporosis, sarcopenia, Alzheimer's disease and cardiovascular diseases.[27–32]

AIS is the leading neurological disorder, yet the relationship between irisin levels and the severity of AIS remains controversial. A clinical investigation in Norway compared 47 patients with mild ischaemic stroke with an equivalent cohort of 47 age- and gender-matched controls. The study reports no significant difference in irisin levels between the patients with stroke and the control group. The results do not show any distinction based on gender, age, stroke classification or infarct volume. Serum levels of FNDC5 were significantly lower in patients with stroke compared with controls, which contradicts the supposed pathophysiological relationship between irisin and FNDC5.[33] Additionally, a Polish study involving 46 patients with AIS, with diabetes as an exclusion criterion, and 32 controls devoid of cerebrovascular disease reports diminished irisin levels in the AIS group compared with the control group.[34] However, these findings do not establish a correlation between irisin levels and stroke severity. Furthermore, studies within the Chinese population have yet to clarify the relationship between these variables.[35,36]

This case-control study in Shunde, Guangdong Province, China, investigates the impact of irisin on AIS. The primary objective is to compare irisin levels between patients with AIS and those without stroke. Additionally, a subgroup analysis is performed among patients with stroke to assess the relationship between irisin levels and AIS within this specific population. This study explores the correlation between irisin levels and the severity of motor dysfunction in patients with AIS and further examines its prognostic value for AIS diagnosis. Our study provides a regional perspective on the association between serum irisin levels and AIS, and this geographically focused research not only fills a gap in the research in this area but also offers further evidence for the potential role as an AIS biomarker.

Methods

Study Population

This cohort study included patients with AIS who were admitted to Shunde Hospital of Southern Medical University in Guangdong Province between February 2023 and December 2023. During the same period, hospitalised patients without a diagnosis of AIS were age-matched and included in the control group. Acute ischaemic stroke was defined according to the criteria established by the World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease.[37] Validation was based on reports of magnetic resonance imaging (MRI) or diffusion-weighted imaging (DWI) examination within 24 hours of admission that indicated new cerebral infarction lesions or cerebral artery occlusion.

The inclusion criteria were as follows: (1) sudden onset of symptoms; (2) neurologic deficit lasting >24 hours (eg unilateral facial or limb weakness or numbness, speech impairment or other neurologic deficits); (3) imaging evidence of a worrisome lesion, particularly MRI with low T1 signal, high T2 signal and high signal on DWI with decreased apparent

diffusion coefficient; (4) exclusion of non-vascular causes; (5) computed tomography or MRI excluded cerebral haemorrhage; and (6) first diagnosis with no history of AIS.

The Fugl–Meyer scale is a widely used tool for assessing hemiplegic limb motor function post-stroke, known for its excellent intra- and inter-rater reliability, as well as high construct validity.[38] Better motor function is indicated by higher Fugl–Meyer scores. Therefore, patients with AIS were categorised into four groups based on their scores: mild (96–99 points), moderate (85–95 points), obvious (50–84 points) and severe (<50 points).

The exclusion criteria for this study were the presence of uncontrolled infectious diseases, autoimmune diseases, end-stage renal disease, severe hepatic and renal insufficiency, mental illness or malignant tumours. Additionally, those who did not provide informed consent or had haemolysed blood samples were excluded.

The control group included those who met the exclusion criteria and were not diagnosed with AIS. The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of Shunde Hospital, Southern Medical University (No. KYLS20221006). All participants provided written informed consent.

Clinical Variables

Demographic data, including age, sex, height and weight, were collected at baseline. Additionally, information on vascular risk factors (eg hypertension, diabetes mellitus [DM], hypercholesterolemia and history of smoking) was obtained.

Conventional risk factors for AIS included as covariates in this study were as follows: (1) hypertension, defined according to current Chinese guidelines for its management, including patients with systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg or those who had received antihypertensive treatment;[39] (2) type 2 DM, defined as fasting blood glucose (FBG) ≥7.0 mmol/L or glycated haemoglobin A1C (HbA1C) ≥6.5% or treatment with hypoglycaemic medication;[40] (3) smoking status, where patients were classified as smokers if they had smoked regularly in the past year, and those who had never smoked or had quit smoking for >1 year were classified as non-smokers.[41]

Brain imaging using MRI and cardiac ultrasound was conducted 24 hours after hospital admission as part of routine procedures. Upon admission, a board-certified neurologist evaluated patients with AIS using the modified Rankin Scale and the National Institutes of Health Stroke Scale. The motor function of hemiplegic limbs was assessed in patients with AIS using the Fugl–Meyer scale by a certified rehabilitation practitioner who was blinded to the laboratory data.

Blood Collection and Laboratory Test

All blood samples were collected on the first day of admission under a state of fasting. The samples underwent centrifugation twice at 3,000 g for 5 minutes each to separate the serum, which was then stored at −80°C until testing. Biochemical measurements were performed using standard laboratory methods. Enzymatic assays were used to measure serum levels of total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), homocysteine, creatinine (Cr) and uric acid (UA). The hexokinase method was used to measure fasting glucose levels, whereas the rate method was used to measure alanine transaminase (ALT). High-sensitivity C-reactive protein (hs-CRP) was determined through an immunoturbidimetric assay.

Serum irisin levels were measured using enzyme-linked immunosorbent assay kits (Code No. DY9420-05; R&D Systems, USA) and DuoSet™ Ancillary Reagent Kit 2 (Code No. DY008B R&D Systems, USA) in duplicate, following the manufacturer's instructions. The sensitivity range of the assay was 250 pg/mL–8,000 pg/mL. Levels below the lower detection limit were considered non-detected and were deemed to have no practical significance. The assay was conducted in an independent laboratory without clinical and neuroimaging data access.

Statistical Analysis

Categorical variables were presented as numbers and percentages, and statistical analysis used the chi-squared test. Continuous variables were expressed as mean ± standard deviation or median with interquartile range (IQR). For normally distributed data, *t*-tests were employed, whereas non-normally distributed data were analysed using the

Wilcoxon signed-rank and Mann–Whitney *U*-tests. Pearson's correlation coefficient (r) was used to assess the relationship between serum irisin levels and traditional risk factors and clinical baseline data. Multivariable logistic regression analysis was conducted to adjust for traditional stroke risk factors (eg age and sex). Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the association with AIS.

All statistical analyses were performed using SPSS Statistics for Windows version 27.0 and Prism version 9.5. A significance level of $p < 0.05$ was considered statistically significant.

Results

Baseline Characteristics of the Study Population

In this study, a total of 125 patients with AIS (68.8% men) and 135 age-matched control patients (47.4% men) were included based on predefined criteria (Figure 1). The baseline demographic and clinical characteristics of all participants are presented in Table 1. The median age of all participants was 65.0 years (IQR 55.0, 73.0), with a median age of 65.0 years (IQR 54.0, 74.0) in the AIS group and 65.0 years (IQR 57.0, 73.0) in the control group. There was no statistically significant difference between them ($p = 0.839$). A higher proportion of the AIS group consisted of men and individuals with a history of hypertension and smoking compared with the control group. The levels of SBP, DBP, FBG, HbA1C, hs-CRP, Cr and UA were found to be significantly higher in patients with AIS compared with the controls. Other conventional risk factors for AIS, including age, body mass index (BMI), history of DM, heart rate, TC, TG, low-density lipoprotein cholesterol (LDL-C), platelet count and ALT, did not exhibit significant differences between both groups ($p > 0.05$).

Enzyme-linked immunosorbent assay analysis showed that irisin levels were significantly lower in the AIS group compared with the control group (1,564 [1,220, 1,903] vs 1,723 [1,328, 2,268] pg/mL, $p = 0.012$). The AIS cohort was further divided into subgroups based on hemiplegic limb motor function, categorised using the simple Fugl–Meyer score into mild (96–99 points), moderate (85–95 points), obvious (50–84 points) and severe (<50 points) groups. No significant difference in irisin levels was observed across the AIS subgroups based on the severity of limb motor function (Figure 2).

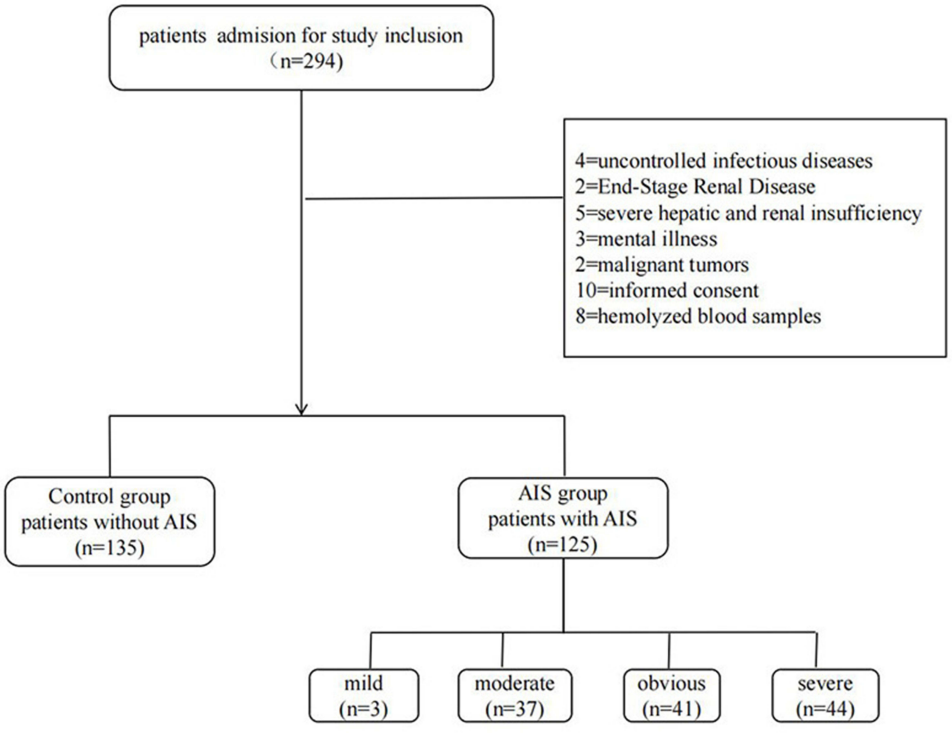

Figure 1 Study flow diagram in the present study.

Table 1 Demographic and Clinical Characteristics of AIS Patients and Controls

	All Participants (n=260)	AIS Group (n=125)	Control Group (n=135)	P
Men [n(%)]	150(57.7%)	86(68.8%)	64(47.4%)	<0.001
Age (years)	65(55,73)	65(54,74)	65 (57,73)	0.839
BMI	23.79±3.51	23.85±3.33	23.75±3.68	0.823
Hypertension [n(%)]	177(68.1%)	101(80.8%)	76(56.3%)	<0.001
Smoking[n(%)]	68 (26.2%)	45 (36.0%)	23 (17.0%)	<0.001
SBP (mm Hg)	135 (123,156)	148(130,167)	129(118,142)	<0.001
DBP (mm Hg)	80(73,89)	85(75,96)	78(71.5,84)	<0.001
HR (bpm)	76(68,85)	76(67,86)	76(69,84)	0.707
DM [n(%)]	81(31.2%)	45(36.0%)	36(26.7%)	0.104
FBG (mmol/L)	5.5(4.8,6.7)	5.96(5.06,6.98)	5.26(4.73,6.21)	0.002
HbA1c (%)	6.1(5.8,6.7)	6.3(5.9,6.9)	6.00(5.8,6.4)	<0.001
TC (mmol/L)	4.7(3.7,5.5)	4.66(3.70,5.51)	4.67(3.76,5.47)	0.771
TG (mmol/L)	1.5(1.1,1.9)	1.52(1.13,1.96)	1.50(1.10,1.89)	0.637
LDL-C (mmol/L)	2.87(2.22,3.33)	2.95(2.40,3.53)	2.77(2.17,3.25)	0.084
PLT (*10^9/L)	232(190,270)	232(191,264)	230(188.5,270.5)	0.856
hs-CRP (mg/L)	2.4(0.9,5.6)	4.30(1.50,5.60)	1.4(0.5,5.0)	<0.001
ALT (U/L)	20(13.5,28.0)	20(14,28)	20(13,28)	0.719
Scr (umol/L)	72(61,90)	77(64,95)	69.6(58.2,84.0)	0.005
UA (umol/L)	366(288,447)	381(304,458)	344(268,436)	0.026
LVEF (%)	67(64,70)	66.4(63,69)	67(65,71)	0.017
Irisin(pg/mL)	1648(1278,2079)	1564(1220,1903)	1723(1328,2268)	0.012

Abbreviations: BMI, body mass index; SBP, Systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; FBG, Fasting blood glucose; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; PLT, Platelets; hs-CRP, Hypersensitive C-reactive protein; ALT, glutamic-pyruvic transaminase; Scr, serum creatinine; UA, uric acid; LVEF, left ventricular ejection fraction; Irisin, Irisin.

Correlations Between Serum Irisin Level and Other Baseline Variables

The correlations between serum irisin levels and other baseline variables are presented in Table 2. No statistically significant correlation was found between irisin levels and age, gender, SBP, DBP, history of hypertension or diabetes or other covariates (eg FBG, HbA1C, TC, HDL-C, TG and serum Cr) ($p > 0.05$), which was consistent with the results from

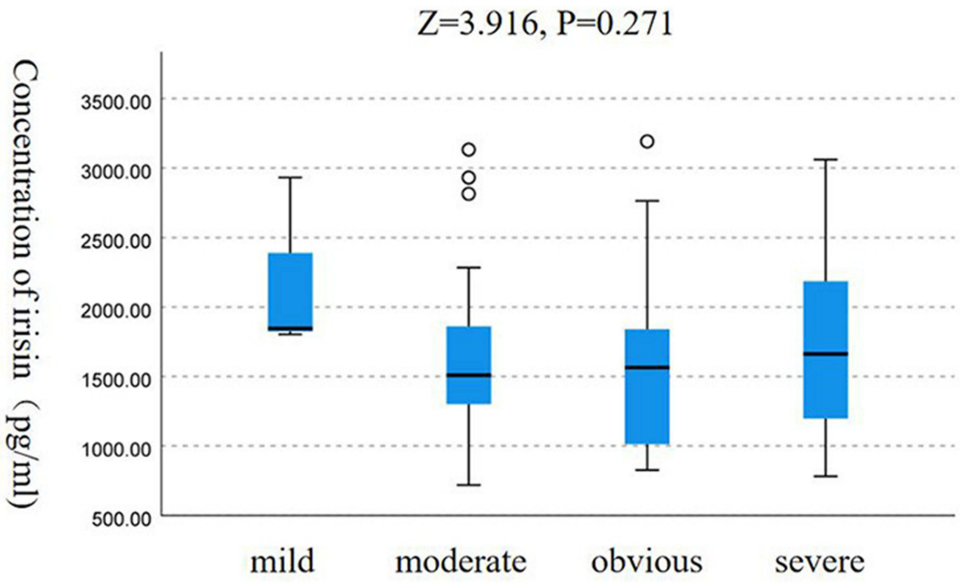

Figure 2 The difference between irisin and severity of motor function in hemiplegic limbs of AIS patients.

Table 2 Correlation of Irisin and Other Baseline Variables

	All Participants (n=260)		AIS Group (n=125)		Control Group (n=135)	
	r	P	r	P	r	P
Age*	−0.120	0.053	−0.164	0.067	−0.095	0.274
Sex	0.003	0.958	−0.126	0.161	0.017	0.845
BMI	0.030	0.636	−0.056	0.539	0.096	0.267
Hypertension	−0.024	0.702	0.087	0.332	−0.002	0.979
Diabetes mellitus	−0.047	0.454	0.002	0.978	−0.052	0.551
Smoking	0.005	0.935	0.210	0.019	−0.105	0.225
SBP*	−0.068	0.277	0.099	0.270	−0.076	0.379
DBP*	−0.016	0.798	0.029	0.746	0.071	0.411
FBG*	0.000	0.999	0.109	0.224	−0.035	0.690
HbA1c*	0.052	0.406	0.182	0.042	−0.005	0.950
TC*	0.066	0.291	0.104	0.249	0.046	0.600
TG*	0.067	0.283	0.106	0.242	0.046	0.600
LDL-C*	0.041	0.515	0.136	0.131	−0.006	0.944
PLT*	−0.018	0.767	−0.047	0.599	−0.010	0.911
hs-CRP*	−0.094	0.133	0.088	0.328	−0.117	0.178
Scr*	−0.059	0.340	0.046	0.609	−0.099	0.251
UA*	0.047	0.453	0.106	0.237	0.055	0.527
LVEF*	−0.105	0.091	−0.158	0.078	−0.136	0.117

Notes: * All are biased variables, and logarithmic transformations are performed.
Abbreviations: BMI, body mass index; SBP, Systolic blood pressure; DBP, diastolic blood pressure; FBG, Fasting blood glucose; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; PLT, Platelets; hs-CRP, Hypersensitive C-reactive protein; Scr, serum creatinine; UA, uric acid; LVEF, left ventricular ejection fraction.

the control group. However, a positive correlation was observed between irisin levels and HbA1C and a history of smoking within the AIS group ($p = 0.042$ and $p = 0.019$, respectively). No statistically significant correlation was found with the other baseline variables ($p > 0.05$).

Association of Serum Irisin with Acute Ischaemic Stroke

The univariate logistic regression analysis results suggest an inverse association between serum irisin levels and the risk of AIS. Specifically, for each 100 pg/mL increase in irisin, the OR decreased by 0.948 (95% CI: 0.917–0.979). These findings indicate that irisin may have a protective effect against AIS. After adjusting for age and sex, which are known to be associated with irisin levels, the adjusted OR was calculated as 0.946 (95% CI: 0.914–0.979, $p = 0.001$) per 100 pg/mL increase in irisin concentration, indicating a significant correlation. After adjusting for all other significant predictors, including a history of hypertension and DM, smoking, SBP, DBP, BMI, LDL cholesterol and HbA1C, irisin remained an independent predictor of AIS with an adjusted OR of 0.938 (95% CI: 0.899–0.977, $p = 0.002$) (Table 3).

The receiver operating characteristic (ROC) curve analysis showed that serum irisin has diagnostic potential in predicting AIS (area under the curve [AUC] = 0.591, 95% CI: 0.522–0.659, $p = 0.012$) (Table 4 and Figure 3). According to the ROC curves, irisin levels >1,949 pg/mL at admission predicted AIS with the highest sensitivity (79.2%) and specificity (61.5%) (Figure 3).

Table 3 Association of Serum Irisin with AIS Patients by Multivariate Logistic Regression Analysis

Risk Factors	Adjusted OR[a]	95% CI	P-value
Irisin (per100pg/mL increment)	0.938	0.899–0.977	0.002
Sex	0.530	0.271–1.035	0.063
Age	1.002	0.975–1.029	0.900
Hypertension	2.059	1.040–4.076	0.038
Diabetes mellitus	0.804	0.365–1.768	0.587
SBP	1.021	1.004–1.038	0.015
DBP	1.023	0.994–1.054	0.12
BMI	0.941	0.861–1.028	0.180
LDL-C	1.120	0.809–1.551	0.493
HbA1c	1.240	0.958–1.603	0.102
Smoking	1.896	0.907–3.964	0.089

Notes: [a]Adjusted for age, sex, hypertension history, diabetes mellitus, SBP, DBP, BMI, LDL-C, HbA1c and smoking.

Abbreviations: SBP, Systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; LDL-C, low density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin.

Table 4 ROC Curves of Serum Irisin for Diagnosis of AIS

Variable	AUC	95% CI	P-value
Irisin	0.591	0.522–0.659	0.012

Discussion

The prognosis of AIS primarily depends on factors such as the volume and location of the infarct, the duration of the ischaemic insult and the severity of the initial cerebrovascular compromise. Clinical observations reveal variability in outcomes among patients with similar lesion characteristics, posing challenges in accurately predicting the severity and

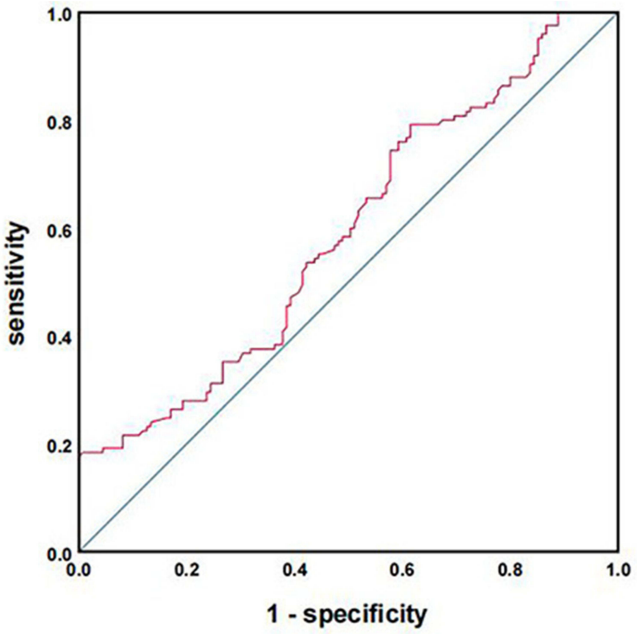

Figure 3 The ROC curve of Irisin for AIS.

outcome of AIS. Therefore, identifying biomarkers capable of predicting early neurological complications following an ischaemic event is crucial. Such biomarkers can aid in classifying the severity of AIS and determining its prognosis effectively.

Recent investigations have suggested that serum irisin levels may indicate neurological disorder severity.[42] However, the association between serum irisin levels and the severity of AIS remains controversial. Kazimierczak-Kabzińska A et al demonstrated that patients with AIS had lower serum irisin levels compared with those without cerebrovascular afflictions.[34] However, the study did not find a correlation between irisin levels and stroke severity. This finding is limited by the modest cohort size, which included only 46 patients with ischaemic stroke and 32 controls. Çalık M et al observed that patients with minor strokes had significantly reduced levels of BDNF and epidermal growth factor compared with healthy individuals; however, there was no significant difference in basic fibroblast growth factor and serum irisin levels between both groups.[43] Their study was limited by specific inclusion criteria focusing on patients diagnosed with lacunar or cortical/non-lacunar strokes or transient ischaemic attacks, excluding those with hemiplegia, a common and severe manifestation of stroke. This selection criterion limits the generalisability of the findings to the entire spectrum of patients with AIS, potentially overlooking variations in neurotrophic factor and irisin levels present in more severely affected stroke populations. A study from Turkey enrolled 180 patients with AIS,[24] but it did not include a control group. Subgroup analyses within the AIS cohort showed that individuals with neurological deficits had significantly lower serum irisin levels compared with those who remained asymptomatic. In contrast to previous research, the present study examined 125 individuals with moderate-to-severe AIS who experienced persistent neurological impairments (eg unilateral facial or limb weakness or numbness, aphasia or other deficits) lasting >24 hours. Our results showed a significant difference between the moderate-to-severe AIS group and the control group, with the former exhibiting markedly lower levels of serum irisin.

Irisin is a myokine induced by physical activity. Empirical evidence supports that exercise leads to a significant increase in circulating irisin levels.[44] Serum levels vary depending on exercise intensity, with endurance training particularly enhancing its release.[45] However, the onset of AIS results in varying degrees of limb paresis, which alters myokine release profiles and reduces musculoskeletal activity. This could contribute to the lower levels of irisin observed in patients with AIS compared with controls.

The study results suggest that serum irisin levels could be a prognostic indicator for AIS incidence, with an AUC of 0.591 (95% CI: 0.522–0.659, $p = 0.012$). Consistent with our findings, a comprehensive cohort study conducted across three Chinese stroke centres involving over 1,500 AIS cases revealed that reduced irisin levels predicted unfavourable outcomes (AUC = 0.75, 95% CI: 0.70–0.81) and mortality (AUC = 0.83, 95% CI: 0.78–0.87) at a 6-month follow-up.[35] However, the modest AUC suggests that although irisin may have some relevance in the context of AIS, its role as a prognostic indicator should be further investigated. Future studies should focus on larger cohorts and consider longitudinal designs to better assess the relationship between irisin levels and clinical outcomes in patients with AIS. Similarly, a study in Japan found a correlation between increased serum irisin levels and a decreased incidence of cerebrovascular diseases among healthy men.[46] Consequently, irisin could be considered a predictive biomarker for the prevalence of AIS, which may have significant implications for the clinical management of cerebrovascular disorders.

Using univariate logistic regression analysis on the entire study cohort, we found that for every 100 pg/mL increase in serum irisin levels, there was a 6% decrease in the risk of experiencing AIS. This association between irisin levels and AIS remained statistically significant even after adjusting for several confounding factors, including age,[12] sex,[47,48] hypertension,[49] smoking and diabetes.[50] These findings support the hypothesis that fluctuations in irisin levels, independent of common vascular risk factors, are associated with AIS risk. This evidence suggests a potential lifestyle intervention strategy for stroke prevention, where young and healthy individuals may benefit from incorporating high-intensity interval training into their routine. This type of training is known to boost irisin secretion effectively.[33,51,52] However, older adults may benefit more from regular resistance training,[13] which is also known to enhance irisin levels and is often more feasible and sustainable for this age group compared with high-intensity workouts.[53,54] Overall, our findings provide valuable insights into how modifiable lifestyle factors, specifically exercise modalities that increase irisin levels, could serve as preventive measures against AIS. These non-invasive interventions offer a promising approach for individuals and public health strategies aiming to reduce the incidence of stroke.

The observed inverse correlation between serum irisin levels and AIS incidence suggests a complex interplay of biological factors. Irisin, known to modulate inflammation and enhance neurogenesis, may exert its protective effects through several pathways. First, irisin has been shown to reduce neuroinflammation, a key factor in the pathogenesis of AIS. By mitigating inflammatory responses, irisin could potentially limit stroke-induced brain injury. Second, irisin's role in improving neuronal function and promoting the synthesis of BDNF implies a neuroprotective mechanism that could be leveraged in therapeutic strategies. The correlation between irisin levels and the severity of hemiplegic limb motor impairment in individuals with AIS remains unclear. Our investigation documents a relationship between irisin levels and limb motor dysfunction, assessed via the simplified Fugl–Meyer Assessment, in patients with AIS. Subgroup analysis within the AIS cohort revealed a complex association between circulating irisin levels and the severity of hemiplegic limb motor impairment, categorised by Fugl–Meyer Assessment scores. Specifically, participants with mild hemiplegia exhibited higher levels of irisin compared with those in the moderate, obvious and severe hemiplegia groups. However, among individuals with moderate-to-severe hemiplegia, irisin levels did not show significant differences. This suggests a potential threshold effect where irisin levels plateau or become less responsive beyond a certain severity of motor impairment. Despite these observations, the analysis did not establish a statistically significant correlation between irisin levels and the overall severity of hemiplegic limb motor function among patients with AIS ($p = 0.271$). This outcome indicates that although detectable differences in irisin levels exist between certain subgroups defined by motor function impairment severity, these differences do not linearly correlate with the degree of motor impairment across the entire spectrum of severity. This finding underscores the intricate relationship between irisin and the neurological and functional consequences of ischaemic stroke, suggesting that factors beyond muscle activity and irisin levels may significantly influence recovery and functional outcomes in this patient population. These observed outcomes may be influenced by methodological limitations (eg the lack of dynamic monitoring of irisin levels). To gain deeper insights into the relationship between irisin and hemiplegic impairment following AIS, expanding the participant cohort, continuously quantifying irisin levels and improving precision in assessing limb motor function may be essential.

This study has several limitations. First, as a cohort study, the research was only able to establish a correlation between serum irisin levels and AIS, without determining causation. Further research, particularly prospective cohort studies, is essential to strengthen our conclusions. Second, the circadian pattern of irisin secretion remains unclear.[47] Our study's fixed morning interval for blood sampling may not align with other investigations, potentially introducing data discrepancies. Furthermore, blood samples were collected at only one time point, upon admission. This approach does not capture the dynamic changes in serum irisin levels that may occur over the course of the disease or in response to treatment. The temporal profile of irisin levels could provide valuable insights into its role as a biomarker for AIS, including its potential for monitoring disease progression and therapeutic efficacy. Future studies with serial sampling at multiple time points during the acute and subacute phases of AIS are warranted to explore these changes and to further validate irisin as a prognostic biomarker. There is also a selection bias in the comparative analysis between patients with AIS and the controls, as data were solely collected from one hospital, limiting generalisability. Additionally, this study assessed the association between irisin levels and AIS only at admission, without evaluating the impact of subsequent irisin fluctuations on AIS progression. Therefore, further research is needed to understand the implications of dynamic irisin variations on AIS onset and progression.

Our study contributes to the existing body of research by further exploring the relationship between serum irisin levels and AIS in a regional context. While previous studies, such as the work by Tu et al,[35] have established an association between decreased irisin levels and poor functional outcomes in ischemic stroke patients, our findings provide additional evidence supporting an inverse correlation between irisin levels and AIS incidence, specifically within the population of Southern China. This regional focus is crucial, as suggested by Çalık et al,[43] who highlighted the importance of understanding the etiological and clinical associations of irisin in the context of ischemic stroke. Additionally, our research complements the findings of Kaydok et al,[55] who examined the relationship between serum irisin levels and spasticity severity in chronic stroke patients, by investigating the potential of irisin as a prognostic biomarker for AIS in the acute phase. The geographical variation in irisin levels and their association with AIS, as seen in our study, underscores the importance of regional-specific research. This is particularly relevant for developing targeted therapeutic and preventive strategies that take into account the local population's genetic, environmental, and lifestyle

factors. Collectively, these studies enhance our understanding of irisin's role as a potential biomarker for AIS and emphasize the need for further investigation into its clinical applications.

Conclusion

This study revealed significantly lower serum irisin levels in patients with AIS, suggesting a potential role for irisin as a prognostic biomarker. Although we did not find a significant correlation between irisin levels and motor function in hemiplegic limbs, our findings indicate that irisin levels may be inversely associated with stroke severity. This implies that irisin could serve as an indicator of the severity of AIS, rather than being directly linked to motor function outcomes. The potential protective effect of irisin in AIS warrants further investigation, and the predictive value of serum irisin levels in stroke prognosis should be confirmed through well-designed prospective studies focused on stroke severity as the primary endpoint.

Data Sharing Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Shunde Hospital, Southern Medical University (NO: KYLS20221006). Written informed consent was obtained from all participants.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All of the authors had no any personal, financial, commercial, or academic conflicts of interest separately.

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