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ORIGINAL RESEARCH

Effect of Insulin Resistance on Prognosis of Intravenous Thrombolysis in Acute Ischemic Stroke Patients with or Without Type 2 Diabetes Mellitus

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Introduction: This study aims to investigate the significance of insulin resistance (IR) markers in predicting 48-hour hemorrhagic transformation and 3-month poor prognosis in acute ischemic stroke (AIS) patients of intravenous thrombolysis (IVT), with or without type 2 diabetes mellitus (T2DM).

Methods: A total of 1352 patients with AIS treated with IVT between January 2019 and December 2023 were retrospectively reviewed. We analyzed the prognostic value of IR markers, including the triglyceride-glucose (TyG) index, triglyceride and body mass index (TYG-BMI), and the insulin resistance metabolic score (METS-IR), in AIS patients who received IVT with or without T2DM. The primary outcome was 48-hour hemorrhagic transformation and 3-month poor prognosis (modified Rankin Scale [mRS] ≥ 3).

Results: Among 1181 enrolled patients, 328 were diagnosed with T2DM, representing 27.8% of the cohort. T2DM group showed a higher proportion of poor prognosis (23% vs.11%, $p < 0.001$), but no significant difference in hemorrhagic transformation between the two groups. TyG index, TyG-BMI, and METS-IR all demonstrated predictive value for 3-month poor prognosis, with the TyG index showing the highest predictive accuracy [area under the curve (AUC): 0.848]. The optimal cutoff point for predicting poor prognosis was 7.409, with sensitivity of 0.762 and specificity of 0.855 ($p < 0.001$). However, all three indexes were limited in their ability to predict hemorrhagic transformation.

Conclusion: Elevated TyG index is an independent risk factor for 3-month poor prognosis in AIS patients of IVT with or without type T2DM, with the TyG index showing the highest predictive value. These findings provide a new understanding that IR can be used as a therapeutic target for AIS patients of IVT.

Keywords: TyG index, TYG-BMI, METS-IR, hemorrhagic transformation, poor prognosis

Introduction

Stroke is the leading cause of high morbidity and mortality in China, especially with type 2 diabetes (T2DM). Intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (r-tPA) is the first-line treatment for AIS,[1] but the risk of symptomatic intracranial hemorrhage (SICH) is still as high as three-quarters of patients with poor prognosis.[2,3] People with T2DM are at a higher risk of developing cerebrovascular disease and have a much higher rate of further cerebrovascular complications compared to the general population. Therefore, when making treatment decisions for AIS patients in the general population as well as those with T2DM, it is crucial for clinicians to assess the risks of hemorrhagic transformation and poor prognosis, as this plays a significant role in managing cerebral infarction.

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Numerous studies have confirmed the role of insulin resistance (IR) and lipid metabolism dysregulation in the progression of cerebrovascular diseases.[4,5] Research has shown that IR is a primary pathophysiological mechanism in T2DM, a factor influencing the progression of large vascular complications, and a contributing factor to cerebrovascular diseases in patients without T2DM.[6,7] Many methods have been developed to estimate IR, such as hyperglycemic clamp, hyperinsulin-positive clamp test (HEC), and homeostasis model assessment of IR (HOMA-IR), which are not practical in clinical settings.

Therefore, there is an ongoing search for simpler and more reliable indicators to estimate the progression of IR without the need for insulin testing. Triglyceride-glucose (TyG) index, triglyceride and body mass index (TYG-BMI), and the insulin resistance metabolic score(METS-IR) are simple and easy to obtain clinically reliable indicators of IR[8] and independent predictors of atherosclerosis progression in the general population and patients with T2DM.[6,7] The efficacy of IVT is often influenced by various factors, including metabolic and inflammatory conditions, such as IR. Limited studies have reported the effect of IR on clinical outcomes or relapse after stroke, while few studies in the real world have looked at thrombolysis patient cohorts, mainly limited by sample size or analyzing only patients with diabetes. As such, identifying reliable indicators to predict hemorrhagic transformation and poor prognosis in AIS patients treated with IVT with or without type T2DM remains a critical issue. This study aims to investigate the effects of the TyG index, TyG-BMI, and METS-IR on the prognosis of IVT in AIS patients with or without T2DM.

Materials and Methods

Study Design and Patient Selection

The study included 1352 patients with AIS treated with IVT at our stroke center from January 2019 to December 2023. The Xiangyang No.1 People's Hospital Human Research Ethics Committee has approved the study protocol (Approval No. XYYYE20250018). We included patients who met the following criteria: (1) age ≥ 18 years; (2) Patients diagnosed with AIS within 4.5 h of onset; (3) Receiving IVT with alteplase and non-large vessel occlusion confirmed by computed tomography angiography (CTA) or magnetic resonance angiography (MRA); (4) Head CT was reviewed 24–36 hours after IV. The study excluded patients with prestroke modified Rankin Scale (mRS) scores ≥2 or with incomplete data. The flow chart of patient selection is shown in Figure 1.

Data Collection

Clinical data of AIS patients were collected by consulting electronic medical records. These included age, sex, height, weight, stroke risk factors (hypertension, diabetes, hyperlipidemia, coronary heart disease, atrial fibrillation, smoking, alcohol consumption), and laboratory tests (including hemoglobin, creatinine, fasting blood glucose, total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL), high density lipoprotein (HDL)). Based on laboratory tests and anthropometric results, the following indicators were calculated:

Body mass index (BMI) = ratio of weight (kg) to height squared (m2),

TyG index = ln[TG (mg/dl) × FPG (mg/dl)/2],[9]

TYG-BMI = TyG index × BMI (kg/m2),[10]

METS-IR = ln {[2 × FPG (mg/dl) + TG (mg/dl)] × BMI (kg/m2)}/ln[HDL-C (mg/dl)][11]

Stroke severity was assessed by the National Institutes of Health Stroke Scale (NIHSS) at admission and 24 hours after IV.[12] According to the ORG 10172 test of acute stroke treatment (TOAST) standard,[13] the etiology of AIS patients was divided into large atherosclerosis (LAA), small artery occlusion (SAO), cardiac embolism (CE), other (SOE) and unidentified subtype (SUE). Macrovacular occlusion (LVO) is defined as the occlusion of the first and second segments of the middle cerebral artery (MCA), the internal carotid artery (ICA) and its extremities, the tandem occlusion involving ICA-MCA, or the basilar artery occlusion. Hemorrhagic transformation (HT) refers to the European Cooperative Acute Stroke Study (ECASS)[14] classification criteria and is defined as intracranial hemorrhage found by CT examination within 48 hours after AIS onset. Hemorrhagic infarction (HI) and parenchymal hematoma (PH) are classified as types of HT. sICH was defined as a type of intracranial hemorrhage associated with an increase in NIHSS score of ≥4 points from baseline or death within 7 days.[15] Modified Rankin Scale (mRS) scores at 3 months after AIS were collected by

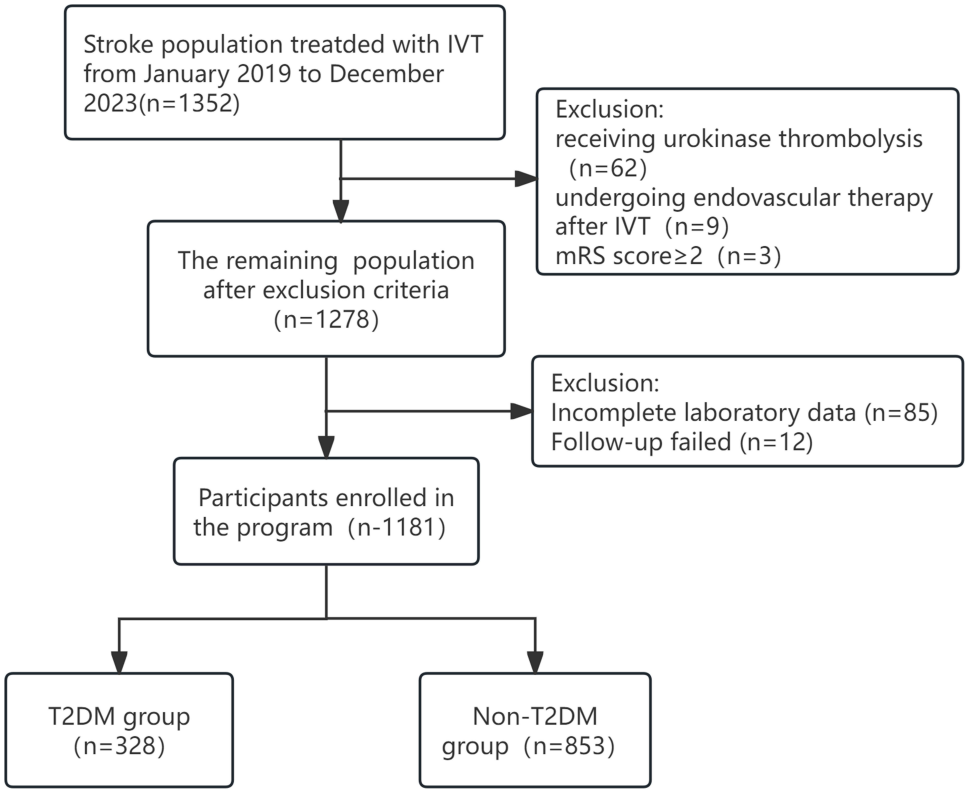

Figure 1 The flow chart of patient selection.

telephone interviews with two trained physicians to assess functional outcomes. The primary outcome was 48-hour hemorrhagic transformation and 3-month poor prognosis (mRS ≥ 3).

Statistical Analysis

Continuous variables that conform to the normal distribution are represented by mean ± SD, and continuous variables that do not conform to the normal distribution are represented by the median and interquartile distance (IQR). Categorical variables are expressed in frequency and percentage terms. Differences between the two groups were compared by student *t* test, Mann–Whitney *u*-test or Chi-square test. Odds ratio (or) was calculated by logistic regression to analyze the influence of each factor on HT and poor prognosis. ROC curve analysis was used to determine the cutoff values of TyG index, TYG-BMI, and METS-IR for predicting HT and poor prognosis, and to calculate the sensitivity and specificity of these values. We used SPSS 25.0 software (SPSS Inc., Chicago, Illinois, USA) for statistical analysis, and a two-tailed $p < 0.05$ was considered statistically significant.

Results

The study included 1181 patients with AIS, of whom 328 (27.8%) had T2DM, and 853 (72.2%) were non-T2DM patients. All patients underwent head and neck CTA or DSA to exclude acute large vessel occlusion. Three hundred and twenty-six patients received DSA during hospitalization, and 5 patients received carotid artery stents, 3 patients received middle cerebral artery M1 stents, and 11 patients received vertebral artery stents. The median NIHSS score on admission was 5. A total of 35 patients (3%) showed HT within 48 hours after the head CT examination, of which 9 patients (0.76%) had sICH, and 4 patients (0.34%) died during follow-up. A total of 171 patients (14%) had a poor prognosis at 3 months, and 2 patients died during follow-up due to pulmonary infection.

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Baseline Clinical Characteristics of Patients in the Two Groups are Shown in Table 1

Compared with the non-T2DM group, the T2DM group had higher rates of hypertension (82% vs 67%, $p < 0.001$) and coronary heart disease (22% vs 12%, $p < 0.001$). They also had a higher body mass index (25.07 ± 3.22 vs 23.70 ± 3.36, $p < 0.001$), higher smoking rates (48% vs 36%, $p = 0.002$), and a longer duration of diabetes at the time of hospital admission (41.54 ± 7.19 vs 38.77 ± 6.00, $p < 0.001$). However, there was no significant difference in the time from symptom onset to intravenous thrombolysis between the two groups (3.014 ± 1.15 vs 2.98 ± 1.16, $p = 0.608$).

Laboratory Tests of Patients in the Two Groups are Shown in Table 2

Compared with the non-T2DM group, leukocytes (7.91 ± 2.54 vs 6.99 ± 2.72, $p < 0.001$), neutrophils (5.53 ± 2.79 vs 4.88 ± 2.55, $p < 0.001$), C-reactive protein (8.78 ± 25.84 vs 4.93 ± 19.66, $p = 0.015$), uric acid (320.78 ± 97.97vs 305.16 ± 87.67, $p = 0.012$), urea (5.84 ± 2.29 vs 5.42 ± 1.69, $p < 0.001$), creatinine (83.76 ± 68.43 vs 71.89 ± 21.15, $p = 0.002$), eGFR [97.9 (73.38,115.62) vs 101 (86.8,117.68), $p = 0.005$] were also higher, but TC was lower (4.19 ± 1.04 vs 4.34 ± 0.97, $p = 0.016$). Of course, there were statistically significant differences in HBA1c, FBG and EBG between the two groups ($p < 0.001$), but no statistically significant differences in TG, LDL-C and HDL ($p > 0.05$).

The Comparison of IR and Clinical Outcomes Between the Two Groups is Shown in Table 3

Compared with the non-T2DM group, the T2DM group had significantly higher TyG index (7.58 ± 0.65 vs 6.89 ± 0.46, $p < 0.001$), TyG-BMI (190.45 ± 32.45 vs 163.67 ± 27.69, $p < 0.001$), and METS-IR (2.35 ± 0.27 vs 2.18 ± 0.32, p <

Table 1 Basic Characteristics of T2DM and Non-T2DM Group [n (%), (±s), M (P25, P75)]

Clinical Characteristics	Total (n = 1181)	T2DM Group (n = 328)	Non-T2DM Group (n = 853)	P Value
Demographic data				
Sex men	695 (58.85%)	195(59%)	500(59%)	0.843
Age (year)	67(59,73)	68(61,73)	67(58,73)	0.043
BMI (kg/m2)	24.08 ± 3.38	25.07 ± 3.22	23.70 ± 3.36	<0.001
SBP (mmHg)	144.53 ± 3.4961	146.44 ± 20.17	143.8 ± 20.10	0.044
DBP (mmHg)	83.07 ± 13.159	82.72 ± 11.95	83.21 ± 13.60	0.547
Stroke risk factors				
Smoking	745(63%)	157(48%)	307(36%)	0.002
Drinking history	820(69%)	121(37%)	357(42%)	0.224
Hypertension	841(71%)	270(82%)	571(67%)	<0.001
Coronary heart disease	174(15%)	73(22%)	101(12%)	<0.001
Atrial fibrillation	102(9%)	31(9%)	71(8%)	0.563
Hyperlipemia	280(24%)	85(26%)	195(23%)	0.285
History of stroke	46(4%)	14(4%)	32(4%)	0.737
TOAST classification				<0.001
LAA	349	147	202	
SAO	721	151	562	
CE	92	26	66	
SOE+SUE	19	4	23	
Scales or times				
DNT (min)	39.54 ± 6.474	41.54 ± 7.19	38.77 ± 6.00	<0.001
OIT (h)	2.99 ± 1.16	3.014 ± 1.15	2.98 ± 1.16	0.608
Admission NIHSS score	4(2,6)	4(3,6)	3(2,5)	<0.001
NIHSS after 24 hours of IVT	2(1,4)	3(1,4)	2(1,4)	<0.001

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LAA, large atherosclerosis; SAO, small artery occlusion; CE, cardiac embolism; SOE, other and SUE unidentified subtype; DNT, Door to Needle Time; OIT, Time from onset to intravenous thrombolysis.

Table 2 Laboratory Tests in T2DM and Non-T2DM Groups [n (%), (±s), M (P25, P75)]

Variable	Total (n = 1181)	T2DM Group (n = 328)	Non-T2DM Group (n = 853)	P Value
Blood count				
Leukocyte (10^9/L)	7.62 ± 2.70	7.91 ± 2.54	6.99 ± 2.72	<0.001
Neutrophil (10^9/L)	5.06 ± 2.64	5.53 ± 2.79	4.88 ± 2.55	<0.001
Lymphocyte (10^9/L)	1.51 ± 1.41	1.50 ± 0.65	1.52 ± 1.61	0.901
Hemoglobin (g/L)	135.54 ± 34.55	133.84 ± 18.16	136.19 ± 39.058	0.295
Platelet (10^9/L)	203.49 ± 77.841	201.99 ± 54.69	204.07 ± 85.10	0.682
Coagulation count				
PT (s)	11.2 (10.5,11.7)	11.2 (10.5,11.7)	11.2 (10.5,11.7)	0.594
APTT (s)	25.9 (23.7,28.4)	25.4 (23.5,27.6)	26.2 (23.86,28.8)	<0.001
FIB (g/L)	3.04 ± 1.11	3.07 ± 1.02	3.03 ± 1.15	0.55
Dimer (mg/L)	0.44 (0.2,1.04)	0.5 (0.24,1.21)	0.42 (0.2,0.94)	0.007
Lipid profile				
TC (mmol/L)	4.30 ± 0.99	4.19 ± 1.04	4.34 ± 0.97	0.016
TG (mmol/L)	1.35 ± 0.71	1.69 ± 0.94	1.22 ± 0.54	0.501
LDL-C (mmol/L)	3.38 ± 19.33	4.74 ± 31.85	2.85 ± 11.29	0.296
HDL (mmol/L)	1.35 ± 5.06	1.35 ± 4.75	1.36 ± 5.17	0.979
sdLDL-C (mmol/L)	388.07 ± 188.65	385.61 ± 186.84	389.02 ± 189.44	0.781
LP (a) (nmol/L)	121.69 (159.26,238.38)	99.1 (48.92,234.17)	126.2 (62,247.2)	0.005
Biochemistry				
HCY (umol/L)	18.15 ± 11.21	17.84 ± 9.56	18.27 ± 11.78	0.56
Glycosylated hemoglobin	6.26 ± 1.34	7.8 ± 1.64	5.67 ± 0.44	<0.001
FBG (mmol/L)	6.28 ± 1.99	8.37 ± 2.63	5.48 ± 0.69	<0.001
EBG (mmol/L)	8.15 ± 3.09	11.17 ± 4.07	6.99 ± 1.39	<0.001
CRP [mg/L]	6.00 ± 21.62	8.78 ± 25.84	4.93 ± 19.66	0.015
Urea (mmol/L)	5.54 ± 1.88	5.84 ± 2.29	5.42 ± 1.69	<0.001
Crea (umol/L)	75.19 ± 40.61	83.76 ± 68.43	71.89 ± 21.15	0.002
eGFR (mL/min/1.73m2)	100.2 (84,116.5)	97.9 (73.38,115.62)	101 (86.8,117.68)	0.005
UA (umol/L)	309.50 ± 90.88	320.78 ± 97.97	305.16 ± 87.67	0.012
TB (umol/L)	14.96 ± 6.65	15.26 ± 7.29	14.85 ± 6.39	0.378
ALT (IU/L)	16.3 (12.5,22.2)	17.9 (13.5,24.53)	15.9 (12.3,21.3)	0.001
AST (IU/L)	23.2 (19.31,30.6)	23.8 (18.8,31.26)	23.1 (19.4,30.05)	0.392
Albumin (g/L)	40.88 ± 4.04	40.43 ± 4.35	41.06 ± 3.90	0.017
Globulin (g/L)	28.84 ± 10.39	28.31 ± 4.65	29.04 ± 11.88	0.28

Abbreviations: PT, prothrombin time; APTT, activated partial thrombin time; FIB, fibrinogen; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol; sdLDL-C, small and dense LDL cholesterol; LP, (a) lipoprotein a; HCY, homocysteine; eGFR, glomerular filtration rate; FBG, fasting blood glucose; EBG, emergency blood glucose; UA, uric acid; total bilirubin glucose.

0.001). Additionally, the proportion of patients with poor prognosis at 3 months was higher in the T2DM group (23% vs 11%, $p < 0.001$).

The Comparison of Safety Endpoint Events Between the Two Groups is Shown in Table 4

There was no statistically significant difference in the primary safety outcomes, including any ICH, sICH and 3-month mortality between the two groups, but there was a statistically significant difference in extracranial bleeding (9.8% vs 2.5%, $p < 0.001$) with a higher rate of gingival bleeding in diabetic patients (5.5% vs 0.8%, $P < 0.001$). In terms of complications, patients with diabetes had higher rates of pulmonary infection (9.9% vs 4.8%, $p = 0.002$) hepatic and renal insufficiency (4.8% vs 1.7%, $p = 0.005$) and lower limb venous thrombosis (5.8% vs 1.9%, $p = 0.001$).

Table 3 Comparison of IR Indexes and Clinical Outcomes Between the Two Groups [n (%), (±s)]

Variable	Totality (n = 1181)	T2DM Group (n = 328)	Non-T2DM Group (n = 853)	P Value
IR index				
TyG	7.08 ± 0.61	7.58 ± 0.65	6.89 ± 0.46	<0.001
TyGBMI	171.11 ± 31.45	190.45 ± 32.45	163.67 ± 27.69	<0.001
METSIR	2.23 ± 0.32	2.35 ± 0.27	2.18 ± 0.32	<0.001
Primary effective outcome				
Poor prognosis	171 (14%)	76 (23%)	95 (11%)	<0.001
Secondary effective outcome				
3 months mRS Score	1 (0,2)	2 (1,2)	1 (0,2)	<0.001
Excellent functional outcome in 3 months	789 (66.8%)	153 (46.6%)	636 (74.6%)	<0.001
Good functional prognosis at 3 months	1136 (96.1%)	313 (95.4%)	823 (96.6)	0.343
24-hour NIHSS score change	1.61 ± 2.14	1.78 ± 2.34	1.56 ± 2.09	0.187

Table 4 Comparison of Safety Endpoint Events Between the Two Groups [n (%), (±s)]

Variable	Totality (n = 1181)	T2DM group (n = 328)	Non-T2DM group (n = 853)	P Value
Primary safe outcome				
Any ICH	35 (3%)	9 (3%)	26 (3%)	0.851
sICH	9 (0.76%)	3 (0.9%)	6 (0.7%)	0.715
3-month mortality rate	7 (0.6%)	3 (0.9%)	4 (0.5)	0.056
Secondary safe outcome				
Any extracranial blood	53 (4.5%)	32 (9.8%)	21 (2.5%)	<0.001
Gingival congestion	25 (2.1%)	18 (5.5%)	7 (0.8%)	<0.001
Gastrointestinal bleeding	19 (1.6%)	8 (2.4%)	11 (1.3%)	0.195
Adverse event				
Pulmonary infection	71 (6%)	31 (9.9%)	40 (4.8%)	0.002
Urinary tract infection	2 (0.1%)	0	2 (0.2%)	1
Acute coronary syndrome	7 (0.6and)	3 (1%)	4 (0.5%)	0.4
Liver and kidney dysfunction	29 (2.5%)	15 (4.8%)	14 (1.7%)	0.005
Venous thrombosis of lower extremity	34 (2.9%)	18 (5.8%)	16 (1.9%)	0.001

Multivariate Logistic Regression Analysis was Performed on the Influencing Factors of 3-month Poor Prognosis

The influencing factors for 3-month poor prognosis were shown in Table 5, including gender, stroke history, admission NIHSS score, small and dense low-density lipoprotein cholesterol, hemoglobin, lymphocyte count, TyG index and METS-IR.

Multivariate Logistic Regression Analysis was Performed on the Factors Affecting the Occurrence of HT

Table 6 lists independent predictors of HT, including platelet count, D-dimer, FBG, and TG. Independent predictors for further study of sICH include prothrombin time and TC, with odds ratios (OR) [95% CI] of 1.649 (1.208, 2.251) and 2.157 (1.259, 3.696), respectively.

Table 5 Multivariate Logistic Regression Analysis Was Performed on the Influencing Factors of 3-month Poor Prognosis

Variable	B	SE	Wald	OR	95% CI	P Value
Sex	−1.025	0.364	7.939	0.359	0.176~0.732	0.005
History of stroke	1.182	0.571	4.288	3.26	1.065~9.98	0.038
sdLDL-C (mg/L)	−0.002	0.001	6.737	0.998	0.996~0.999	0.009
METSIR	−1.404	0.443	10.039	0.246	0.103~0.585	0.002
Direct bilirubin	0.096	0.053	3.261	1.101	0.992~1.223	0.071
ALT (IU/L)	−0.014	0.009	2.362	0.987	0.97~1.004	0.124
AST (IU/L)	0.02	0.01	3.647	1.02	0.999~1.04	0.056
TyG	0.186	0.018	107.475	1.204	1.163~1.247	<0.001
Hemoglobin (g/L)	−0.021	0.008	7.133	0.979	0.964~0.994	0.008
Lymphocyte (10^9/L)	−0.584	0.249	5.493	0.558	0.342~0.909	0.019
NIHSS after 24 hour Of IVT	0.517	0.051	104.425	1.677	1.519~1.852	<0.001

Table 6 Multivariate Logistic Regression Analysis Was Performed for the Influencing Factors of HT

Variable	B	SE	Wald	OR	95% CI	P Value
D-dimer (mg/L)	0.153	0.046	11.357	1.166	1.066~1.275	0.001
TG (mmol/L)	1.239	0.272	20.794	3.452	2.027~5.88	<0.001
FBG (mmol/L)	−0.186	0.093	3.964	0.83	0.691~0.997	0.046
(A/G)	0.251	0.224	1.262	1.286	0.829~1.993	0.261
Platelet (10^9/L)	−0.012	0.005	6.238	0.989	0.98~0.998	0.013

Prediction of 3-month Poor Prognosis After IVT in AIS Patients by TyG Index, TYG-BMI and METS-IR

Figure 2A shows that the area under ROC curve of TyG index for predicting 3-month poor prognosis was (AUC 0.848, 95% CI 0.813–0.884), the Youden index was 0.617, and the cutoff point was 7.409, $P < 0.001$ (sensitivity = 0.762, specificity = 0.855). The prognostic value of TyG-BMI in predicting poor prognosis (AUC 0.82, 95% CI 0.782–0.857), Youden index 0.547, cutoff point 183.264, $P < 0.001$ (sensitivity = 0.779; specificity = 0.768); The prognostic value of METS-IR in predicting poor prognosis (AUC 0.692, 95% CI 0.649–0.735), Youden index 0.319, cutoff point 2.32, $P < 0.001$ (sensitivity = 0.605; specificity = 0.714).

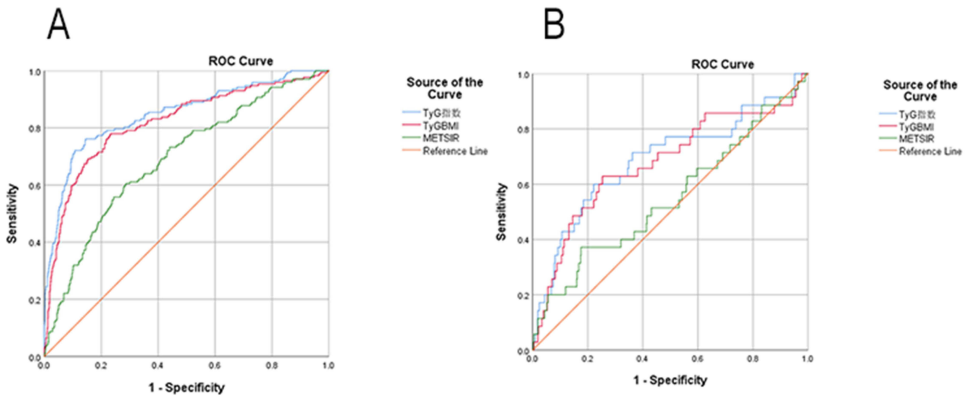

Figure 2 The receiver operating characteristic (ROC) curves predict TyG index, TYG-BMI, and METS-IR for different outcomes in AIS patients of IVT. (**A**) 3-month poor prognosis after IVT, (**B**) HT after IVT.

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Prediction of HT After IVT in AIS Patients by TyG Index, TYG-BMI and METS-IR

Figure 2B shows that the area under ROC curve for TyG index to predict HT was (AUC 0.689, 95% CI 0.5855–0.793), the Youden index was 0.378, and the cutoff point was 7.417, $P < 0.001$ (sensitivity = 0.6, specificity = 0.778). The prognostic value of TyG-BMI in predicting HT (AUC 0.677, 95% CI 0.573 to 0.782), Youden index 0.376, cutoff point 188.031, $P < 0.001$ (sensitivity = 0.629; specificity = 0.747); The prognostic value of METS-IR in predicting HT (AUC 0.55, 95% CI 0.442–0.658), Youden index 0.195, cutoff point 2.453, $P < 0.001$ (sensitivity = 0.371; specificity = 0.824).

Discussion

Our study is the first to use all three measures (TyG index, TYG-BMI, and METS-IR) to assess the risk of HT and 3-month poor prognosis in AIS patients of IVT with or without T2DM. This single-center retrospective study showed that an elevated TyG index was an independent risk factor for 3-month poor prognosis after IV, but none of the three indicators were independent risk factors for early HT after IV. TyG index, TYG-BMI and METS-IR all had predictive value for 3-month poor prognosis after IV in AIS patients, with the TyG index showing the highest predictive value. However, the predictive value of these indices for HT after IV was limited.

Through the grouping analysis of T2DM and non-T2DM patients, we found that the prognosis of AIS patients with T2DM was significantly worse, which was consistent with the results of previous studies,[16,17] but the results of various studies were different in terms of HT after IV. In this study, it was also observed that patients in the T2DM group had significant gingiva and digestive tract bleeding after IV, which was worthy of clinicians' attention. Three indicators (TyG index, TYG-BMI, METS-IR) serve as surrogate indicators of IR and can be used as indirect indicators of metabolic syndrome. As is well known, IR is not only a key factor in metabolic disorders, closely linked to dyslipidemia, obesity, and diabetes, but it also damages vascular endothelial cells. This damage promotes platelet adhesion, activation, and aggregation,[18] as well as abnormal lipid metabolism, inflammatory responses, proliferation of vascular smooth muscle cells and interstitial cells, and thickening of the vascular intima.[19] These processes contribute to arterial stenosis or occlusion, thereby promoting the development and progression of atherosclerosis, as well as increasing the risk of cardiovascular and cerebrovascular diseases. At the same time, IR can cause hemodynamic disorders in the case of hypotension or cerebral hypoperfusion, and destroy brain metabolism through inflammation and oxidative stress mechanisms, thus aggravating the injury of ischemic stroke.[20] Therefore, we aimed to use easily measurable alternative markers of IR to investigate early HT and 3-month poor prognosis in AIS patients of IVT.

Data from the UK Biobank cohort (involving 273,368 individuals) showed that TyG index was superior to glucose and triglyceride alone in predicting stroke occurrence, suggesting that TyG index may be a good biomarker for predicting IR in stroke outcomes.[21] Our findings were consistent with those of Toh et al, who found that the TyG index was associated with 90-day poor prognosis in AIS patients who received IV, while no significant correlation was observed with sICH outcomes.[22–25] In our study, multivariate logistic regression showed that TyG index was an independent risk factor for 3-month poor prognosis after IV in AIS patients, and the risk of poor prognosis increased by 1.204-fold for every unit increase in TyG index. Chen et al conducted a study on stroke patients hospitalized in intensive care unit (ICU) and found that TyG index was an important predictor of severe disturbance of consciousness and in-hospital death of cerebrovascular patients in ICU and had certain predictive value for the severity of disturbance of consciousness and in-hospital mortality of cerebrovascular patients.[26] In our study, the predictive value of TyG index for 3-month poor prognosis was 0.848 (95% CI 0.813–0.884, $P < 0.001$) and 0.689 (95% CI 0.5855–0.793, $P < 0.001$) for HT. Compared with TYG-BMI and METS-IR indicators, the TyG index has a higher predictive value, but the TyG index is not a reliable biomarker of HT. Therefore, it may help to distinguish patients with a poor risk prognosis for closer monitoring or early intervention. Another study found that the higher the TyG index, the worse the prognosis for AIS patients. It seems that the TyG index is not only a good prognostic indicator for monitoring AIS patients after IV but also has similar value in other diseases.

Obesity indicators in patients with ischemic stroke are often negatively correlated with clinical prognosis, which is known as the stroke-obesity paradox.[27] According to the Northern Manhattan Stroke Study,[28] higher BMI and WC are associated with lower severity of new strokes and better outcomes in ischemic stroke populations. Some studies have

suggested that IR may be one of the mechanisms leading to the obesity paradox in AIS patients.[29] Yu et al found that TyG-WC and TyG-BMI, which are indices combining TyG with waist circumference (WC) and BMI respectively, were related to the severity and short-term outcomes of AIS. With the increase of TyG-WC and TyG-BMI, the severity of stroke decreased and the short-term outcome was better.[30] This phenomenon was not found in this study. At present, obesity paradox has been confirmed to exist in a variety of diseases, including acute myocardial infarction, stroke and coronary heart disease.[31] However, some studies have suggested that the obesity paradox in stroke is not valid and may be due to selective bias.[32] Recent studies have shown that the obesity paradox is not universal and that various variables such as gender, uric acid levels and insulin sensitivity influence its existence. For the first time, we evaluated the predictive effect of TyG-BMI on HT and poor prognosis. In addition to our study, a cohort study of 9406 participants showed that TYG-WC and TYG-BMI were important predictors for middle-aged and elderly people with new ischemic stroke, and the predictive value was higher than TyG.[33]

METS-IR, a composite score used to assess IR, is more relevant to IR than the pathophysiology of IR because it combines glucose, lipids, and metabolic markers. The results of this study are consistent with previous studies, which jointly emphasize the adverse effect of IR on the prognosis after IVT of ischemic stroke.[34,35] In addition, the results of this study further support and validate the conclusions of previous studies that have highlighted the adverse effects of metabolic syndrome on AIS patients. We demonstrated that METS-IR may be used as a prognostic factor for poor prognosis and HT but with insufficient sensitivity (32%) and specificity (82%) for HT and low predictive value. Therefore, it is necessary to further investigate METS-IR index as an important predictor of HT.

IR indicators are closely related to adverse outcomes after IV in AIS. Higher levels of IR may enhance inflammation and pre-thrombotic events, and exacerbate ischemic response after IVT,[36] resulting in worse prognosis for patients. Recent research suggests that IR should be a therapeutic target for improving clinical outcomes after ischemic stroke. Post-stroke IR intervention trials have demonstrated that pioglitazone can reduce the risk of stroke recurrence and myocardial infarction in non-T2DM patients or transient ischemic attack.[37] Our study suggests that an insulin replacement indicator represented by the TyG index may be a reliable predictor of poor prognosis after IVT and may provide additional information for IVT treatment strategies in AIS patients.

The main advantage of this study is the large sample size. The study is the first to use three new markers of IR and atherosclerosis progression (TyG index, TYG-BMI, and METS-IR) simultaneously to assess prognosis in AIS thrombolytic patients. However, the study should take into account its limitations. First, this is a single-center, retrospective, and observational study, so the results may indicate an association, but not causation. Therefore, our findings should be confirmed in a multicenter prospective study. Second, the study did not collect information about patients taking lipid-lowering drugs, which may have weakened the strength of the association to some extent. Third, the TyG index, TYG-BMI, and METS-IR are used as alternative markers of IR, but may not fully capture the complexity of IR. Direct measurements, while more invasive and complex, may provide a more accurate assessment. Fourth, the study population may lack ethnic and genetic diversity limiting the applicability of the findings to different populations. The inclusion of different populations in future studies will improve generalisability.

Conclusion

In this study, only the TyG index was identified as an independent risk factor for 3-month poor prognosis in AIS patients of IVT with or without T2DM, while none of the IR markers were independent risk factors for HT. TyG index, TyG-BMI, and METS-IR all showed predictive value for poor prognosis, with the TyG index having the highest predictive value, but all three had limited predictive value for HT. These findings provide a new understanding that IR can be used as a therapeutic target in AIS patients of IVT, warranting further investigation into the impact of antidiabetic treatments on post-IVT outcomes.

Ethics Approval and Informed Consent

The study protocol was approved by the Ethics Committee of Xiangyang No.1 People's Hospital in accordance with the principles of the Declaration of Helsinki (No. XYYYE 20250018). Since this was a retrospective, non-interventional study, and the patient's information was anonymous and confidential, signed informed consent was waived.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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