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Research article

An innovative metabolic index for insulin resistance correlates with early neurological deterioration following intravenous thrombolysis in minor acute ischemic stroke patients

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ABSTRACT

Background and purpose: The composite score for insulin resistance (IR), known as the Metabolic Score of Insulin Resistance (METS-IR), serves as an assessment tool for IR and has been previously linked to symptomatic intracranial hemorrhage and poor functional outcomes in patients with acute ischemic stroke (AIS). Despite these associations, the impact of METS-IR on early neurological deterioration (END) in patients with minor AIS who underwent intravenous administration of recombinant tissue-type plasminogen activator (IV-rtPA) remains inadequately established. This investigation explored the link between METS-IR and END in patients with minor AIS receiving IV-rtPA treatment.

Methods: In this study, a cohort comprising 425 consecutive patients with National Institutes of Health Stroke Scale Score (NIHSS)≤5 who underwent IV-rtPA treatment was included. The METS-IR was computed using the formula ln METS-IR=ln (2 × FBG + TG) × BMI/ln (HDL). END was defined as a NIHSS ≥2 within 24 h post IV-rtPA administration, while poor functional outcome was defined as a modified Rankin Scale (mRS) of 2–6. Multivariate logistical regression was performed to investigate the association between METS-IR and both poor functional outcomes and END.

Results: Among the 425 enrolled patients, 64 (15.1 %) patients experienced END, while 80 (18.8 %) had poor functional outcomes three months post-discharge. Upon adjusting for confounding factors, a higher METS-IR emerged as an independent predictor for both END and poor functional outcomes. Similarly, noteworthy findings were observed when METS-IR was defined as a categorical group. The restricted cubic spline (RCS) analysis indicated a linear relationship between METS-IR and END ($P = 0.593$ for non-linearity, $P = 0.034$ for overall). The incorporation of METS-IR into the conventional model resulted in a significant enhancement of predictive accuracy for both END and poor functional outcomes.

Conclusion: METS-IR emerges as an independent predictor for END and poor functional outcome at three months post-discharge in patients with minor AIS subjected to IV-rtPA. Considering its

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simplicity and clinical accessibility as an indicator of IR, METS-IR may hold guiding significance in clinical practice.

1. Introduction

Since 2015, stroke has become the leading cause of death and disability in Chnia, and the prevalence continuous to increase. Base on the data from a large, nationally representative sample of adults aged 40 years or older, the estimated prevalence of stroke in China in 2020 were 2.6 % [1,2]. A high proportion of acute ischemic stroke (AIS) cases are attributed to minor strokes, potentially owing to favorable collateral status. Despite over half of AIS patients exhibiting mild neurological impairments at the onset, it is crucial to recognize that minor strokes are not inherently minor. In the long term, 10%–30 % of patients may undergo early neurological deterioration (END) and progress to severe disability [3,4]. The risk of post-thrombolysis END of minor stroke was reported to be strongly determined by occlusion site and thrombus length [5]. The most prevalent mechanisms leading to END in this population involve the absence of recanalization and infarct growth within the vascular territory. The optimal treatment strategy for minor stroke remains uncertain. However, intravenous thrombolysis was recommended by international guidelines for disabling minor stroke patients within a 4.5h window of stroke onset. Additionally, endovascular therapy may be considered a reasonable option in minor strokes induced by an internal carotid artery or proximal middle cerebral artery occlusion [3,6,7]. Nevertheless, more than half of patients with minor strokes can attain a good prognosis through conservative medical management [8]. Aggressive treatment may not be appropriate for these patients. Considering the potential risks of thrombolysis and endovascular therapy, identifying patients who are likely to have END is clinically important.

Insulin resistance (IR) exhibits a significant association with unfavorable clinical responses in patients with AIS after intravenous thrombolysis [9]. While the euglycemic-hyperinsulinaemic clamp (EHC) technique is considered the benchmark for evaluating IR in clinical settings, its clinical application is restricted due to its expensive, complex, and invasive nature [10]. To facilitate clinical diagnosis, various non-insulin-based IR scores have been developed. In several observational studies, the ratio of two biochemical indicators, including the triglyceride glucose index and the triglyceride to high-density lipoprotein cholesterol ratio, has been utilized to reflect IR indirectly. The findings consistently affirm that these indices can effectively predict END, stroke recurrence, and unfavorable prognosis in patients with AIS [11–13]. Nevertheless, these fasting surrogates of IR fail to characterize the influence of metabolic factors on insulin sensitivity. Considering the limitations, a novel metabolic score of insulin resistance (METS-IR) was established to estimate insulin action. METS-IR integrates non-insulin fasting blood biomarkers and anthropometric measurements to provide a more comprehensive estimation of IR [14]. The ability of METS-IR to assess insulin action was validated against EHC, demonstrating a superior ability compared to other surrogate IR indices [14]. Recent observational investigations have affirmed that METS-IR is correlated with poor outcomes and symptomatic intracranial hemorrhage in patients with AIS subjected to endovascular thrombectomy [15,16]. However, limited investigations have examined the link between METS-IR and END in minor AIS patients subjected to intravenous thrombolysis. Therefore, this study aims to utilize the pre-defined METS-IR to investigate its predictive significance for END in patients with minor AIS undergoing intravenous thrombolysis.

2. Methods

2.1. Study populations

In this retrospective cohort investigation, information was acquired from consecutive AIS patients undergoing intravenous thrombolysis at the Department of Neurology, Huia'an 82 Hospital, and The Second Affiliated Hospital of Xu Zhou Medical School, spanning January 2018 to December 2022. The inclusion criteria for this study encompassed AIS patients who experienced symptoms within a 4.5-h window, with the following specifications: (1) age 18 years or older; (2) treatment with intravenous recombinant tissue-type plasminogen activator (IV-rtPA); (3) baseline National Institutes of Health Stroke Scale (NIHSS) score $\leq$5; (4) no further endovascular treatment. Exclusion criteria comprised: (1) a diagnosis of autoimmune diseases, malignant tumor, major organ failure, or other severe systemic diseases; (2) incomplete clinical data. All participants provided informed consent, and the study protocol received approval from the Ethic Committee of The Second Affiliated Hospital of Xu Zhou Medical School and Huai'an 82 Hospital.

2.2. Data collection

Demographic data, past medical history, previous antiplatelet use, vascular risk factors, time from symptom onset to IV-rtPA treatment (OTT), and laboratory biomarkers were all retrieved from medical records. Trained medical staff conducted anthropometric measurements using standard methods. The severity of stroke was determined utilizing the NIHSS, and stroke subtypes were sorted following the Trail of Org 10172 in Acute Stroke Treatment (TOAST) criteria [17]. Symptomatic intracranial hemorrhage (sICH) was identified *via* CT scans and characterized as per the Heidelberg Bleeding Classification criteria [18]. A poor functional outcome was characterized by a modified Rankin Scale (mRS) score of 2–6 three months after discharge.

2.3. Definition of END

In this research, END was defined as a ≥2-point elevation in NIHSS score from admission to 24 h following IV-rtPA [19]. Evaluations of neurological deficits were conducted by two certified neurologists who were blinded to the clinical data.

2.4. Evaluation of METS-IR

The METS-IR calculation formula, as outlined in a prior study [14], is expressed as follows: METS-IR = ln (2 × FBG + TG) × BMI/ln (HDL).

FBG: fasting blood glucose (mg/dl);

TG: Triglyceride (mg/dl);

BMI: body mass (kg)/the square of height (m^2);

HDL: High-density Lipoprotein (mg/dl).

Venous blood samples were collected on the morning following admission, between 06:00 and 08:00, after a fasting period of more than 8 h.

2.5. Statistical analysis

The normality of variables was tested by means of the Kolmogorov-Smirnov test. Continuous variables were expressed as mean (standard deviation) or median (quartile) depending on the normality of the data. Categorical variables were presented as percentages. Group comparisons for categorical variables were executed utilizing the chi-squared test, while for continuous variables, the student-t test, one-way ANOVA, Mann-Whitney *U* test, and Kruskal-Wallis test were utilized as appropriate.

The predictive significance of METS-IR for both END and poor functional outcomes was assessed using multivariable binary logistical regression models. Based on the results of univariate analyses, variables with $P < 0.05$ and age, gender were introduced into the binary logistical regression. In model 1, adjustments were made for age and gender. Model 2 expanded on model 1 by including

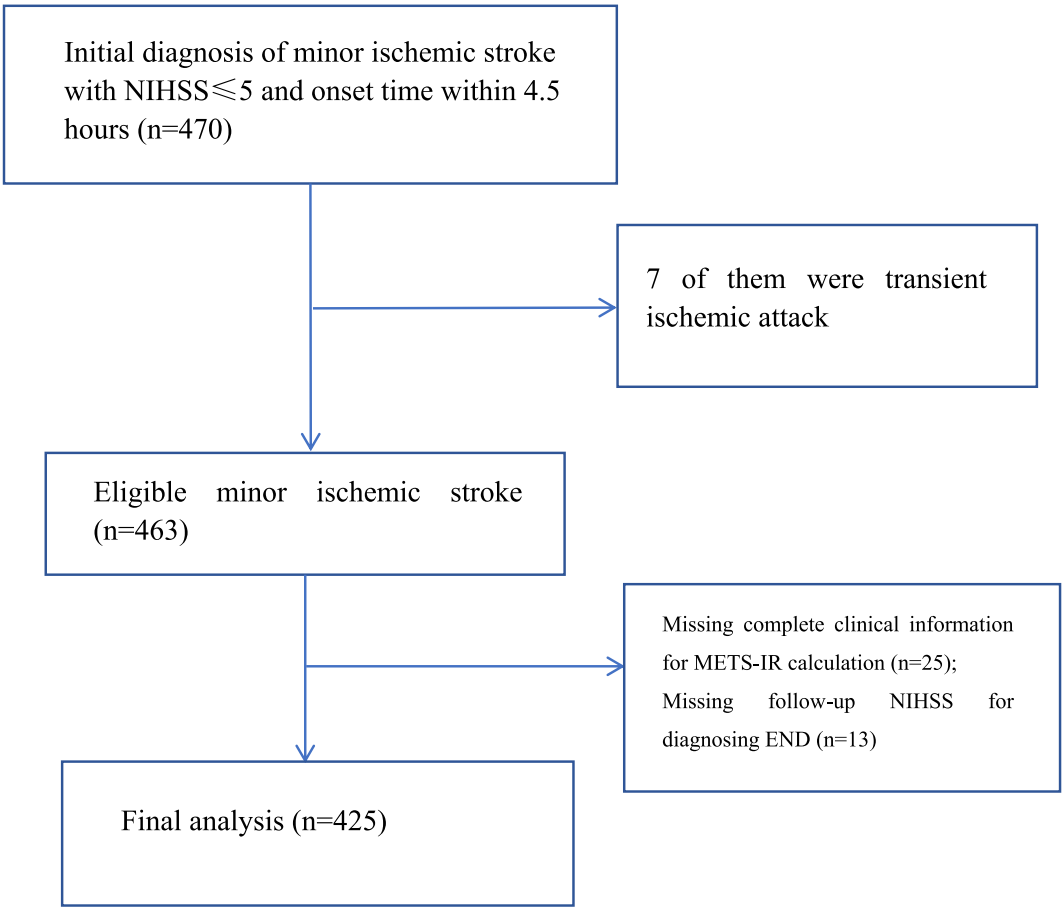

Fig. 1. Study flowchart. A total of 425 patients were included in the final analysis.

variables such as diabetes mellitus (DM), strokesubtype, sICH, proximal artery occlusion, and C-reactive protein (CRP), fasting glucose, glycosylated hemoglobin (HbAlc). Patients were sorted into four groups based on METS-IR quartile values, with the lowest quartile group serving as the reference. A restricted cubic spine analysis was then executed to evaluate the shape of the link between METS-IR and the risk of poor functional outcome and END [20]. Four knots were selected at the 5th, 35th, 65th, and 95th percentiles, with adjustments made for covariates included in model 2. The net reclassification index (NRI) and integrated discrimination improvement (IDI) were performed to assess the predictive significance of incorporating METS-IR into the conventional risk factors model [21].

A significance level of <0.05 for two-tailed *P*-values was adopted. Data analysis was executed utilizing several statistical software packages, including SPSS 26.0 (SPSS Inc, Chicago, IL, USA) and R statistical software v 4.3.1 (R Foundation, Vienna, Australia).

3. Results

3.1. Patients baseline features

In this study, 470 minor stroke patients who underwent IV-rtPA were initially considered. Among them, 25 patients lacked complete clinical information for METS-IR calculation, and 13 patients did not have follow-up NIHSS scores for diagnosing END, 7 of them were transient ischemic attack. Following the exclusion of these cases, a total of 425 eligible patients with minor strokes were ultimately incorporated into the analysis, the flow chart is shown in Fig. 1. Among this cohort, 64 (15.1 %) patients experienced END, and 80 (18.8 %) had a poor functional outcome three months after discharge. The mean age of the patients was 66.0 years, with a male representation of 66.1 %. sICH occurred in 5 (1.6 %) patients. The median admission NIHSS was 3 (interquartile range, 2–4), and the mean METS-IR score was 37.0 (±5.7).

Baseline features of patients with and without END are depicted in Table 1. In comparison with the non-END group, patients in the

Table 1
Baseline data according to END.

Variables	Total (n = 425)	END (n = 64)	Non-END (n = 361)	P
Demographic characteristics				
Age, years	66.0 (10.5)	67.3 (11.3)	65.7 (10.4)	0.290
Male, n (%)	281 (66.1)	44 (68.8)	237 (65.7)	0.670
BMI, kg/m^2	24.5 (3.0)	24.7 (3.4)	24.4 (3.0)	0.550
Vascular risk factors, n (%)				
Hypertension	274 (64.5)	44 (68.8)	230 (63.7)	0.481
DM	144 (33.9)	29 (45.3)	115 (31.9)	0.045
Atrial fibrillation	43 (10.1)	3 (4.7)	40 (11.1)	0.174
Coronary heart disease	53 (12.5)	4 (6.3)	49 (13.6)	0.147
Smoking	173 (40.7)	27 (42.2)	146 (40.4)	0.793
Clinical data				
Baseline SBP, mmHg	152.4 (21.5)	155.1 (21.7)	151.9 (21.4)	0.283
Baseline DBP, mmHg	86.6 (14.1)	88.2 (15.2)	86.4 (13.8)	0.326
Admission NIHSS	3 (2–4)	3 (2–4)	3 (2–4)	0.386
Previous antiplatelet, n (%)	90 (21.2)	14 (21.9)	76 (21.1)	0.882
OTT, min	146.8 (58.9)	146.6 (66.2)	146.9 (57.6)	0.975
Proximal arterial occlusion, n (%)	19 (4.5)	8 (12.5)	11 (3.0)	0.001
Stroke subtype, n (%)				0.007
LAA	86 (20.2)	23 (35.9)	63 (17.5)	
CE	39 (9.2)	4 (6.3)	35 (9.7)	
SAO	239 (56.2)	31 (48.4)	208 (57.6)	
Others and undetermined	61 (14.4)	6 (9.4)	55 (15.2)	
sICH, n (%)	7 (1.6)	5 (7.8)	2 (0.6)	<0.001
Poor outcomes, n (%)	80 (18.8)	52 (81.3)	28 (7.8)	<0.001
Laboratory data				
WBC count, 10^9/L	7.7 (2.5)	7.6 (2.1)	7.7 (2.6)	0.613
CRP, mg/L	4.6 (2.9)	5.5 (2.9)	4.3 (2.8)	0.024
PLT count, 10^9/L	217.4 (65.5)	211.0 (63.3)	218.5 (65.9)	0.395
LDL, mmol/L	3.0 (1.0)	3.3 (0.9)	3.0 (1.0)	0.041
HDL, mmol/L	1.3 (0.3)	1.3 (0.2)	1.3 (0.3)	0.705
TC, mmol/L	4.8 (1.2)	5.0 (1.0)	4.7 (1.2)	0.067
TG, mmol/L	1.6 (0.9)	1.6 (1.0)	1.6 (0.9)	0.673
FIB, g/L	3.6 (0.8)	3.7 (0.6)	3.6 (0.9)	0.302
Hcy, umol/L	11.6 (8.9–15.3)	11.1 (8.9–15.8)	11.6 (9.0–15.1)	0.400
Fasting glucose, mmol/L	6.4 (2.4)	7.5 (2.8)	6.2 (2.2)	<0.001
HbAlc, %	5.8 (5.5–6.5)	6.1 (5.7–7.8)	5.8 (5.4–6.7)	0.004
METS-IR	37.0 (5.7)	38.9 (5.8)	36.7 (5.6)	0.005

SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; NIHSS, National Institutes of Health Stroke Scale; OTT, Onset-to-treatment; LAA, Large Artery Atherosclerosis; CE, Cardio Embolism ; SAO, Small Artery Occlusion; END, Early Neurological Deterioration; SICH, Symptomatic Intracranial Hemorrhage; WBC, White blood cell counts; PLT, Platelet; LDL, Low-density Lipoprotein; HDL, High-density Lipoprotein; TC, Total Cholesterol; TG, Triglyceride; FIB; Fibrinogen; HbAlc, Glycosylated hemoglobin; METS-IR, Metabolic score of insulin resistance.

END group exhibited an elevated proportion of DM (45.3 % vs. 31.9 %, $P = 0.045$), large artery atherosclerotic stroke (35.9 % vs. 17.9 %, $P = 0.007$) and proximal artery occlusion (12.5 % vs. 3.0 %, $P = 0.001$) and were more prone to sICH and poor functional outcome (7.8 % vs. 0.6 %, $P < 0.001$) (70.3 % vs. 0.8 %, $P < 0.001$). Additionally, the END group exhibited higher levels of C-reactive protein CRP (7.1 vs. 4.2, $P = 0.004$), fasting glucose (7.5 vs. 6.2, $P < 0.001$), HbAlc (6.1 vs. 5.8, $P = 0.014$) and METS-IR (38.9 vs. 36.7, $P = 0.005$).

The baseline attributes of patients stratified by METS-IR quartiles are depicted in Table 2. Patients in the higher METS-IR quartiles group were younger (69.8 vs. 65.9 vs. 64.7 vs. 63.7, $P < 0.001$), more likely to be male (52.0 % vs. 61.3 % vs. 73.8 % vs. 76.4 %, $P = 0.001$) and more prone to diabetes (22.6 % vs. 22.9 % vs. 41.7 % vs. 48.6 %, $P < 0.001$). They also exhibited an elevated proportion of smoking (29.4 % vs. 34.9 % vs. 46.7 % vs. 50.9 %, $P = 0.004$) and were more prone to experience END (6.9 % vs. 16.0 % vs. 14.0 % vs. 22.7 %, $P = 0.014$), sICH (0.0 % vs. 0.9 % vs. 0.9 % vs. 4.5 %, $P = 0.045$) and poor functional outcome (8.5 % vs. 23.6 % vs. 16.3 % vs. 26.6 %, $P = 0.003$). Additionally, they had elevated white blood cell counts (7.1 vs. 7.9 vs. 7.7 vs. 8.2, $P = 0.017$), Triglyceride (1.1 vs. 1.4 vs. 1.6 vs. 2.1, $P < 0.001$), fasting glucose (5.3 vs. 5.3 vs. 6.0 vs. 6.1, $P < 0.001$) and HbAlc (5.8 vs. 5.6 vs. 6.1 vs. 6.1, $P < 0.001$).

3.2. Association of METS-IR with END and poor functional outcome at three months after discharge in multivariate analysis

Upon adjusting for potential confounding factors, METS-IR maintained a significant association with END and poor functional outcome in both model 1 (OR, 1.079; 95 % CI, 1.027–1.134; $P = 0.003$) (OR, 1.082; 95 % CI, 1.033–1.133; $P = 0.001$) and model 2 (OR, 1.126; 95 % CI, 1.039–1.221; $P = 0.004$) (OR, 1.118; 95 % CI, 1.017–1.229; $P = 0.021$). When METS-IR was treated as a categorical group, similar significant results were observed in model 1 (second quartile vs. first quartile; OR, 2.851; 95 % CI, 1.117–7.276; $P = 0.028$; fourth quartile vs. first quartile; OR, 4.617; 95 % CI, 1.848–11.536; $P = 0.001$), and in model 2 (fourth quartile vs. first quartile; OR, 4.945; 95 % CI, 1.326–18.436; $P = 0.017$). Additionally, the risk of poor functional outcome exhibited a significant elevation with

Table 2
Baseline characteristics of subgroups based on metabolic score.

Variables	Q1 (n = 102)	Q2 (n = 106)	Q3 (n = 107)	Q4 (n = 110)	P
Demographic characteristics					
Age, years	69.8 (10.1)	65.9 (10.6)	64.7 (9.7)	63.7 (10.6)	<0.001
Male, n (%)	53 (52.0)	65 (61.3)	79 (73.8)	84 (76.4)	0.001
BMI, kg/m^2	21.4 (2.2)	23.6 (1.9)	25.1 (2.4)	27.1 (2.4)	<0.001
Vascular risk factors, n (%)					
Hypertension	61 (59.8)	61 (57.5)	71 (66.4)	81 (73.6)	0.060
DM	23 (22.5)	24 (22.6)	45 (42.1)	52 (47.3)	<0.001
Atrial fibrillation	8 (7.8)	12 (11.4)	13 (12.1)	10 (9.1)	0.708
Coronary heart disease	12 (12.0)	10 (9.4)	15 (14.0)	16 (14.5)	0.665
Smoking	30 (29.4)	37 (34.9)	50 (46.7)	56 (50.9)	0.004
Clinical data					
Baseline SBP, mmHg	151.0 (21.1)	152.6 (23.7)	152.8 (20.8)	153.0 (20.4)	0.907
Baseline DBP, mmHg	84.5 (12.2)	86.1 (13.9)	86.6 (14.1)	89.1 (15.6)	0.114
Admission NIHSS	3 (2–4)	3 (2–4)	3 (2–4)	3 (2–4)	0.849
Previous antiplatelet, n (%)	15 (14.7)	23 (21.7)	25 (23.4)	27 (24.5)	0.304
OTT, min	148.7 (62.3)	150.5 (54.5)	146.4 (62.8)	141.9 (56.4)	0.731
Proximal arterial occlusion, n (%)	6 (5.9)	4 (3.8)	5 (4.7)	4 (3.6)	0.853
Stroke subtype, n (%)					0.952
LAA	17 (16.7)	22 (20.8)	24 (22.4)	23 (20.9)	
CE	9 (8.8)	11 (10.4)	11 (10.3)	8 (7.3)	
SAO	58 (56.9)	60 (56.6)	59 (55.1)	62 (56.4)	
Others and undetermined	18 (17.6)	13 (12.3)	13 (12.1)	17 (15.5)	
sICH, n (%)	0 (0.0)	1 (0.9)	1 (0.9)	5 (4.5)	0.045
END, n (%)	7 (6.9)	17 (16.0)	15 (14.0)	25 (22.7)	0.014
poor outcomes, n (%)	9 (8.5)	25 (23.6)	17 (16.3)	29 (26.6)	0.003
Laboratory data					
WBC count, 10^9/L	7.1 (2.5)	7.9 (2.6)	7.7 (2.4)	8.1 (2.5)	0.033
CRP, mg/L	4.3 (3.4)	5.0 (3.4)	4.9 (2.6)	4.4 (1.9)	0.674
PLT count, 10^9/L	208.8 (58.0)	223.4 (67.5)	220.4 (67.3)	216.6 (68.2)	0.409
LDL, mmol/L	2.9 (1.0)	3.1 (1.0)	3.0 (0.9)	3.1 (1.0)	0.323
HDL, mmol/L	1.5 (0.4)	1.3 (0.3)	1.2 (0.3)	1.1 (0.2)	<0.001
TC, mmol/L	4.7 (1.1)	4.8 (1.2)	4.7 (1.2)	4.9 (1.1)	0.655
TG, mmol/L	1.1 (0.5)	1.4 (0.6)	1.6 (0.9)	2.1 (1.2)	<0.001
FIB, g/L	3.5 (0.8)	3.5 (0.8)	3.5 (0.8)	3.7 (1.0)	0.284
Hcy, umol/L	11.2 (8.6–16.0)	11.3 (8.8–15.0)	11.6 (9.2–14.9)	12.3 (9.7–15.4)	0.790
Fasting glucose, mmol/L	5.3 (4.9–5.7)	5.3 (4.9–6.1)	6.0 (5.3–7.7)	6.1 (5.3–8.8)	<0.001
HbAlc, %	5.8 (5.4–6.1)	5.6 (5.4–6.1)	6.1 (5.5–7.2)	6.1 (5.7–8.0)	<0.001

SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; NIHSS, National Institutes of Health Stroke Scale; OTT, Onset-to-treatment; LAA, Large Artery Atherosclerosis; CE, Cardio Embolism SAO, Small Artery Occlusion; END, Early Neurological Deterioration; SICH, Symptomatic Intracranial Hemorrhage; WBC, White blood cell counts; PLT, Platelet; LDL, Low-density Lipoprotein; HDL, High-density Lipoprotein; TC, Total Cholesterol; TG, Triglyceride; FIB; Fibrinogen; HbAlc, Glycosylated Hemoglobin; METS-IR, Metabolic Score of Insulin Resistance.

increasing METS-IR levels in model 1 (fourth quartile vs. first quartile; OR, 4.486; 95 % CI, 1.955–10.298; $P < 0.001$) (Table 3) .

The restricted cubic spine (RCS) was used to flexibly model and visualize the relationship of METS-IR with poor functional outcome and END. In the RCS regression models, the link between METS-IR and END was found to be linear ($P = 0.830$ for non-linearity, $P = 0.593$ for non-linearity) (Figs. 2 and 3), which indicates that the OR of END might increase with METS-IR score.

The NRI and IDI results showed that the addition of METS-IR can improve the differentiation and reclassification beyond traditional risk factors (age, gender, DM, strokesubtype, sICH, proximal artery occlusion, and CRP, fasting glucose, HbAlc) (Table 4). The risk reclassification for END exhibited significant improvements after incorporating METS-IR (as continuous variable) into model 1 (NRI (continuous), 0.585; 95 % CI, 0.050–0.453; $P = 0.004$; NRI (categorical), 0.251; 95 % CI, 0.050–0.453; $P = 0.015$; IDI, 0.076; 95 % CI, 0.019–0.132; $P = 0.008$) and model 2 (NRI (continuous), 0.500; 95 % CI, 0.133–0.867; $P = 0.008$; NRI (categorical), 0.173; 95 % CI, 0.002–0.343; $P = 0.048$; IDI, 0.061; 95 % CI, 0.015–0.106; $P = 0.009$). Moreover, the risk reclassification for poor functional outcome also improved in model 1 (NRI (continuous), 0.603; 95 % CI, 0.202–1.004; $P = 0.003$; IDI, 0.086; 95 % CI, 0.022–0.151; $P = 0.009$) and in model 2 (NRI (continuous), 0.529; 95 % CI, 0.125–0.933; $P = 0.010$; IDI, 0.030; 95 % CI, 0.000–0.059; $P = 0.050$).

4. Discussion

The findings from this research demonstrated that METS-IR is independently linked to poor functional outcome and END three months after discharge in patients with minor AIS who underwent IV-rtPA. Moreover, the inclusion of METS-IR in the model, alongside conventional risk factors, considerably improves the prediction of END and poor functional outcomes. METS-IR may act as a surrogate marker for IR, aiding clinicians to identify minor AIS patients at an elevated risk of END and poor functional outcomes.

The etiology of END in minor AIS patients has been emphasized consistently, with factors such as occlusion site, thrombus status, hemodynamic instability, and metabolic abnormalities all potentially contributing to this phenomenon [5,22,23]. IR is a multifaceted syndrome linked to hypertension, obesity, and dyslipidemia. It exerts a role in the process of platelet adhesion, activation, and progression [24,25]. Hence, the underlying mechanisms *via* which IR influences END can be elucidated through the following aspects. Firstly, IR may impede the PI3K pathway and activate the MAPK pathway, contributing to a decrease in NO (vasodilator) production and an elevation in ET-1 production (vasoconstrictor). This ultimately results in endothelial dysfunction, disrupting the balance of pro- and anti-coagulation processes [26], thereby promoting the formation of intravascular thrombus. The inhibitory effect on fibrinolysis before reperfusion may diminish the efficacy of IV-rtPA. Secondly, IR facilitates the formation of atherosclerotic and advanced plaques during the advancement of atherosclerosis [27]. Hyperinsulinemia induced by IR is involved in the pathogenesis of atherosclerosis by fostering vascular inflammation, facilitating the growth of vascular smooth muscle cells (VSMCs), influencing pathological cholesterol profiles, inducing hypertension, and facilitating the recruitment of immune cells to the endothelium [28]. Prior studies have shown that IR promotes vascular occlusion, particularly in macrovascular settings [27]. However, the presence of large vascular occlusion is a decisive factor for END in minor AIS patients treated with IV-rtPA [5]. Thirdly, there exists a mutually reinforcing relationship between IR and inflammation. Various inflammatory signaling pathways, such as JNK, IKK/NF-κB, and JAK/STAT, are implicated in inhibiting insulin functions. Concurrently, IR contributes to the initiation of an inflammatory process, recruits monocytes, and activates macrophages through the secretion of chemoattractant protein 1 (MCP 1) [29]. Ischemia, coupled with pro-inflammatory environments, exacerbates the detrimental effects of inflammation on brain tissue. The heightened inflammatory response facilitates the breakdown of the blood-brain barrier (BBB), elevating the risk of hemorrhage and brain edema following reperfusion [30]. Oxidative stress represents another critical factor in IR-mediated brain tissue injury. Mitochondrial dysfunction may play a causative role in IR, as evidenced by a significant increase in the production of mtROS in patients with IR [31]. ROS can react with lipids, leading to the production of a series of neurotoxic substrates such as hydroxynonenal [32]. These substrates play a regulatory role in neuronal apoptosis and are pivotal in contributing to ischemic neuronal death [33]. Moreover, ROS induces various programmed cell death pathways, including pyroptosis, parthanatos, and ferroptosis in endothelial cells [34]. Endothelial dysfunction in the ischemic region can enhance post-reperfusion ischemic injury [35].

METS-IR, a composite score utilized for evaluating IR, exhibits a superior correlation with the pathophysiology of IR compared to

Table 3
Logistic regression analysis showing the impact of METS-IR on END and functional outcome in acute mild ischemic stroke patients treated with intravenous thrombolysis.

outcomes		Model 1		Model 2	
		OR (95 % CI)	P value	OR (95 % CI)	P value
END	METS-IR	1.079 (1.027–1.134)	0.003	1.126 (1.039–1.221)	0.004
	Q1	Reference	Reference	Reference	Reference
	Q2	2.851 (1.117–7.276)	0.028	1.307 (0.354–4.821)	0.687
	Q3	2.497 (0.955–6.533)	0.062	2.893 (0.820–10.212)	0.099
	Q4	4.617 (1.848–11.536)	0.001	4.945 (1.326–18.436)	0.017
Poor functional outcome	METS-IR	1.082 (1.033–1.133)	0.001	1.118 (1.017–1.229)	0.021
	Q1	Reference	Reference	Reference	Reference
	Q2	3.643 (1.591–8.343)	0.002	0.862 (0.193–3.851)	0.845
	Q3	2.394 (0.993–5.770)	0.052	0.821 (0.167–4.027)	0.807
	Q4	4.486 (1.955–10.298)	<0.001	3.830 (0.908–16.161)	0.068

END, Early Neurological Deterioration; METS-IR, Metabolic Score of Insulin Resistance; OR, Odd Ratio; CI, Confident Interval; P for trend.

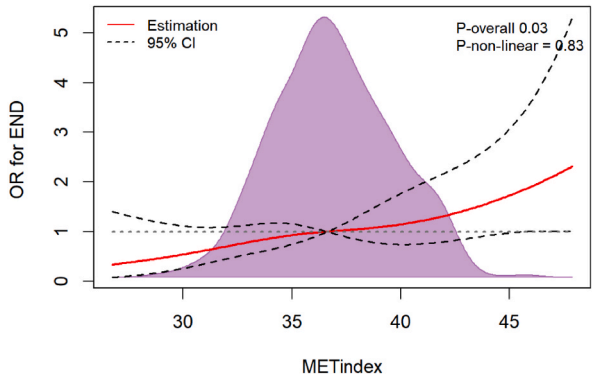

Fig. 2. Restricted cubic spline plot of the relationship between METS-IR and END, four knots at 5th, 35th, 65th, 95th percentiles and adjusted covariates include in model 1.

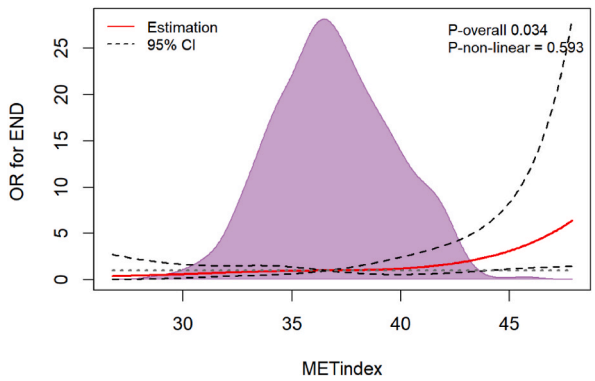

Fig. 3. Restricted cubic spline plot of the relationship between METS-IR and END, four knots at 5th, 35th, 65th, 95th percentiles and adjusted covariates include in model 2.

Table 4
Reclassification statistics (95 % CI) for END and poor functional outcome after the addition of METS-IR.

	NRI (Category)		NRI (Continuous)		IDI	
	Estimate (95 % CI)	P value	Estimate (95 % CI)	P value	Estimate (95 % CI)	P value
END						
Model 1						
METS-IR (continuous)	0.251 (0.050–0.453)	0.015	0.585 (0.183–0.987)	0.004	0.076 (0.019–0.132)	0.008
METS-IR (quartiles)	0.196 (−0.009–0.400)	0.062	0.400 (−0.007–0.806)	0.054	0.049 (0.010–0.088)	0.014
Model 2						
METS-IR (continuous)	0.173 (0.002–0.343)	0.048	0.500 (0.133–0.867)	0.008	0.061 (0.015–0.106)	0.009
METS-IR (quartiles)	0.116 (−0.041–0.272)	0.148	0.595 (0.248–0.943)	<0.001	0.045 (0.011–0.079)	0.011
Poor outcome						
Model 1						
METS-IR (continuous)	0.150 (−0.061–0.360)	0.163	0.603 (0.202–1.004)	0.003	0.086 (0.022–0.151)	0.009
METS-IR (quartiles)	0.111 (−0.110–0.333)	0.325	0.418 (0.012–0.824)	0.044	0.058 (0.012–0.104)	0.013
Model 2						
METS-IR (continuous)	0.071 (−0.160–0.303)	0.545	0.529 (0.125–0.933)	0.010	0.059 (0.008–0.111)	0.023
METS-IR (quartiles)	−0.019 (−0.203–0.166)	0.844	0.542 (0.150–0.935)	0.007	0.030 (0.000–0.059)	0.050

NRI, Net Reclassification Improvement; IDI, Integrated Discrimination Improvement; OR, Odd Ratio; CI, Confident Interval; P for trend. METS-IR, Metabolic Score of Insulin Resistance. Model 1 adjusted for age, sex. Model 2 adjusted for vatable included in model 1 as well as admission NIHSS score, sICH, proximal artery occlusion, C-reactive protein.

other non-insulin-based IR scores, as it comprehensively incorporates indicators of glucose, blood lipid, and metabolism [14]. The findings of this research align with previous studies, collectively highlighting the detrimental impact of IR in ischemic stroke. In addition, the results of this research contribute further support to and validate previous research conclusions that underscore the adverse effects of metabolic syndrome on END and AIS patients [36,37].

Nevertheless, the current research has various potential limitations that warrant consideration when interpreting the findings. Firstly, it is imperative to acknowledge that this is a retrospective study, and the exclusion of patients with NIHSS>5 and those with incomplete data introduces inherent biases. Secondly, the sample size is relatively limited, and the research was conducted in a single country. The limited number of patients who experienced END in minor AIS patients subjected to IV-rtPA may constrain the statistical power. Thirdly, the results of this research lack comparison with patients with minor AIS who did not receive IV-rtPA or those who underwent endovascular thrombectomy, including these comparison groups would provid more comprehensive understanding of the impact of METS-IR across different treatment modalities. Fourth, METS-IR is used as a surrogate marker for insulin resistance, and while it integrates several metabolic indicators, it may not fully capture the complexity of insulin resistance. Direct measurements, although more invasive and complex, might provide more accurate assessments. Fifth, the follow-up period for assessing poor functional outcomes is three months. Longer follow-up periods could provide insights into the long-term effects of METS-IR on stroke outcomes. Sixth, the study population may lack ethnic and genetic diversity, limiting the applicability of the findings to different populations. Including diverse populations in future research would enhance the generalizability.

5. Conclusion

In conclusion, METS-IR emerges as an independent predictor of poor functional outcome and END three months after discharge in minor AIS patients subjected to IV-rtPA. Serving as a simple and clinically accessible indicator of IR, METS-IR holds potential guiding significance in clinical practice.

Ethical approval

This study was approved by the Human Research Ethics Committee of Huai'an 82 Hospital and The Second Affiliated Hospital of Xu Zhou Medical School (approval number: [2021]111301) on November 13, 2021. Written informed consent was obtained from participants or legal representatives. The questionnaires were anonymized, and patients were free to opt out of participation in the study whenever they were uncomfortable.

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Data availability on statements

The data generated in this study are available on reasonable request to the corresponding authors.

CRediT authorship contribution statement

Ling Wang: Writing – original draft, Investigation, Conceptualization. **Ting Hu:** Investigation, Formal analysis. **Rongrong Li:** Software, Methodology. **Li Xu:** Formal analysis. **Yingying Wang:** Data curation. **Qiantao Cheng:** Formal analysis, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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