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ORIGINAL RESEARCH

A Novel Metabolic Score for Insulin Resistance and Symptomatic Intracranial Hemorrhage in Ischemic Stroke Patients After Endovascular Thrombectomy

Shuaiyu Chen[1,*], Yan E[1,*], Xiaohao Zhang[1,*], Bin Wei[1], Siyu Wang[1], Zhaohan Xu[1], Pengyu Gong[2], Yi Xie[3], Chunhua Qin[1], Yingdong Zhang[1]

[1]Department of Neurology, Nanjing First Hospital, Nanjing Medical University, Nanjing, People's Republic of China; [2]Department of Neurology, Affiliated Hospital of Nantong University, Nantong, People's Republic of China; [3]Department of Neurology, Jinling Hospital, Medical School of Nanjing University, Nanjing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Chunhua Qin; Yingdong Zhang, Department of Neurology, Nanjing First Hospital, Nanjing Medical University, No. 68 Changle Road, Nanjing, People's Republic of China, Tel/Fax +86 2552271000, Email 15366136164@163.com; zhangyingdong@njmu.edu.cn

Background and Purpose: Insulin resistance plays a pivotal role in the pathophysiology of ischemic stroke. This study aimed to determine the relationship between the novel metabolic score for insulin resistance (METS-IR) and symptomatic intracranial hemorrhage (sICH) after endovascular thrombectomy (EVT) in stroke patients.

Methods: We retrospectively included patients with large artery occlusion in the anterior circulation and treated by EVT from 2 stroke centers (Nanjing First Hospital from September 2019 to April 2022, and Jinling Hospital from September 2019 to July 2021). The METS-IR was used as an alternative marker of insulin resistance and calculated using laboratory data after admission. sICH was diagnosed according to the Heidelberg Bleeding Classification.

Results: Of the 410 enrolled patients (mean age, 69.8 ± 11.7 years; 60.7% men), 50 (12.2%) were diagnosed as sICH. After adjusting for demographic characteristics, poor collateral status, and other potential confounders, higher METS-IR was revealed to be independently associated with sICH (odds ratio, 1.076; 95% confidence interval, 1.034−1.120; $P = 0.001$). Similar significant results were obtained when defining METS-IR as a categorical variable. The restricted cubic spline uncovered a linear relationship between METS-IR and sICH ($P < 0.001$ for linearity). Furthermore, adding METS-IR to the conventional model significantly improved the risk prediction for sICH (net reclassification improvement = 15.8%, $P = 0.035$; integrated discrimination index = 2.6%; $P = 0.017$).

Conclusion: This study demonstrated a significant association between METS-IR score and sICH in ischemic stroke patients treated with EVT. It could help monitor and manage sICH in patients after EVT.

Keywords: METS-IR, insulin resistance, ischemic stroke, symptomatic intracranial hemorrhage, endovascular thrombectomy

Introduction

Several randomized controlled trials have revealed that endovascular thrombectomy (EVT) substantially improves the outcome of ischemic stroke patients caused by a large vessel occlusion in the anterior circulation.[1] Nevertheless, successful recanalization by EVT does not always translate into a good outcome for patients. Symptomatic intracranial hemorrhage (sICH) is one of the feared complications, which may occur in 16% of Asian patients and reduce the benefit-risk ratio of EVT.[2–5] Therefore, early and accurate identification of sICH is of substantial clinical importance for continuously improving the prognosis after EVT.

It has been reported that insulin resistance is the main pathophysiological determinant of type 2 diabetes.[6] Insulin resistance may increase the risk of metabolic syndrome and atherosclerotic cardiovascular diseases.[7,8] Some preliminary

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studies indicated that higher insulin resistance was correlated with poor outcome in stroke patients after thrombolytic treatment.[9,10] At present, insulin resistance can be evaluated by many methods. The euglycaemic-hyperinsulinaemic clamp technique is the gold standard for measuring insulin resistance. However, it is unsuitable for epidemiological studies due to its complex, expensive, and invasive shortcomings.[11] Given this limitation, several non-insulin-based insulin resistance scores, which combined simple routine biochemical indicators such as triglyceride to high-density lipoprotein cholesterol ratio and triglyceride glucose index, have been developed.[12–14] Nevertheless, these indexes ignore the role of nutritional status in insulin sensitivity. Recently, Bello-Chavolla et al established a novel metabolic score of insulin resistance (METS-IR), which showed a higher concordance with the euglycaemic-hyperinsulinaemic clamp in assessing insulin resistance.[15] Several studies have shown that METS-IR is related to several cardiovascular events, including diabetes and ischemic heart disease.[15,16] Furthermore, a predictive role of METS-IR score has been highlighted in endothelial dysfunction and inflammatory activity.[17,18] Nonetheless, the association between METS-IR and sICH in ischemic stroke patients after EVT treatment is still unknown. Therefore, in this study, we tried to evaluate the association of METS-IR with the sICH occurrence in ischemic stroke patients treated after EVT.

Methods

Study Population

The study was a retrospective cohort analysis based on prospectively collected data from 2 advanced stroke centers in China (Nanjing First Hospital from September 2019 to April 2022, and Jinling Hospital from September 2019 to July 2021). The inclusion criteria of this study were as follows: (1) treated with a stent-like retriever or aspiration system; (2) aged 18 years or older; (3) had a proximal intracranial large vessel occlusion in the anterior circulation (including internal carotid artery and middle cerebral artery). The exclusion criteria of patients were as follows: (1) without complete clinical data for calculating the METS-IR index; (2) without follow-up imaging data for evaluating the sICH; (3) diagnosed with a concomitant aneurysm, arteriovenous malformation, moyamoya disease, or hematological system diseases. This study was approved by the Ethics Committee of Nanjing First Hospital and Jingling Hospital. All procedures performed in studies involving human participants were in accordance with the ethical standards of Nanjing First Hospital and Jingling Hospital and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Due to its retrospective nature; patient consent was waived. Patient data was confidentiality maintained in Nanjing First Hospital and Jingling Hospital.

Baseline Data Collection

We collected the following data for analysis: 1) demographic characteristics including age, sex, and body mass index (BMI); 2) medical history; 3) clinical and laboratory data including pre-procedural blood pressure, lipid profile, fasting blood glucose, and high-sensitivity C-reactive protein (Hs-CRP); 4) stroke characteristics including baseline NIHSS score, pre-treatment ASPECTS, stroke subtypes, vascular occlusion site, and collateral status; 5) procedural characteristics including prior intravenous thrombolysis (IVT) or not, time from onset to recanalization, successful reperfusion or not, and procedural model. The stroke subtype was defined according to the criteria of Trial of Org 10,172 in Acute Stroke Treatment. Collateral status was assessed based on the digital subtraction angiography using the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology grading system, with grades 0–1 representing poor collateral status, and grades 2–4 representing moderate to excellent.[19] Successful reperfusion was defined as a modified Thrombolysis in Cerebral Infarction score of 2b or 3.[20]

Calculation of METS-IR Index

METS-IR was calculated as described:[15,17] METS-IR = ln(2×fasting blood glucose [mg/dL] + triglyceride [mg/dL])×BMI [kg/m^2]/ln (high-density lipoprotein [mg/dL]). All the blood indicators were derived from the laboratory examination at the next morning (8:00 a.m.) after admission.

Definition of sICH

A follow-up imaging (non-contrast computed tomography or magnetic resonance imaging) was performed 24–72 hours after EVT or whenever the clinical symptom deteriorations. In this study, sICH was diagnosed based on Heidelberg Bleeding Classification criteria.[21] For the ascertaining of sICH, all images were independently reviewed by two neuroradiologists who were blinded to the clinical data. In case of disagreement, final results were sought by consensus and discussed with a third neuroradiologist.

Statistical Analysis

We presented medians and interquartile ranges or means and standard deviations for continuous variables and frequencies and percentages for categorical variables. Differences between the groups were explored using the Student *t*-test, Mann–Whitney *U*-test, one-way ANOVA and Kruskal–Wallis test for continuous variables, and Fisher exact test or $\chi 2$ test for categorical variables, where appropriate. We performed the multivariable binary logistic regression models to evaluate the association of METS-IR and sICH. Model 1: adjusted for age and sex; Model 2: adjusted for variables included in Model 1 as well as baseline ASPECTS and poor collateral circulation; Model 3: adjusted for variables included in Model 2 as well as baseline NIHSS score, successful reperfusion, stroke subtypes, and diabetes mellitus. We also explored the pattern and magnitude of the association of METS-IR with the risk of sICH using restricted cubic splines with 4 knots (at 5th, 35th, 65th, and 95th percentiles) adjusted for covariates included in model 3.[22] Furthermore, the net reclassification index and integrated discrimination improvement were calculated to evaluate the predictive value of adding METS-IR to the conventional risk factors model.[23]

All statistical tests were conducted with SPSS version 24.0 (SPSS Inc, Chicago, IL, USA) and R statistical software version 4.0.0 (R Foundation, Vienna, Austria). In all analyses, differences were considered statistically significant with a P value < 0.05.

Results

Patient Characteristics

In this study, 452 patients treated with a stent-like retriever or aspiration system in the MCA/ICA were screened for analysis. We excluded 32 patients without complete clinical data for calculating the METS-IR index, 3 patients without follow-up imaging data for evaluating the sICH, and 7 patients diagnosed with a concomitant aneurysm, arteriovenous malformation, moyamoya disease, or hematological system diseases. Finally, the study cohort comprised 410 consecutive patients with a mean age of 69.8 years (60.7% male). The median NIHSS at admission was 14 (interquartile range, 10–18), pre-treatment ASPECTS was 9.0 (interquartile range, 8.0–9.0), and 39.8% of patients were co-treated with IVT. There were 204 (49.8%) patients with poor collateral status. Successful reperfusion was achieved in 89.3% of patients. The mean METS-IR score was 38.4 ± 8.4. The details regarding demographic characteristics, clinical and laboratory data, neurological data, and procedural characteristics stratified by METS-IR quartiles were shown in Table S1. The participants with higher METS-IR were younger, more likely to suffer from hypertension and diabetes, had higher fast blood glucose and triglyceride, and had lower high-density lipoprotein than those with lower METS-IR. More importantly, participants with higher METS-IR had an increased risk of sICH.

Association Between METS-IR and sICH

According to Heidelberg Bleeding Classification, fifty patients (12.2%) were classified as sICH occurrence within 72 hours after EVT treatment. As shown in Table 1, in univariate analysis, poor collateral circulation was more common in patients with sICH than those without sICH (66.0% versus 47.5%; $P = 0.014$). The baseline ASPECT score (median, 8.0 versus 9.0; $P = 0.001$) was lower in patients with sICH than those without sICH. Furthermore, patients with sICH had higher NIHSS score at 24 h post-stroke (median, 24.0 versus 10.0; $P = 0.001$), fasting blood glucose (160.0 ± 71.4 mg/dL versus 129.5 ± 46.3 mg/dL; $P = 0.001$) and METS-IR (43.0 ± 11.4 versus 37.8 ± 7.7; $P = 0.001$).

As indicated by Table 2, after adjusting for age, sex, baseline ASPECTS, poor collateral circulation, and other covariates, the multivariate logistic analysis showed that the odds of sICH increased significantly with elevated METS-IR

Table 1 Clinical Characteristics of Study Participants According to Patients with and without ICH

Variables	With sICH, n = 50	Without sICH, n = 360	*P* value
Demographic characteristics			
Age, years	68.9 ± 11.4	69.9 ± 11.8	0.543
Male, n (%)	32 (64.0)	217 (60.3)	0.614
Body mass index, kg/m^2	25.2 ± 4.2	24.1 ± 3.6	0.071
Vascular risk factors, n (%)			
Hypertension	36 (72.0)	244 (67.8)	0.361
Diabetes mellitus	11 (22.0)	97 (26.9)	0.457
Hyperlipidemia	8 (16.0)	40 (11.1)	0.314
Atrial fibrillation	21 (42.0)	116 (32.2)	0.170
Coronary heart disease	6 (12.0)	58 (16.1)	0.453
Smoking	19 (38.0)	140 (38.9)	0.904
Clinical data			
Systolic blood pressure, mmHg	141.2 ± 22.0	137.4 ± 22.5	0.271
Diastolic blood pressure, mmHg	83.1 ± 14.9	82.7 ± 13.9	0.828
Time from puncture to recanalization, min	79.0 (70.0, 126.5)	80.0 (61.0, 113.0)	0.144
Time from onset to recanalization, min	380.0 (220.0, 462.5)	338.0 (235.0, 555.0)	0.896
Baseline NIHSS, score	14.5 (10.0, 18.0)	13.5 (10.0, 17.0)	0.416
24 h NIHSS, score	24.0 (14.0, 32.0)	10.0 (5.0, 15.0)	0.001
Baseline ASPECTS, score	8.0 (7.0, 9.0)	9.0 (8.0, 9.0)	0.001
Stroke subtypes, n (%)			0.234
Atherosclerotic	27 (54.0)	160 (44.4)	
Cardioembolic	21 (42.0)	162 (45.0)	
Others	2 (4.0)	38 (10.6)	
Previous use of antiplatelet agents, n (%)	15 (30.0)	74 (20.6)	0.129
Prior intravenous thrombolysis, n (%)	25 (50.0)	138 (38.7)	0.124
Poor collateral status, n (%)	33 (66.0)	171 (47.5)	0.014
Successful reperfusion, n (%)	42 (84.0)	324 (90.0)	0.199
Procedural models, n (%)			0.250
Pure thrombectomy	34 (68.0)	272 (75.6)	
Need for rescue therapy*	16 (32.0)	88 (24.4)	
Vascular occlusion site, n (%)			0.186
Internal carotid artery	22 (44.0)	124 (34.4)	
Middle cerebral artery	28 (56.0)	236 (65.6)	
Laboratory parameters			
Fasting blood glucose, mg/dL	160.0 ± 71.4	129.5 ± 46.3	0.001
Hs-CRP, mg/L	8.2 (2.9, 35.1)	9.7 (3.1, 23.0)	0.819
Total cholesterol, mg/dL	159.3 ± 53.5	160.5 ± 41.6	0.864
Triglyceride, mg/dL	99.1 (77.4, 148.0)	89.0 (64.8, 125.4)	0.066
Low-density lipoprotein, mg/dL	78.9 (59.2, 112.6)	92.8 (68.9, 115.7)	0.139
High-density lipoprotein, mg/dL	39.8 ± 13.0	46.9 ± 31.4	0.124
METS-IR	43.0 ± 11.4	37.8 ± 7.7	0.001

Notes: *Rescue therapy includes balloon angioplasty, permanent implantation of a stent, intraarterial thrombolysis, or intraarterial tirofiban infusion.

Abbreviations: ASPECTS, the Alberta Stroke Program Early Computed Tomography Score; Hs-CRP, hyper-sensitive C-reactive protein; METS-IR, metabolic score for insulin resistance; NIHSS, National Institute of Health Stroke Scale; sICH, symptomatic intracranial hemorrhage.

score (fourth quartile vs the first quartile, odds ratio [OR], 4.586; 95% confidence interval [CI], 1.661−12.659; P = 0.003). A similar independent association was also observed when METS-IR was defined as a continuous variable (OR, 1.076; 95% CI, 1.034−1.120; P = 0.001). These associations were further confirmed by subgroup analysis (Table S2). A similar independent association was also observed when METS-IR was defined as a continuous variable. Restricted cubic splines further confirmed the linear relationship between METS-IR score and sICH (P = 0.841 for nonlinearity, P < 0.001 for linearity; Figure 1), which suggests that the OR of sICH might increase with METS-IR score. In addition,

Table 2 Multivariate Regression Analysis for METS-IR and sICH

Variables	Model 1		Model 2		Model 3	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
METS-IR (per 1-unit increase)	1.071 (1.034–1.110)	0.001	1.063 (1.023–1.105)	0.002	1.076 (1.034–1.120)	0.001
METS-IR quartile						
First quartile	Reference		Reference		Reference	
Second quartile	1.444 (0.524–3.980)	0.417	1.202 (0.368–3.920)	0.374	1.622 (0.567–4.643)	0.367
Third quartile	1.374 (0.459–3.780)	0.539	1.632 (0.500–5.324)	0.558	1.325 (0.453–3.878)	0.608
Fourth quartile	3.806 (1.529–9.472)	0.004	2.749 (1.039–8.048)	0.045	4.586 (1.661–12.659)	0.003

Notes: Model 1 included age and sex; Model 2 included age, sex, 24 h NIHSS, pre-treatment ASPECTS and poor collateral status; Model 3 included age, sex, pre-treatment ASPECTS, poor collateral status, baseline NIHSS score, successful reperfusion, stroke subtypes and diabetes mellitus.
Abbreviations: CI, confidence interval; METS-IR, metabolic score for insulin resistance; OR, odds ratio; sICH, symptomatic intracranial hemorrhage.

adding METS-IR to a model containing conventional risk factors significantly improved risk reclassification for sICH (Table 3, category-free net reclassification index, 0.158 (95% CI, 0.011−0.305, $P = 0.035$); integrated discrimination improvement, 0.026 (95% CI, 0.006−0.047, $P = 0.017$).

Discussion

In the current study, we revealed for the first time that insulin resistance, estimated by METS-IR, was associated with increasing the risk of sICH in patients with acute ischemic stroke following EVT treatment. This association remained significant after adjusting for age, sex, pre-treatment ASPECTS, poor collateral status, baseline NIHSS score, successful reperfusion, stroke subtypes, and diabetes mellitus.

We observed that 12.2% of patients experienced sICH within 72 hours after EVT according to the Heidelberg Bleeding Classification criteria, which is higher than that reported in randomized controlled trial studies.[1] Meanwhile, the sICH rate in our cohort was slightly higher than that reported in the MR CLEAN registry (6.0%)[24] and the North American Solitaire Stent Retriever Acute Stroke registry (9.9%).[25] This discrepancy could be partially attributed to the more prevalent of intracranial atherosclerotic disease in Chinese ischemic stroke patients. It may be more difficult for

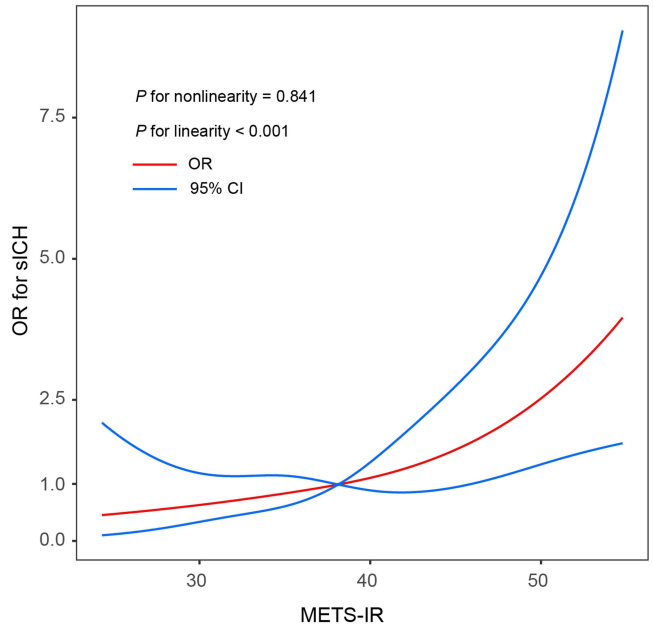

Figure 1 Restricted cubic spline plot of the association between METS-IR and risk of sICH. The association was fitted with restricted cubic spline with 4 knots (at 5th, 35th, 65th, 95th percentiles) adjusted for confounders included in model 3.
Abbreviations: METS-IR, metabolic score for insulin resistance; OR, odds ratio; sICH, symptomatic intracranial hemorrhage.

Table 3 Reclassification Statistics (95% CI) for sICH After the Addition of METS-IR

Models	NRI (Category)		IDI	
	Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value
Model 1				
+ METS-IR (continuous)	0.121 (−0.006–0.248)	0.061	0.025 (0.009–0.040)	0.002
+ METS-IR (quartiles)	0.117 (0.002–0.231)	0.046	0.048 (0.013–0.084)	0.008
Model 2				
+ METS-IR (continuous)	0.152 (0.014–0.294)	0.031	0.056 (0.015–0.096)	0.007
+ METS-IR (quartiles)	0.244 (0.093–0.395)	0.002	0.031 (0.012–0.051)	0.003
Model 3				
+ METS-IR (continuous)	0.078 (−0.068–0.025)	0.205	0.049 (0.009–0.090)	0.013
+ METS-IR (quartiles)	0.158 (0.011–0.305)	0.035	0.026 (0.006–0.047)	0.017

Notes: Model 1 included age and sex; Model 2 included age, sex, 24 h NIHSS score, pre-treatment ASPECTS and poor collateral status; Model 3 included age, sex, pre-treatment ASPECTS, poor collateral status, baseline NIHSS score, successful reperfusion, stroke subtypes and diabetes mellitus.

Abbreviations: CI, confidence interval; IDI, integrated discrimination improvement; METS-IR, metabolic score for insulin resistance; NRI, net reclassification improvement; sICH, symptomatic intracranial hemorrhage.

patients with large vessel occlusions to be recanalized than those with cardioembolic stroke, as the former was commonly accompanied by severe arteriosclerosis. Several studies revealed that age, baseline stroke severity, high blood pressure, high baseline glucose levels, Hs-CRP levels, pre-treatment ASPECT score, NIHSS ≥15.5 at 24 post-stroke hours, and longer onset to treatment delays were potential predictors of sICH following EVT.[3,24,26,27] However, our results did not identify advanced age, high baseline NIHSS score, Hs-CRP levels as predictive factors of sICH. This discrepancy might be ascribed to the difference in study populations, sample size, and the definition and time of determining sICH.

Insulin resistance is a systemic disorder impacting several organs and insulin-regulated pathways. It is characterized by elevated insulin levels but reduced physiological effects.[28] Though the relationship between METS-IR and the sICH after EVT was confirmed in this study, the mechanism remained unknown. Based on the published literature, some potential mechanisms might mediate this association. Firstly, several proinflammatory cytokines related to insulin resistance are increased within the brain after stroke.[29] In patients with higher METS-IR, the cytokines may promote the local inflammatory responses, thus inducing the blood-brain barrier dysfunction and aggravating the neuronal injury after ischemic insults.[30,31] Secondly, insulin resistance-related vessel injury contributes to the formation of sICH. Under normal physiological conditions, insulin acts on the insulin receptor in endothelial cells, thereby resulting in vessel relaxation.[32] However, under insulin resistance status, vasoconstriction is stimulated. What is more, the endothelia express adhesion proteins, such as vascular cell adhesion molecule-1 and E-selectin, were significantly increased, leading to elevated permeability of the endothelia, and therefore potentially developing the sICH.[28] Other possible pathways include causing cerebral autoregulation dysfunction, increasing oxidative stress, activating platelet, and impairing the endogenous fibrinolytic capacity.[33–36] However, further investigations will be needed to elucidate other possible pathogenetic mechanisms involved in this association.

We acknowledged that our study has several limitations. Firstly, due to the nature of the observational study, we could not determine the causal relationship between METS-IR and sICH. Secondly, although the METS-IR has been shown to correlate well with the clamp-derived technique, our study did not compare the discriminative ability of METS-IR with clamp-derived method in predicting sICH. Thirdly, this study did not record the complications like infection, which might influence the glucose level after admission. Finally, this study was conducted on Chinese populations. Since the prevalence of large artery atherosclerosis in Chinese ischemic stroke patients is different from that in European-American ancestry patients, further studies based on other ethnic groups are warranted to confirm our findings.

In conclusion, the present analysis demonstrates that insulin resistance assessed by METS-IR is significantly associated with sICH in acute ischemic stroke patients treated with EVT. These findings suggest that insulin resistance may be an effective parameter in monitoring the sICH after EVT.

Data Sharing Statement

The raw data supporting the conclusions of this article will be made available by the corresponding authors, without undue reservation.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest to disclose for this work.

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