

Post–Glucose Load Measures of Insulin Resistance and Prognosis of Nondiabetic Patients With Ischemic Stroke

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Background—Insulin resistance is associated with an increased risk of cardiovascular events in the general population. This study aimed to estimate the association between post–glucose load measures of insulin resistance and prognosis of nondiabetic patients with ischemic stroke.

Methods and Results—Data were derived from the ACROSS-China (Abnormal Glucose Regulation in Patients with Acute Stroke across China) registry. Patients with ischemic stroke without a history of diabetes mellitus were included. Two post–glucose load measures of insulin sensitivity, the insulin sensitivity indices ISI(composite) and the $ISI_{0,120}$, were calculated. Outcomes included stroke recurrence, all-cause death, and poor functional outcome at 12 months. Among 1203 patients, 63.3% were male with an average age of 62.1 years. At 12 months, 168 (14.4%) patients had recurrent stroke, 111 (9.2%) had died, and 288 (24.4%) had poor outcome. After adjustment for potential covariates, the first quartile of the ISI(composite) was associated with increased 12-month stroke recurrence (adjusted hazard ratio 2.02, 95% CI 1.28–3.18, $P=0.003$), death (adjusted hazard ratio 2.78, 95% CI 1.59–4.86, $P<0.001$), and poor outcome (adjusted odds ratio 2.67, 95% CI 1.69–4.21, $P<0.001$) compared with the fourth quartile. Similar results were observed for the $ISI_{0,120}$ but with a larger magnitude of association. Using a multivariable regression model with restricted cubic spline, we found an L-shaped association between the insulin sensitivity indices and the risk of each end point.

Conclusions—In this large-scale registry, post–glucose load measures of insulin resistance with the ISI(composite) and the $ISI_{0,120}$ were associated with 12-month poor outcomes of nondiabetic patients with ischemic stroke. (*J Am Heart Assoc.* 2017;6:e004990. DOI: 10.1161/JAHA.116.004990.)

Key Words: diabetes mellitus • insulin resistance • outcome • stroke

Insulin resistance is associated with development and progression of atherosclerosis and hypercoagulability.^{1,2} Previous studies have shown that insulin resistance is associated with an increased risk of coronary heart disease and stroke in the nondiabetic population.^{3–7} Recent studies have also shown that insulin resistance is associated with worse outcomes in patients with acute ischemic stroke who

are treated with intravenous thrombolysis.^{8,9} Few studies, however, have focused on the clinical outcome of general ischemic stroke.¹⁰ The association between insulin resistance and clinical outcome of general ischemic stroke is still unclear. The recently published IRIS (Insulin Resistance Intervention after Stroke) trial¹¹ showed that pioglitazone reduced the risk of stroke or myocardial infarction in

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nondiabetic stroke patients with insulin resistance. More evidence of the association of insulin resistance and outcome of stroke is required.

Insulin resistance in previous studies was assessed mostly by the homeostasis model assessment of insulin resistance (HOMA-IR), a measurement based on fasting plasma glucose and insulin levels.^{8–10} A previous study showed greater risk of cardiovascular disease associated with an increase in 2-hour plasma glucose levels compared with an increase in fasting plasma glucose levels.¹² The insulin sensitivity index (ISI) is based on post–glucose load measures. The ISI reflects whole-body or peripheral insulin resistance, not only hepatic insulin resistance as reflected by the HOMA-IR.¹³ A previous study showed that insulin resistance calculated by post–glucose load measures, but not by fasting insulin, was associated with a risk of incident ischemic stroke.⁷ Few studies, however, have reported an association between post–glucose load measures of insulin resistance and prognosis with ischemic stroke. In this study, we evaluated the hypothesis that post–glucose load measures of insulin resistance are associated with poor outcome in nondiabetic patients with ischemic stroke, using a nationwide prospective stroke registry in China.

Methods

Study Participants

Data were derived from the ACROSS-China (Abnormal Glucose Regulation in Patients with Acute Stroke across China) registry. Details of the rationale, design, and methodology of the ACROSS-China study were published previously.¹⁴ In brief, ACROSS-China is a nationwide prospective cohort study investigating the prevalence of abnormal glucose regulation in hospitalized patients with a first-ever stroke within 14 days after onset and the association of abnormal glucose regulation with the outcome of stroke from 2008 to 2009 across China. The protocol and data collection of the ACROSS-China study were approved by the ethics committee of Beijing Tiantan Hospital and all participating centers. Written informed consent was obtained from all participants or their representatives before data collection. Patients with ischemic stroke without a history of diabetes mellitus were included in this study.

Acute ischemic stroke was diagnosed according to the World Health Organization criteria¹⁵ with confirmation by brain computed tomography or magnetic resonance imaging. Stroke severity was assessed by the National Institutes of Health Stroke Scale within 24 hours after admission. The etiologic subtypes of ischemic stroke were classified according to the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria.¹⁶

Data Collection

Baseline data on demographics, medical history, cardiovascular risk factors, and medical treatment were collected within 24 hours after admission. Data collection was performed through face-to-face interviews by trained interviewers (neurologists from participating hospitals) with a standardized protocol. Medical history included a history of diabetes mellitus, hypertension, dyslipidemia, atrial fibrillation (history of atrial fibrillation confirmed by at least 1 electrocardiogram), and coronary heart disease. Cardiovascular risk factors included blood pressure, low-density lipoprotein, high-density lipoprotein, triglycerides, body mass index (BMI; calculated as weight [kg] divided by the square of height in meters [m²]) and smoking status. Complications of pulmonary or urinary infection and medication used during hospitalization were also recorded.

Assessment of Insulin Resistance

The standard oral glucose tolerance test was performed in patients without previously diagnosed diabetes mellitus during the morning hours (7–11 AM) on day 14±3 after stroke onset or prior to discharge (if the hospital stay was <14 days) according to the World Health Organization criteria.¹⁷ Venous blood samples were obtained after an overnight fast of at least 8 hours and again at 2 hours after a 75-g oral glucose challenge. Fasting and 2-hour postload glucose levels were measured with an enzymatic method, and fasting and 2-hour postload insulin levels were measured with a competitive radioimmunoassay (Diagnostic Products Corp).¹⁸

Two post–glucose load measures of insulin sensitivity were calculated. The Matsuda ISI (composite) was calculated as follows: $ISI(\text{composite}) = 10\,000 / \sqrt{(G_0 \times I_0 \times G_{120} \times I_{120})}$. G_0 and G_{120} represent plasma glucose concentrations at times 0 and 120 minutes, and I_0 and I_{120} represent insulin concentrations at times 0 and 120 minutes. Units for the ISI (composite) are $\text{mg} \times \text{mU} / \text{dL} \times \text{L}$.¹⁹ The Gutt $ISI_{0,120}$ was calculated as $ISI_{0,120} = m / [G \times \log_{10}(I)]$, in which $m = [75\,000 \text{ mg} + (\text{fasting glucose} - 2\text{-hour glucose}) \times 0.19 \times \text{body weight kg}] / 120 \text{ minutes}$, G represents mean fasting and 2-hour glucose concentrations, and I represents mean fasting and 2-hour insulin concentrations. Units for the $ISI_{0,120}$ are $\text{mg} \times \text{L}^2 / \text{mmol} \times \text{mU} \times \text{min}$.²⁰ For both ISI indices, a lower ISI value indicates a higher level of insulin resistance.

Patient Follow-up and Outcomes Assessment

Patients were followed up for outcomes through centralized telephone interviews at 12 months after stroke onset. Telephone interviews were performed by trained interviewers based on a shared standardized interview protocol. The

outcomes included stroke recurrence, all-cause death, and poor functional outcome at 12 months. Stroke recurrence was defined as an aggravated primary neurological deficit, a new neurological deficit, or rehospitalization with a diagnosis of ischemic or hemorrhagic stroke.²¹ Death was confirmed on a death certificate from either the local citizen registry or the attended hospital. Poor functional outcome was defined as a modified Rankin Scale score of 3 to 6.²²

Statistical Analysis

The baseline characteristics were compared among quartiles of ISI using the chi-square test for categorical variables and ANOVA or the Kruskal–Wallis test for continuous variables.

The associations of the 2 ISIs and the outcomes of stroke were estimated. For the outcomes of stroke recurrence and death, adjusted hazard ratios (HRs) with their 95% CIs were estimated by a Cox regression model. The proportional hazards assumption for the Cox models was examined by adding a time-dependent covariate with interaction of the ISIs

and a logarithmic function of survival time in the model. For the outcome of poor functional outcome at 12 months, adjusted odds ratios with their 95% CIs were estimated using a logistic regression model. For each outcome, 3 multivariable regression models were performed. In model 1, we adjusted for demographics, stroke severity and subtype, and cardiovascular risk factors. In model 2, we also adjusted for complications of pulmonary or urinary infection during hospitalization. In model 3, we further adjusted for treatment during hospitalization. We further evaluated the pattern and magnitude of associations between the ISI and the risk of outcome events using a Cox or logistic regression model with restricted cubic splines for ISI (continuous measures), adjusting for all covariates (model 3). The ISI of the third quartile was treated as the reference, and the 5 knots for spline were placed at the 5th, 25th, 50th, 75th, and 95th percentiles of the ISI.

All reported *P* values were 2-sided with *P*<0.05 considered significant. All analyses were conducted with SAS 9.4 (SAS Institute Inc).

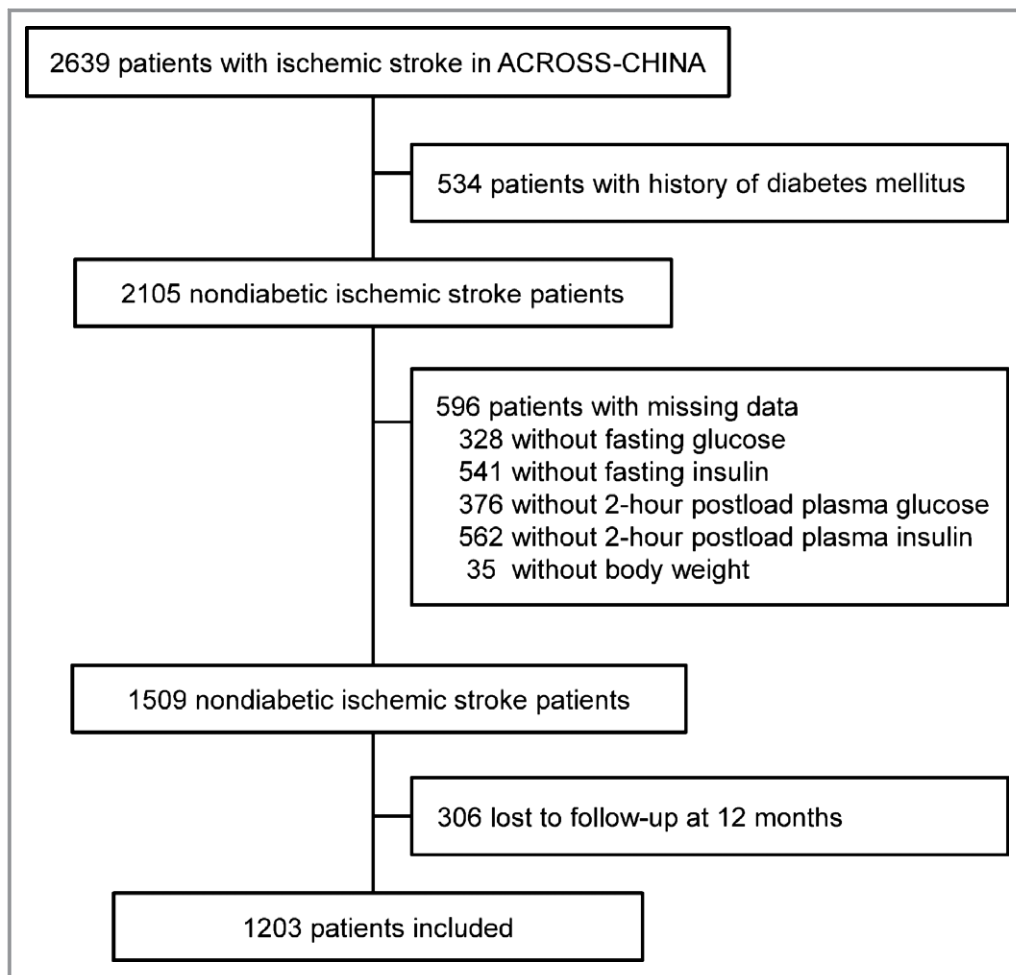


Figure 1. Flow diagram of the participant selection. ACROSS-CHINA indicates Abnormal Glucose Regulation in Patients with Acute Stroke across China.

Results

Study Participants

A total of 2105 nondiabetic patients with ischemic stroke participated in the ACROSS-China study (Figure 1). After excluding patients with missing data on glucose, insulin, or body weight and those lost to follow-up at 12 months, 1203 (57.1%) patients were included in this analysis. Baseline characteristics of the included and excluded patients were well balanced except that those who were excluded for missing data

on glucose, insulin, or body weight had higher fasting and 2-hour insulin levels and lower ISI(composite), and those who were excluded for loss to follow-up had higher stroke severity, lower 2-hour glucose and insulin levels, and higher ISIs (Table 1).

The mean age of the study participants was 62.1 ± 12.8 years, and 758 (63.3%) patients were male. The median ISI(composite) was 4.0 (interquartile range 2.3–7.1), whereas the median $ISI_{0,120}$ was 51.1 (interquartile range 35.8–76.9). Baseline characteristics of the patients by quartiles of the ISI(composite) and $ISI_{0,120}$ are shown in

Table 1. Baseline Characteristics of Included and Excluded Participants

Characteristics	Included (n=1203)	Excluded for Missing Glucose, Insulin, or Weight Data (n=596)	Excluded for Loss to Follow-up (n=306)
Sex (male), n (%)	758 (63.3)	400 (67.3)	199 (65.7)
Age (y), mean (SD)	62.1±12.8	62.3±13.0	63.3±12.6
NIHSS score at admission, median (IQR)	4 (2–8)	4 (2–8)	5 (2–9)
BMI (kg/m ²), mean (SD)	24.9±3.8	24.3±3.5	24.3±3.6
Systolic blood pressure (mm Hg), mean (SD)	146.6±21.1	145.4±20.8	144.7±22.4
Diastolic blood pressure (mm Hg), mean (SD)	85.9±12.1	85.9±11.9	85.8±13.6
Triglyceride at admission (mmol/L), mean (SD)	1.74±1.14	1.69±1.05	1.59±0.96
HDL at admission (mmol/L), mean (SD)	1.20±0.35	1.18±0.41	1.21±0.32
History of hypertension, n (%)	725 (60.3)	356 (59.7)	182 (59.5)
History of hyperlipidemia, n (%)	140 (11.6)	56 (9.4)	28 (9.2)
History of atrial fibrillation, n (%)	74 (6.2)	34 (5.7)	27 (8.8)
History of coronary heart disease, n (%)	145 (12.1)	76 (12.8)	38 (12.4)
Smoking, n (%)			
Current smoker	680 (56.5)	347 (58.2)	182 (59.5)
Ever smoker	122 (10.1)	53 (8.9)	30 (9.8)
Nonsmoker	401 (33.3)	196 (32.9)	94 (30.7)
TOAST subtypes, n (%)			
Cardioembolism	75 (6.2)	35 (5.9)	26 (8.5)
Large artery atherosclerosis	737 (61.4)	403 (67.6)	173 (56.5)
Small artery occlusion	318 (26.4)	123 (20.6)	76 (24.8)
Other/undetermined	31 (2.6)	15 (2.5)	11 (3.6)
Undefined	42 (3.5)	20 (3.4)	20 (6.5)
Fasting glucose (mmol/L), median (IQR)	5.2 (4.6–5.9)	5.3 (4.7–6.1)*	5.0 (4.5–5.7)
Fasting insulin (mU/L), median (IQR)	8.0 (5.1–12.4)	8.9 (6.4–13.0)*	8.0 (5.6–12.0)
2-hour glucose (mmol/L), median (IQR)	8.8 (7.0–11.8)	8.8 (7.1–11.9)*	7.9 (6.7–10.1)
2-hour insulin (mU/L), median (IQR)	51.3 (22.7–92.6)	56.0 (33.3–110.0)*	38.8 (18.4–90.4)
ISI(composite), median (IQR)	4.0 (2.3–7.1)	3.3 (2.4–5.4)*	4.7 (2.5–9.3)
$ISI_{0,120}$, median (IQR)	51.1 (35.8–76.9)	—	61.5 (41.4–90.8)

BMI indicates body mass index; HDL, high-density lipoprotein; IQR, interquartile range; ISI, insulin sensitivity index; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

*Analyses were performed only for available data: n=268 for fasting glucose, n=55 for fasting insulin, n=220 for 2-hour glucose, n=34 for 2-hour insulin, and n=21 for ISI(composite).

Table 2. Baseline Characteristics in Relation to the Insulin Resistance States Measured by ISI(Composite)

	ISI(Composite)				P Value
	Q1 (n=307)*	Q2 (n=294)	Q3 (n=299)	Q4 (n=303)	
Sex (male), n (%)	168 (55.3)	196 (67.1)	195 (65.2)	199 (65.9)	0.009
Age (y), mean (SD)	63.3±12.5	61.8±12.7	62.0±13.3	61.3±12.9	0.34
BMI (kg/m ²), mean (SD)	25.6±3.6	25.0±4.0	24.6±4.0	24.5±3.6	<0.001
Systolic blood pressure (mm Hg) mean (SD)	147.8±20.0	147.5±21.2	145.4±21.5	145.8±21.8	0.43
Diastolic blood pressure (mm Hg) mean (SD)	86.8±12.1	85.3±12.1	84.8±12.2	86.8±11.8	0.07
Triglyceride at admission (mmol/L), mean (SD)	2.08±1.40	1.74±0.93	1.65±1.13	1.48±0.93	<0.001
HDL at admission (mmol/L), mean (SD)	1.15±0.43	1.18±0.32	1.19±0.29	1.27±0.36	<0.001
History of hypertension, n (%)	216 (70.4)	174 (59.2)	164 (54.9)	171 (56.4)	<0.001
History of hyperlipidemia, n (%)	43 (14.0)	41 (13.9)	24 (8.0)	32 (10.6)	0.06
History of atrial fibrillation, n (%)	19 (6.2)	16 (5.4)	16 (5.4)	23 (7.6)	0.64
History of coronary heart disease, n (%)	40 (13.0)	23 (7.8)	34 (11.4)	48 (15.8)	0.02
Smoking, n (%)					<0.001
Current smoker	206 (67.1)	145 (49.3)	164 (54.9)	165 (54.5)	
Previous smoker	35 (11.4)	28 (9.5)	32 (10.7)	27 (8.9)	
Nonsmoker	66 (21.5)	121 (41.2)	103 (34.5)	111 (36.6)	
Medicine use during hospitalization, n (%)					
Antihypertensive drugs	158 (51.5)	132 (44.9)	134 (44.8)	115 (38.0)	0.01
Diuretics	13 (4.2)	9 (3.1)	5 (1.7)	5 (1.7)	0.14
Beta blockers	16 (5.2)	11 (3.7)	15 (5.0)	8 (2.6)	0.35
Statin	174 (56.7)	170 (57.8)	149 (49.8)	126 (41.6)	<0.001
Intravenous alteplase	6 (2.0)	13 (4.4)	8 (2.7)	10 (3.3)	0.35
Antiplatelet	203 (66.1)	199 (67.7)	184 (61.5)	168 (55.5)	0.009
Anticoagulation	26 (8.5)	21 (7.1)	14 (4.7)	17 (5.6)	0.24
Pulmonary infection, n (%)	25 (8.1)	15 (5.1)	22 (7.4)	28 (9.2)	0.27
Urinary infection, n (%)	14 (4.6)	12 (4.1)	13 (4.4)	4 (1.3)	0.11
NIHSS score at admission, median (IQR)	4 (2–8)	4 (2–8)	4 (2–9)	4 (2–7)	0.70
TOAST subtypes, n (%)					0.11
Large artery atherosclerosis	188 (61.2)	193 (65.7)	179 (59.9)	177 (58.4)	
Small artery occlusion	91 (29.6)	70 (23.8)	79 (26.4)	78 (25.7)	
Cardioembolism	21 (6.8)	14 (4.8)	20 (6.7)	20 (6.6)	
Other/undetermined	2 (0.7)	7 (2.4)	10 (3.3)	12 (4.0)	
Undefined	5 (1.6)	10 (3.4)	11 (3.7)	16 (5.3)	

BMI indicates body mass index; HDL, high-density lipoprotein; IQR, interquartile range; ISI, insulin sensitivity index; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

*Quartiles of ISI(composite): Q1, ≤2.2; Q2, 2.3–3.9; Q3, 4.0–7.0; Q4, ≥7.1.

Tables 2 and 3, respectively. Patients with lower ISI values were more likely to be older and female and to have a higher body mass index, a history of hypertension, higher levels of fasting glucose and triglyceride, and lower high-density lipoprotein levels at admission. These patients also were more likely to be current or previous smokers and to have subtypes of large artery atherosclerosis and small artery

occlusion and received more antihypertensive, statin, and antiplatelet agents during hospitalization.

Association of the ISI With Clinical Outcomes

Table 4 shows the association between the ISI(composite) and clinical outcomes of ischemic stroke. Patients in the

Table 3. Baseline Characteristics in Relation to Insulin Resistance States Measured by ISI_{0,120}

	ISI _{0,120}				P Value
	Q1 (n=300)	Q2 (n=301)	Q3 (n=301)	Q4 (n=301)*	
Sex (male), n (%)	170 (57.2)	194 (64.5)	194 (64.7)	200 (66.9)	0.08
Age (y), mean (SD)	64.4±11.9	62.4±12.9	61.2±12.8	60.6±13.5	0.005
BMI (kg/m ²), mean (SD)	25.7±3.9	25.1±3.7	24.6±4.2	24.3±3.2	<0.001
Systolic blood pressure (mm Hg) mean (SD)	149.0±20.1	146.1±21.7	145.6±20.7	145.8±21.8	0.14
Diastolic blood pressure (mm Hg) mean (SD)	86.8±11.8	85.2±12.4	85.0±11.8	86.7±12.2	0.18
Triglyceride at admission (mmol/L), mean (SD)	2.00±1.44	1.77±0.96	1.59±0.89	1.58±1.14	<0.001
HDL at admission (mmol/L), mean (SD)	1.16±0.28	1.17±0.46	1.22±0.33	1.24±0.33	0.003
History of hypertension, n (%)	206 (68.4)	184 (61.1)	176 (58.5)	159 (53.0)	0.001
History of hyperlipidemia, n (%)	35 (11.6)	40 (13.3)	37 (12.3)	28 (9.3)	0.48
History of atrial fibrillation, n (%)	15 (5.0)	19 (6.3)	24 (8.0)	16 (5.3)	0.42
History of coronary heart disease, n (%)	39 (13.0)	30 (10.0)	31 (10.3)	45 (15.0)	0.19
Smoking, n (%)					0.50
Current smoker	175 (58.1)	174 (57.8)	168 (55.8)	163 (54.3)	
Previous smoker	28 (9.3)	38 (12.6)	27 (9.0)	29 (9.7)	
Nonsmoker	98 (32.6)	89 (29.6)	106 (35.2)	108 (36.0)	
Medicine use during hospitalization, n (%)					
Antihypertensive drugs	143 (47.5)	146 (48.5)	125 (41.5)	125 (41.7)	0.17
Diuretics	7 (2.3)	10 (3.3)	9 (3.0)	6 (2.0)	0.74
Beta blockers	15 (5.0)	14 (4.7)	13 (4.3)	8 (2.7)	0.49
Statin	160 (53.2)	179 (59.2)	152 (50.5)	128 (42.7)	<0.001
Intravenous alteplase	5 (1.7)	14 (4.7)	6 (2.0)	12 (4.0)	0.09
Antiplatelet	193 (64.1)	201 (66.8)	188 (62.5)	172 (57.3)	0.11
Anticoagulation	20 (6.6)	23 (7.6)	19 (6.3)	16 (5.3)	0.72
Pulmonary infection, n (%)	26 (8.6)	22 (7.3)	15 (5.0)	27 (9.0)	0.23
Urinary infection, n (%)	10 (3.3)	10 (3.3)	15 (5.0)	8 (2.7)	0.46
NIHSS score at admission, median (IQR)	4 (2–8)	5 (2–9)	4 (2–8)	4 (2–7)	0.07
TOAST subtypes, n (%)					0.002
Large artery atherosclerosis	192 (63.8)	202 (67.1)	176 (58.5)	167 (55.7)	
Small artery occlusion	87 (28.9)	69 (22.9)	78 (25.9)	84 (28.0)	
Cardioembolism	13 (4.3)	20 (6.6)	23 (7.6)	19 (6.3)	
Other/undetermined	3 (1.0)	2 (0.7)	10 (3.3)	16 (5.3)	
Undefined	6 (2.0)	8 (2.7)	14 (4.7)	14 (4.7)	

BMI indicates body mass index; HDL, high-density lipoprotein; IQR, interquartile range; ISI, insulin sensitivity index; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

*Quartiles of ISI_{0,120}: Q1, ≤35.7; Q2, 35.8–51.0; Q3, 51.1–76.8; Q4, ≥76.9.

lower ISI(composite) categories were associated with a higher risk of 12-month stroke recurrence, death, and poor outcome (*P* for trend 0.002, <0.001, and <0.001, respectively). With adjustment for demographics, stroke severity and subtype, and cardiovascular risk factors (model 1) and further adjustment for complications during hospitalization (model 2), we found that the first quartile of the ISI(composite) (≤2.2) was

significantly associated with increased 12-month stroke recurrence, death, and poor outcome compared with the fourth quartile of the ISI(composite) (≥7.1). After adding the variables of treatment during hospitalization for adjustment (model 3), the first quartile of the ISI(composite) remained associated with increased 12-month stroke recurrence, death and poor outcome (adjusted HR 2.02, 95% CI 1.28–3.18,

Table 4. Adjusted HRs and ORs of Outcomes at 12 Months According to Insulin Resistance States Measured by the ISI (Composite)

Outcomes	ISI(Composite) Groups	n	Events, n (%)	Model 1*		Model 2†		Model 3‡	
				HR/OR (95% CI)§	P Value	HR/OR (95% CI)§	P Value	HR/OR (95% CI)§	P Value
Stroke recurrence	Q4 (≥7.1)	293	30 (10.2)	Ref.		Ref.		Ref.	
	Q3 (4.0–7.0)	294	41 (13.9)	0.85 (0.44–1.66)	0.63	1.35 (0.84–2.17)	0.22	1.32 (0.82–2.12)	0.25
	Q2 (2.3–3.9)	285	39 (13.7)	1.56 (0.85–2.86)	0.15	1.34 (0.83–2.17)	0.24	1.35 (0.83–2.19)	0.22
	Q1 (≤2.2)	291	58 (19.9)	2.59 (1.49–4.50)	<0.001	2.02 (1.28–3.17)	0.002	2.02 (1.28–3.18)	0.003
	Q1 vs Q2–4			2.18 (1.48–3.22)	<0.001	1.64 (1.18–2.29)	0.003	1.65 (1.18–2.30)	0.003
Death	Q4 (≥7.1)	303	19 (6.3)	Ref.		Ref.		Ref.	
	Q3 (4.0–7.0)	299	17 (5.7)	1.34 (0.83–2.15)	0.23	0.90 (0.46–1.75)	0.75	0.90 (0.46–1.76)	0.75
	Q2 (2.3–3.9)	294	27 (9.2)	1.33 (0.82–2.15)	0.25	1.62 (0.88–2.99)	0.12	1.69 (0.92–3.11)	0.09
	Q1 (≤2.2)	307	48 (15.6)	2.00 (1.27–3.14)	0.003	2.62 (1.51–4.57)	<0.001	2.78 (1.59–4.86)	<0.001
	Q1 vs Q2–4			1.64 (1.17–2.28)	0.004	2.14 (1.45–3.16)	<0.001	2.22 (1.49–3.29)	<0.001
Poor outcome	Q4 (≥7.1)	297	53 (17.8)	Ref.		Ref.		Ref.	
	Q3 (4.0–7.0)	293	63 (21.5)	1.14 (0.72–1.81)	0.58	1.15 (0.72–1.83)	0.57	1.12 (0.70–1.80)	0.63
	Q2 (2.3–3.9)	287	68 (23.7)	1.46 (0.92–2.33)	0.11	1.49 (0.94–2.39)	0.09	1.49 (0.93–2.39)	0.10
	Q1 (≤2.2)	304	104 (34.2)	2.70 (1.73–4.21)	<0.001	2.72 (1.73–4.26)	<0.001	2.67 (1.69–4.21)	<0.001
	Q1 vs Q2–4			2.12 (1.50–2.30)	<0.001	2.12 (1.50–3.01)	<0.001	2.09 (1.47–2.97)	<0.001

HR, hazard ratio; ISI, insulin sensitivity index; OR, odds ratio; Ref., reference.

*Model 1: adjusted for sex, age, National Institutes of Health Stroke Score on admission, body mass index, history of hypertension, hyperlipidemia, atrial fibrillation, coronary heart disease, smoker, stroke subtype.

†Model 2: adjusted for model 1 plus pulmonary infection and urinary infection during hospitalization.

‡Model 3: adjusted for model 2 plus antihypertensive, thrombolytic, antiplatelet, and anticoagulation use during hospitalization.

§HR for stroke recurrence and death, and OR for poor outcome.

||Poor outcome: modified Rankin Scale 3–6.

$P=0.003$; adjusted HR 2.78, 95% CI 1.59–4.86, $P<0.001$; and adjusted odds ratio 2.67, 95% CI 1.69–4.21, $P<0.001$, respectively). All proportional hazards assumptions were met ($P=0.99$ for the outcome of stroke recurrence and $P=0.07$ for the outcome of death). When using the second to fourth quartiles of the ISI(composite) as the reference, the first quartile of the ISI(composite) was also significantly associated with an increased risk of all 3 end points (Table 4).

Table 5 shows the associations between the $ISI_{0,120}$ and clinical outcomes of ischemic stroke. For all models, the first quartile of the $ISI_{0,120}$ was associated with increased 12-month stroke recurrence, death, and poor outcome, with a large magnitude of association (model 3: adjusted HR 3.23, 95% CI 2.03–5.13, $P<0.001$; adjusted HR 4.17, 95% CI 2.33–7.45, $P<0.001$; and adjusted odds ratio 3.96, 95% CI 2.50–6.28, $P<0.001$, respectively). All proportional hazards assumptions were met ($P=0.99$ for the outcome of stroke recurrence and $P=0.11$ for the outcome of death). Similar results were observed when using the second to fourth quartiles of the $ISI_{0,120}$ as the reference (Table 5).

Using a multivariable regression model with restricted cubic spline, we found L-shaped associations between the ISI (composite) and the risk of 12-month stroke recurrence,

death, and poor outcome (Figure 2). Similar curves were observed for the associations of the $ISI_{0,120}$ and risk of the 3 end points (Figure 3).

Associations of ISI Components With Clinical Outcomes

In a model that included all individual ISI components and other potential covariates simultaneously, only 2-hour glucose levels were independently associated with a risk of stroke recurrence; however, 2-hour glucose and 2-hour insulin levels (marginally) were independently associated with risk of death. In addition, 2-hour glucose, 2-hours insulin (marginally), and fasting glucose levels were independently associated with a risk of poor outcome (Table 6).

Discussion

In this nationwide large-scale study, we found that insulin resistance based on post-glucose load measures—lower levels of the ISI(composite) and the $ISI_{0,120}$ —was associated with an increased risk of 12-month stroke recurrence, death,

Table 5. Adjusted HRs and ORs of Outcomes at 12 Months According to Insulin Resistance States Measured by the ISI_{0,120}

Outcomes	ISI _{0,120} Groups	n	Events, n (%)	Model 1*		Model 2†		Model 3‡	
				HR/OR (95% CI) [§]	P Value	HR/OR (95% CI) [§]	P Value	HR/OR (95% CI) [§]	P Value
Stroke recurrence	Q4 (≥76.9)	291	26 (8.9)	Ref.		Ref.		Ref.	
	Q3 (51.1–76.8)	296	26 (8.8)	0.96 (0.56–1.66)	0.89	0.96 (0.56–1.67)	0.90	0.96 (0.55–1.65)	0.87
	Q2 (35.8–51.0)	293	39 (13.3)	1.55 (0.94–2.58)	0.09	1.55 (0.93–2.57)	0.09	1.55 (0.94–2.58)	0.09
	Q1 (≤35.7)	283	77 (27.2)	3.26 (2.05–5.17)	<0.001	3.25 (2.04–5.16)	<0.001	3.23 (2.03–5.13)	<0.001
	Q1 vs Q2–4			2.77 (2.02–3.81)	<0.001	2.77 (2.01–3.80)	<0.001	2.75 (2.00–3.78)	<0.001
Death	Q4 (≥76.9)	300	15 (5.0)	Ref.		Ref.		Ref.	
	Q3 (51.1–76.8)	301	11 (3.7)	0.60 (0.27–1.34)	0.21	0.62 (0.28–1.40)	0.25	0.62 (0.28–1.40)	0.25
	Q2 (35.8–51.0)	301	24 (8.0)	1.45 (0.75–2.79)	0.27	1.47 (0.76–2.83)	0.25	1.48 (0.77–2.86)	0.24
	Q1 (≤35.7)	301	61 (20.3)	4.06 (2.27–7.25)	<0.001	4.05 (2.27–7.23)	<0.001	4.17 (2.33–7.45)	<0.001
	Q1 vs Q2–4			3.98 (2.70–5.87)	<0.001	3.88 (2.62–5.74)	<0.001	3.99 (2.69–5.91)	<0.001
Poor outcome	Q4 (≥76.9)	291	50 (17.2)	Ref.		Ref.		Ref.	
	Q3 (51.1–76.8)	297	46 (15.5)	0.75 (0.45–1.24)	0.26	0.77 (0.46–1.28)	0.32	0.76 (0.46–1.27)	0.30
	Q2 (35.8–51.0)	293	71 (24.2)	1.27 (0.79–2.04)	0.32	1.30 (0.81–2.09)	0.28	1.28 (0.79–2.07)	0.31
	Q1 (≤35.7)	300	121 (40.3)	3.90 (2.47–6.14)	<0.001	4.00 (2.53–6.34)	<0.001	3.96 (2.50–6.28)	<0.001
	Q1 vs Q2–4			3.87 (2.73–5.47)	<0.001	3.91 (2.76–5.55)	<0.001	3.90 (2.75–5.54)	<0.001

HR, hazard ratio; ISI, insulin sensitivity index; OR, odds ratio; Ref., reference.

*Model 1: adjusted for sex, age, National Institutes of Health Stroke Score on admission, body mass index, history of hypertension, hyperlipidemia, atrial fibrillation, coronary heart disease, smoker, stroke subtype.

†Model 2: adjusted for model 1 plus pulmonary infection and urinary infection during hospitalization.

‡Model 3: adjusted for model 2 plus antihypertensive, thrombolytic, antiplatelet, and anticoagulation use during hospitalization.

§HR for stroke recurrence and death, and OR for poor outcome.

||Poor outcome: modified Rankin Scale 3–6.

and poor outcome in nondiabetic patients with ischemic stroke in the Chinese population. An L-shaped association between the ISI and risk of poor outcome of stroke was observed, and the first quartile of the ISI was associated with an increased risk of poor outcome of stroke.

Previous studies focused mostly on the association of insulin resistance with the incidence of stroke in the nondiabetic general population.^{4–7} The association between insulin resistance and prognosis of patients with ischemic stroke has rarely been studied. Recent results from Calleja et al⁸ (n=109) and Bas et al⁹ (n=108) showed that insulin resistance was associated with worse outcome in patients with acute ischemic stroke who were treated with intravenous thrombolysis. A preliminary report from Hishinuma et al including 32 patients with stroke without history of diabetes mellitus showed that 3 of 4 patients with recurrent events had insulin resistance.¹⁰ Our study added evidence of the association between insulin resistance and prognosis of nondiabetic patients with ischemic stroke based on a large-scale population. Furthermore, the IRIS trial¹¹ provided evidence that pioglitazone was effective for secondary prevention in nondiabetic patients with stroke and insulin resistance. Although it may be premature to perform routine testing for insulin resistance in patients with ischemic stroke,

testing for insulin resistance and then treating accordingly may have an important role in particular cases that cannot be well stratified by traditional risk factors.⁶

The physiological consequences of insulin resistance include hypertension, dyslipidemia, abnormal fibrinolysis, hyperglycemia, hyperinsulinemia, systemic inflammation, altered vascular endothelial function, and atherogenesis.²³ These metabolic and cellular changes tend to promote atherosclerosis and subsequent stroke.²³ HOMA-IR includes only fasting plasma glucose and insulin levels and is perhaps most widely used for indirectly estimating insulin sensitivity. ISIs based on fasting glucose and fasting insulin levels, such as HOMA-IR, primarily reflect hepatic insulin sensitivity; however, ISIs based on changes in insulin and glucose levels during the oral glucose tolerance test, such as the ISI(composite) and ISI_{0,120}, incorporate both peripheral and hepatic insulin sensitivity.²⁴ Martínez-Hervas et al²⁵ showed that a significant percentage (14.4%) of patients were misclassified with HOMA-IR. Other studies also showed that insulin resistance based on post-glucose load measures, such as the ISI(composite) and ISI_{0,120}, had stronger correlations with the hyperinsulinemic–euglycemic clamp (gold criterion to measure insulin resistance) compared with HOMA-IR.^{24,26} Our study also showed that 2-hour glucose and insulin levels had value over fasting measures.

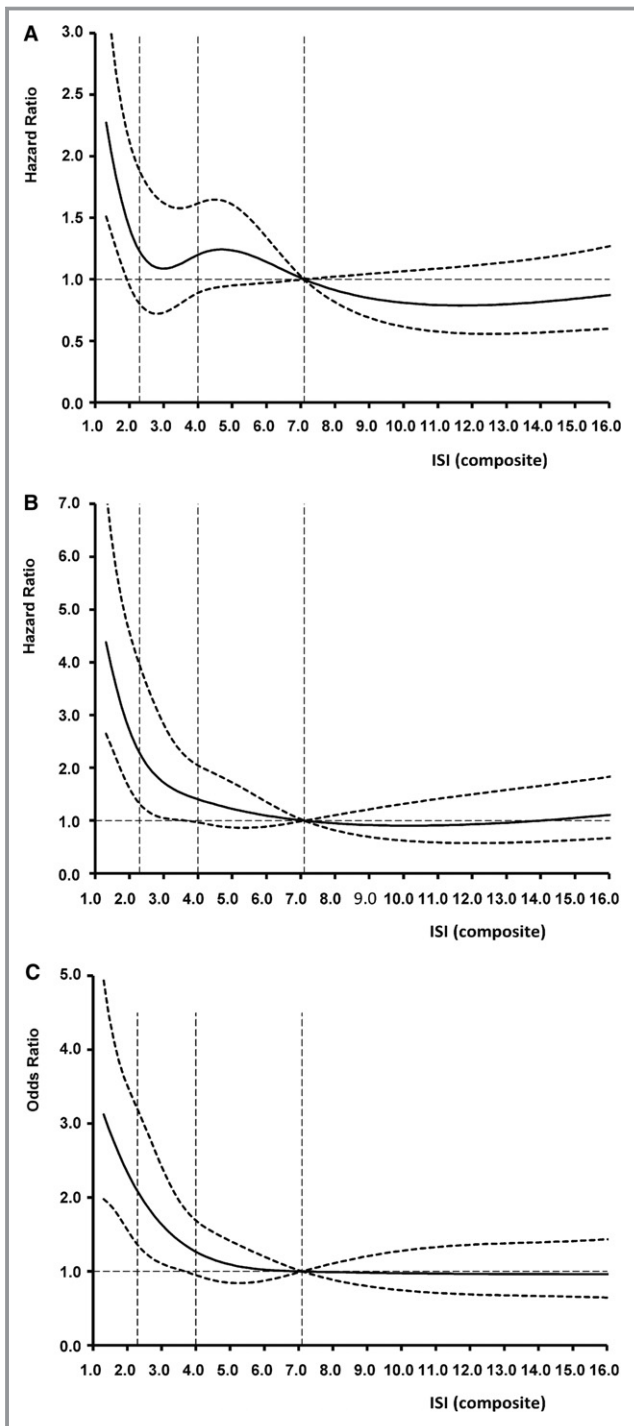


Figure 2. Adjusted hazard and odds ratios for (A) stroke, (B) death, and (C) poor outcome according to the ISI(composite). The solid line indicates adjusted hazard or odds ratios, and the dashed lines indicate the 95% CI bands. Reference is the third quartile of the ISI(composite) (7.1). The vertical dashed lines indicate the first, second, and third quartiles of the ISI(composite). Data were fitted using a Cox/logistic regression model of restricted cubic spline with 5 knots (the 5th, 25th, 50th, 75th, 95th percentiles) for ISI(composite), adjusting for potential covariates. The lowest 5% and highest 5% of participants are not shown. ISI indicates insulin sensitivity index.

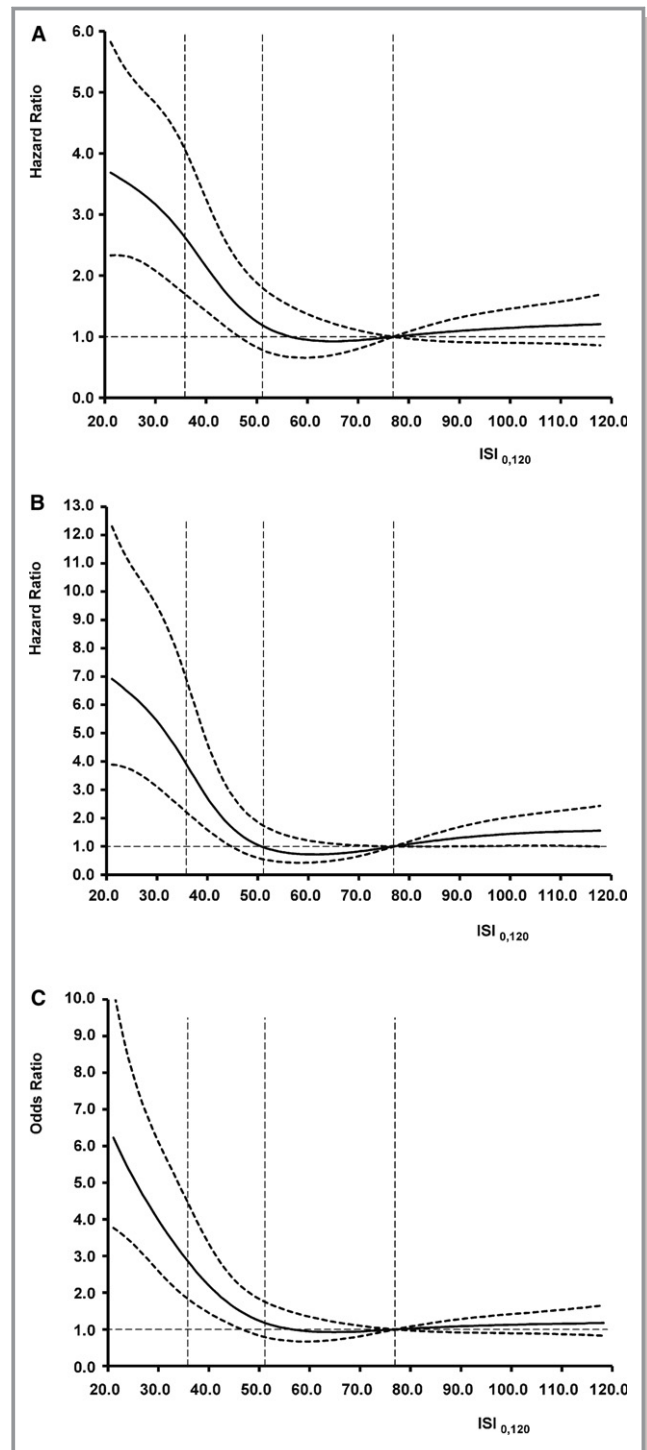


Figure 3. Adjusted hazard and odds ratios for (A) stroke, (B) death, and (C) poor outcome according to ISI_{0,120}. The solid line indicates adjusted hazard or odds ratios, and the dashed lines indicate the 95% CI bands. Reference is the third quartile of ISI_{0,120} (76.9). The vertical dashed lines indicate the first, second, and third quartiles of ISI_{0,120}. Data were fitted using a Cox/logistic regression model of restricted cubic spline with 5 knots (the 5th, 25th, 50th, 75th, 95th percentiles) for ISI_{0,120}, adjusting for potential covariates. The lowest 5% and highest 5% of participants are not shown. ISI indicates insulin sensitivity index.

Table 6. Adjusted HRs and ORs of Outcomes at 12 Months for Components of Insulin Sensitivity Indices in the Full Model

	Stroke Recurrence		Death		Poor Outcome*	
	HR (95% CI) [†]	P Value	HR (95% CI) [†]	P Value	OR (95% CI) [†]	P Value
Fasting glucose (per SD)	1.10 (0.93–1.29)	0.26	1.17 (0.97–1.42)	0.10	1.24 (1.02–1.51)	0.03
Fasting insulin (per SD)	1.01 (0.85–1.20)	0.95	1.14 (0.94–1.38)	0.20	1.07 (0.89–1.29)	0.45
2-hour glucose (per SD)	1.45 (1.21–1.73)	<0.001	1.62 (1.29–2.02)	<0.001	1.58 (1.29–1.92)	<0.001
2-hour insulin (per SD)	1.13 (0.96–1.33)	0.13	1.20 (1.001–1.43)	0.049	1.18 (0.99–1.40)	0.066
Body weight (per SD)	1.09 (0.93–1.29)	0.28	0.87 (0.70–1.08)	0.21	0.92 (0.77–1.10)	0.38

HR, hazard ratio; OR, odds ratio.

*Poor outcome: modified Rankin Scale 3–6.

[†]Adjusted for sex, age, National Institutes of Health Stroke Score on admission; history of hypertension; hyperlipidemia; atrial fibrillation; coronary heart disease; smoker; stroke subtype; pulmonary infection and urinary infection during hospitalization; antihypertensive, thrombolytic, antiplatelet, and anticoagulation use during hospitalization.

Both the ISI(composite) and ISI_{0,120} are derived from a relatively noninvasive and easy-to-perform test, the oral glucose tolerance test. Consequently, these post–glucose load measures of insulin resistance are relatively easy-to-perform and generalizable ways to obtain an estimate of insulin sensitivity in clinical practice and large-scale clinical studies. Our study also indicated a larger magnitude of association between the ISI_{0,120} and outcomes of patients with ischemic stroke that was less effected by adjustment models compared with the ISI (composite). A potential explanation for this finding is that interindividual variability was well considered in the calculation of the ISI_{0,120}. The ISI_{0,120} was developed based on the calculation of glucose uptake considering the influence of body weight on the glucose uptake rate in peripheral tissues, and insulin values were logarithmically transformed to correct for skewness of distribution when calculating the index.²⁰ The 4 components of the ISI(composite) were simply multiplied and treated equally when calculating this index.¹⁹

Several limitations must be acknowledged when interpreting the results. First, 902 (43%) patients were excluded because of missing data or loss to follow-up in 1 year. The oral glucose tolerance test could not be performed in patients with severe stroke because of severe neurological deficits or complications, such as coma, dysphagia, and alimentary tract hemorrhage, indicating poor outcome for these patients. Available data in our study showed that patients who were excluded for missing data of glucose or insulin were more insulin resistant than those who were included. Patients lost to follow-up would have been more likely to die or experience recurrent stroke and severe disability compared with those who remained under follow-up; however, we found that patients who were lost to follow-up were less insulin resistant than those who were included. Considering that two-thirds of patients were excluded for missing data and only one-third of patients were excluded for loss to follow-up, the findings of our current study might be conservative. Second, all hospitals participating in this study were from urban regions of China,

where medical resources and expertise were better than at rural hospitals. Third, we acknowledge the possibility that residual confounding might have influenced the association between insulin resistance and outcomes. Data on physical activity, exercise, diet, and cardiorespiratory fitness were not available or adjusted for in this study. These variables might be associated with insulin resistance and the outcome of stroke.²³

Conclusions

In this nationwide large-scale registry, post–glucose load measures of insulin resistance—lower levels of the ISI (composite) and the ISI_{0,120}, denoting a greater degree of insulin resistance—were associated with 12-month stroke recurrence, death, and poor outcome of nondiabetic patients with ischemic stroke.

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Disclosures

None.

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