Insulin resistance may affect the functional recovery of acute ischemic stroke in non-diabetic patients

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Abstract

Background Insulin resistance is associated with the occurrence of stroke and atherosclerotic disease. However, the relationship between insulin resistance and the prognosis of acute ischemic stroke in nondiabetic patients is unclear. We hypothesized that insulin resistance may affect short-term functional recovery after acute ischemic stroke in nondiabetic patients.

Methods Between May 2014 and December 2016, 1377 consecutive patients with acute ischemic stroke were enrolled from a prospectively maintained stroke registry. After excluding patients with transient ischemic attacks (TIA), pre-stroke disabilities, diabetes mellitus, and patients with incomplete evaluations, 517 patients were included in the study. The homeostasis model assessment of insulin resistance (HOMA-IR) score was used to evaluate the degree of insulin resistance. The factors associated with poor functional outcomes were analyzed using multivariate logistic regression.

Results The patients with the highest quartile of log HOMA-IR index scores were younger and had higher fasting blood glucose, total cholesterol, triglycerides, low-density lipoprotein, and HbA1c levels. Multivariate logistic regression analysis revealed that log HOMA-IR scores were independently associated with poor prognosis after adjusting for age and sex and $p < 0.1$ in univariate analysis.

Conclusion Insulin resistance measured by the HOMA-IR index was associated with the poor functional outcome of non-diabetic stroke patients. This evidence supports treating insulin resistance in acute ischemic stroke patients with blood glucose levels within the normal range.

Background

Insulin resistance is defined as the loss of insulin effectiveness on target tissues and is observed in patients with type 2 diabetes mellitus.[1, 2] Insulin resistance results in impaired glucose utilization and increases hepatic glucose production. Among biomarkers of insulin resistance, the homeostasis model assessment-insulin resistance (HOMA-IR) index is an easy way to assess insulin resistance and is frequently used in epidemiologic studies.[3] Unlike previously identified roles of insulin in nutrient metabolism and its target organs, liver, fat, and muscle, the role of insulin in the central nervous system is still unclear.

In the field of cerebrovascular diseases, recent studies have suggested that a strong relationship exists between insulin resistance and ischemic stroke. Insulin resistance has been reported to be associated with poor clinical outcomes after IV thrombolysis.[4, 5] Pioglitazone improved insulin sensitivity and recurrent cardiovascular disease in patients with ischemic strokes or transient ischemic attacks.[6, 7] A recent study in China reported that insulin resistance was associated with poor 1-year outcomes after acute ischemic strokes.[8] However, the reason for and mechanism of the association between insulin resistance and the prognosis of stroke patients has not been fully identified.

In this study, we hypothesized that insulin resistance may affect short-term functional recovery after acute ischemic strokes in nondiabetic patients. We aimed to determine whether this relationship was affected by stroke severity, stroke subtype, and clinical course.

Methods

Subjects

Between May 2014 and December 2016, 1377 patients with acute ischemic strokes within seven days from symptom-onset were enrolled from a prospectively maintained stroke registry at our institution. In these 1377 patients, patients with transient ischemic attacks (TIA, n = 301) and pre-stroke disabilities (modified Rankin scale (mRS) score ≥ 2, n = 71) were excluded. After excluding the diabetic patients (n = 334) and those without three months of functional outcome data (n = 98) or insulin levels (n = 56), 517 patients were enrolled in the study (Fig. 1). This study was approved by the Institutional Review Board of our institution. Patient consent was waived due to the retrospective registry-based nature of the study.

Insulin Resistance

Fasting glucose and insulin levels were measured within 24 hours of admission. The HOMA-IR was used to assess patients with insulin resistance. HOMA-IR scores were calculated by the following equation: [fasting insulin level (uU/mL)] × [fasting glucose level (mmol/L)] / 22.5. HOMA-IR values were log-transformed due to their non-normal distribution. Subsequently, the log-transformed HOMA-IR values were categorized into quartiles (< 0.23, 0.23–0.36, 0.36–0.53, and > 0.53).

Clinical and Laboratory Variables

Baseline demographics and previous history of hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, peripheral artery disease, or cardiac arrhythmia were collected in all patients. Routine blood tests; chest X-rays; 12-lead electrocardiograms; transthoracic echocardiographies; and brain imaging data, including computed tomography (CT), magnetic resonance imaging (MRI), and cerebral angiographic study using CT or/and MRI, were performed. Stroke severity was assessed by National Institutes of Health Stroke Scale (NIHSS) scores and the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification was used to determine the subtypes of stroke etiology.[9] To assess the clinical course, the presence of early neurological deterioration, defined as an increase in NIHSS score more than 2 points during admission, was collected. Functional outcome three months after the stroke onset was assessed through outpatient visits or centralized telephone follow-ups. Patient follow-ups were processed by a physician or a well-trained stroke nurse using a standardized interview protocol. Poor functional outcome was defined as a score of 3 or more on the mRS score.

Statistical Analysis

All statistical analyses were performed using SPSS (version 23.0, IBM Corp., Armonk NY, USA). The baseline characteristics were compared using Chi-squared ($\chi 2$) tests, independent t-tests, and analysis of

variance (ANOVA) tests, as appropriate. The crude odds ratios (OR) with 95% confidence intervals (CIs) for poor functional outcomes at three months were estimated by using the logistic regression model. The multivariate logistic regression model was used to further evaluate the relationship between HOMA-IR values and poor functional outcome. A two-tailed p-value of less than 0.05 was considered significant.

Results

Demographics and comparison of patients according to log HOMA-IR scores

The mean age of the patients was 65.3 ± 13.5 years and 65.2% were male. The median HOMA-IR value was 2.31 (interquartile range 1.68–3.42). When comparing patients according to the log HOMA-IR values divided into quartiles, age, fasting blood glucose levels, BMI, lipid levels, and HbA1c values were different among the quartiles. The patients in the highest quartile tended to be younger and had higher fasting blood glucose, total cholesterol, triglycerides, low-density lipoprotein, and HbA1c levels (Table 1). The presence of END was not different between the groups. There was no statistical difference in the rate of poor prognosis among the log HOMA-IR quartiles, but the mRS distribution showed a tendency of higher mRS score distributions in the highest quartile (Fig. 2).

Table 1

Baseline characteristics according to log homeostasis model assessment of insulin resistance scores quartiles

	HOMA-IR, quartiles				
	Q1 (n = 129)	Q2 (n = 132)	Q3 (n = 128)	Q4 (n = 128)	p-value
Age (years)	67.7 ± 14.2	65.9 ± 11.0	64.8 ± 13.2	62.6 ± 13.1	0.001
Male sex	79 (61.2)	91 (68.9)	80 (62.5)	87 (68.0)	0.467
Hypertension	58 (45.0)	70 (53.0)	73 (57.0)	72 (56.2)	0.194
Previous coronary artery disease	6 (4.7)	13 (9.8)	9 (7.0)	9 (7.0)	0.446
Previous stroke	11 (8.5)	15 (11.4)	13 (10.2)	9 (7.0)	0.648
Body mass index (kg/m^2)	22.6 ± 2.9	24.0 ± 2.7	24.2 ± 4.1	25.2 ± 3.5	< 0.001
Fasting blood glucose (mg/dL)	93.1 ± 10.5	100.0 ± 13.9	107.2 ± 23.0	120.7 ± 26.1	< 0.001
Total cholesterol level (mg/dL)	184.2 ± 37.5	188.9 ± 42.0	191.5 ± 37.6	196.0 ± 40.4	0.015
Triglycerides level (mg/dL)	101.8 ± 54.1	123.4 ± 72.6	136.2 ± 87.8	154.0 ± 116.6	< 0.001
High-density lipoprotein cholesterol (mg/dL)	47.8 ± 12.9	46.2 ± 12.4	42.5 ± 10.0	44.9 ± 10.6	0.006
Low-density lipoprotein cholesterol (mg/dL)	108.6 ± 32.3	114.8 ± 37.0	117.1 ± 32.9	117.6 ± 33.6	0.029
Hemoglobin A1c (%)	5.5 ± 0.4	5.6 ± 0.4	5.6 ± 0.4	5.7 ± 0.4	0.001
Systolic blood pressure (mmHg)	150.5 ± 28.2	150.3 ± 28.6	150.5 ± 29.6	149.1 ± 28.4	0.723
Diastolic blood pressure (mmHg)	89.3 ± 13.6	88.0 ± 15.5	87.5 ± 16.0	89.7 ± 16.5	0.912
Initial NIHSS score, median (IQR)	3 (1–6)	2 (1–5)	3 (1–5)	3 (1–6)	0.146
TOAST classification subtype					0.953
Large artery atherosclerosis	30 (23.3)	32 (24.2)	37 (28.9)	43 (33.6)	
Data are expressed as the mean ± SD, or n (%).					
HOMA-IR, homeostasis model assessment of insulin resistance scores; NIHSS, National Institutes of Health Stroke Scale (NIHSS); IQR, interquartile range; TOAST, the Trial of Org 10172 in Acute Stroke Treatment;					

	HOMA-IR, quartiles				
Cardioembolism	40 (31.0)	23 (17.4)	18 (14.1)	20 (15.6)	
Small vessel occlusion	25 (19.4)	39 (29.5)	37 (28.9)	25 (19.5)	
Undetermined	28 (21.7)	29 (22.0)	31 (24.2)	31 (24.2)	
Others	6 (4.7)	9 (6.8)	5 (3.9)	9 (7.0)	
Early neurological deterioration	4 (3.1)	12 (9.1)	6 (4.7)	8 (6.2)	0.197
Poor neurological outcome at 3 months	30 (23.3)	29 (22)	34 (26.6)	41 (32.0)	0.254
Data are expressed as the mean ± SD, or n (%).					
HOMA-IR, homeostasis model assessment of insulin resistance scores; NIHSS, National Institutes of Health Stroke Scale (NIHSS); IQR, interquartile range; TOAST, the Trial of Org 10172 in Acute Stroke Treatment;					

Association between log HOMA-IR values and short-term prognosis after ischemic stroke

Of all the subjects, 25.9% had poor prognoses. Table 2 shows a comparison of patients according to their prognosis three months after an acute ischemic stroke. The log HOMA-IR values were higher in patients with poor prognoses ($p = 0.06$). After adjustment for age, sex, and variables with p-values < 0.1 in univariate analysis, the log HOMA-IR scores were independently associated with poor prognosis (OR = 3.877, 95% CI: 1.461–10.288, $p = 0.006$) (Table 2).

Table 2

Factors associated with poor functional outcome at 3 months after ischemic stroke.

	Good prognosis (mRS < 3) (n = 383)	Poor prognosis (mRS ≥ 3) (n = 134)	p-value	Multivariable logistic regression	
				Model 1	Model 2
Age (years)	63.2 (12.9)	71.2 (11.5)	< 0.001	< 0.001	< 0.001
Male sex	251 (65.5)	86 (64.2)	0.858	0.036	0.031
Hypertension	192 (50.1)	81 (60.4)	0.050	0.661	0.597
Previous coronary artery disease	17 (4.4)	20 (14.9)	< 0.001	0.024	0.022
Previous stroke	28 (7.3)	20 (14.9)	0.015	0.326	0.312
HOMA-IR, median (IQR)	2.26 (1.66–3.23)	2.55 (1.75–3.99)	0.019		0.089
Log HOMA-IR, mean (SD)	0.38 ± 0.26	0.45 ± 0.26	0.006	0.006	
Body mass index (kg/m^2)	24.0 ± 3.7	23.8 ± 2.9	0.527		
Fasting blood glucose (mg/dL)	104.4 ± 22.8	107.4 ± 19.0	0.144		
Total cholesterol level (mg/dL)	189.7 ± 38.5	191.4 ± 42.2	0.663		
Triglycerides level (mg/dL)	131.2 ± 89.6	121.8 ± 81.4	0.283		
High-density lipoprotein cholesterol (mg/dL)	45.6 ± 11.7	44.7 ± 11.6	0.449		
Low-density lipoprotein cholesterol (mg/dL)	113.0 ± 33.8	119.0 ± 34.6	0.080	0.001	< 0.001
Hemoglobin A1c (%)	5.6 ± 0.4	5.6 ± 0.4	0.413		
Systolic blood pressure (mmHg)	149.7 ± 29.8	151.4 ± 25.2	0.536		
Diastolic blood pressure (mmHg)	88.3 ± 15.9	89.4 ± 13.9	0.476		

Data are expressed as the mean ± SD, or n (%).

mRS, modified Rankin Scale; HOMA-IR, homeostasis model assessment of insulin resistance scores; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale (NIHSS); TOAST, the Trial of Org 10172 in Acute Stroke Treatment;

	Good prognosis (mRS < 3) (n = 383)	Poor prognosis (mRS ≥ 3) (n = 134)	p-value	Multivariable logistic regression	
				Model 1	Model 2
Initial NIHSS score, median (IQR)	4 (2–5)	6 (3–13)	< 0.001	< 0.001	< 0.001
TOAST classification subtype			< 0.001	0.010	0.010
Large artery atherosclerosis	96 (25.1)	46 (34.3)			
Cardioembolism	71 (18.5)	30 (22.4)			
Small vessel occlusion	113 (29.5)	13 (9.7)			
Undetermined	81 (21.1)	38 (28.4)			
others	22 (5.7)	7 (5.2)			
Early neurological deterioration	11 (2.9)	19 (14.2)	< 0.001	< 0.001	< 0.001
Data are expressed as the mean ± SD, or n (%).					
mRS, modified Rankin Scale; HOMA-IR, homeostasis model assessment of insulin resistance scores; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale (NIHSS); TOAST, the Trial of Org 10172 in Acute Stroke Treatment;					

Discussion

Our study showed that log HOMA-IR scores were significantly associated with the poor functional outcome of non-diabetic ischemic stroke patients. This association remained statistically significant even the age of the highest quartiles of log HOMA-IR was youngest among quartiles and the relationship was sustained after adjusting for cardiovascular risk factors and lipid profile abnormalities.

In this study, the initial stroke severity and the presence of END did not differ between the log HOMA-IR quartiles. These results indicate that the harmful effect of insulin resistance impacts the recovery phase of acute ischemic stroke and is not associated with worsening of a preexisting impairment. A study based on the Fukuoka registry in Japan also reported that HOMA-IR scores were related to poor functional outcomes.[10] There were no associations with the recurrence of stroke or mortality, which supports our hypothesis. Another study reported that the HOMA-IR index scores were associated with increased mortality, recurrent stroke, and poor outcomes.[8] The differences between the study results may be due to different study populations.

Some hypotheses may explain the association between insulin resistance and poor patient outcome after an ischemic stroke. One of them involves the concept of synaptic plasticity. Synaptic plasticity is the ability of a neuron to change the synapse in response to external stimuli and activity. In the brain, the insulin/IGF receptor signaling pathway maintains the balance between neuroprotective and neurotoxic effects.[11–13] Insulin resistance is defined as a loss of this function in insulin ligands. Subsequently, the balance is upset, causing changes in the survival of the neurons and synaptic plasticity. Likewise, the synaptic plasticity of the brain decreases in stroke patients with high insulin resistance, which interferes with its recovery from the primary insult. Second, insulin resistance in muscles may have contributed to the poor prognosis of these patients. Type 2 diabetes mellitus patients evolve whole-body insulin resistance and insulin resistance in skeletal muscles reduces glucose transport pathways, which results in excessive reactive oxygen species and mitochondrial dysfunction.[14, 15] This may interrupt recovery after an acute ischemic stroke. Third, endothelial damage might play a role. Endothelial function is related to vascular reactivity in the cerebral circulation.[16] Insulin and insulin resistance affect the vascular endothelium.[16–18] Furthermore, insulin resistance is a risk factor for atherosclerosis.[19, 20] Endothelial dysfunction, decreased vascular reactivity, and enhanced atherosclerosis might cause recurrent stroke and delayed restoration.

Our study had some strengths. First, we demonstrated that the worsening effect of insulin resistance on ischemic stroke impacted the recovery phase. This finding indicates that we should treat insulin resistance itself, apart from diabetes mellitus, especially in the subacute stage of an acute ischemic stroke. Second, unlike previous studies, we thoroughly investigated the risk factors, including laboratory and clinical factors, associated with poor prognoses. Body mass index, individual lipid levels, and blood pressure levels were collected and adjusted for in the multivariate analysis and the association between insulin resistance and poor clinical outcome remained strong. There were several limitations to this study. First, the HOMA-IR scores were only determined once, within 24 hours of admission. This might not reflect the exact status of insulin resistance during the recovery period. Second, the HOMA-IR index scores for insulin resistance mainly reflect resistance in hepatic metabolism. Third, this was a single-center data review from a comprehensive stroke center in Korea. Consequently, the results cannot be generalized to other populations and races.

Conclusions

Insulin resistance measured by the HOMA-IR index was associated with the poor functional outcome of non-diabetic stroke patients. This finding may strengthen the need for treatment of insulin resistance itself in acute ischemic stroke patients with blood glucose levels within the normal range.

Abbreviations

mRS, modified Rankin scale; HOMA-IR, homeostasis model assessment-insulin resistance; CT, computed tomography; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale, TOAST,

Trial of Org 10172 in Acute Stroke Treatment; ANOVA, analysis of variance; OR, odds ratio; CI, confidence interval

Declarations

Ethics approval and consent to participate

This study was approved by Korea University of College of Medicine Institutional Review Board. Informed consent of study participants was waived because of retrospective study design.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests

Funding

None.

Authors' contributions

YC, CKK and KO contributed to conception and design of the study, YC and CKK analyzed and interpreted the patient data. YC and CKK drafted the manuscript. MK, WKS and KO critically revised the manuscript. All authors read and approved the final manuscript.

Consent for publication

Not applicable.

References

1. Kahn SE. Clinical review 135: The importance of beta-cell failure in the development and progression of type 2 diabetes. J Clin Endocrinol Metab. 2001;86:4047-58.

2. Bergman RN, Ader M. Free fatty acids and pathogenesis of type 2 diabetes mellitus. Trends Endocrinol Metab. 2000;11:351-6.
3. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28:412-9.
4. Bas DF, Ozdemir AO, Colak E, Kebapci N. Higher Insulin Resistance Level is Associated with Worse Clinical Response in Acute Ischemic Stroke Patients Treated with Intravenous Thrombolysis. Transl Stroke Res. 2016;7:167-71.
5. Calleja AI, García-Bermejo P, Cortijo E, Bustamante R, Rojo Martínez E, González Sarmiento E, et al. Insulin Resistance Is Associated With a Poor Response to Intravenous Thrombolysis in Acute Ischemic Stroke. Diabetes Care. 2011;34:2413-7.
6. Kernan WN, Inzucchi SE, Viscoli CM, Brass LM, Bravata DM, Shulman GI, et al. Pioglitazone improves insulin sensitivity among nondiabetic patients with a recent transient ischemic attack or ischemic stroke. Stroke. 2003;34:1431-6.
7. Kernan WN, Viscoli CM, Furie KL, Young LH, Inzucchi SE, Gorman M, et al. Pioglitazone after Ischemic Stroke or Transient Ischemic Attack. N Engl J Med. 2016;374:1321-31.
8. Jing J, Pan Y, Zhao X, Zheng H, Jia Q, Mi D, et al. Insulin Resistance and Prognosis of Nondiabetic Patients With Ischemic Stroke: The ACROSS-China Study (Abnormal Glucose Regulation in Patients With Acute Stroke Across China). Stroke. 2017;48:887-93.
9. Adams HP, Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24:35-41.
10. Ago T, Matsuo R, Hata J, Wakisaka Y, Kuroda J, Kitazono T, et al. Insulin resistance and clinical outcomes after acute ischemic stroke. Neurology 2018;90:e1470-7.
11. Yamaguchi F, Itano T, Mizobuchi M, Miyamoto O, Janjua NA, Matsui H, et al. Insulin-like growth factor I (IGF-I) distribution in the tissue and extracellular compartment in different regions of rat brain. Brain Res. 1990;533:344-7.
12. Baskin DG, Figlewicz DP, Woods SC, Porte D, Jr., Dorsa DM. Insulin in the brain. Annu Rev Physiol. 1987;49:335-47.
13. Le Roith D, Hendricks SA, Lesniak MA, Rishi S, Becker KL, Havrankova J, et al. Insulin in brain and other extrapancreatic tissues of vertebrates and nonvertebrates. Adv Metab Disord. 1983;10:303-40.
14. Zierath JR, Krook A, Wallberg-Henriksson H. Insulin action and insulin resistance in human skeletal muscle. Diabetologia 2000;43:821-35.
15. Di Meo S, Iossa S, Venditti P. Skeletal muscle insulin resistance: role of mitochondria and other ROS sources. J Endocrinol. 2017;233:R15-42.
16. Prakash K, Chandran DS, Khadgawat R, Jaryal AK, Deepak KK. Correlations between endothelial function in the systemic and cerebral circulation and insulin resistance in type 2 diabetes mellitus. Diab Vasc Dis Res. 2016;13:49-55.

17. Muniyappa R, Quon MJ. Insulin action and insulin resistance in vascular endothelium. Curr Opin Clin Nutr Metab. 2007;10:523-30.
18. Hsueh WA, Law RE. Insulin signaling in the arterial wall. Am J Cardiol. 1999;84:21j-4j.
19. Sourij H, Schmoelzer I, Dittrich P, Paulweber B, Iglseder B, Wascher TC. Insulin resistance as a risk factor for carotid atherosclerosis: a comparison of the Homeostasis Model Assessment and the short insulin tolerance test. Stroke. 2008;39:1349-51.
20. Gage MC, Yuldasheva NY, Viswambharan H, Sukumar P, Cubbon RM, Galloway S, et al. Endothelium-specific insulin resistance leads to accelerated atherosclerosis in areas with disturbed flow patterns: a role for reactive oxygen species. Atherosclerosis 2013;230:131-9.

Figures

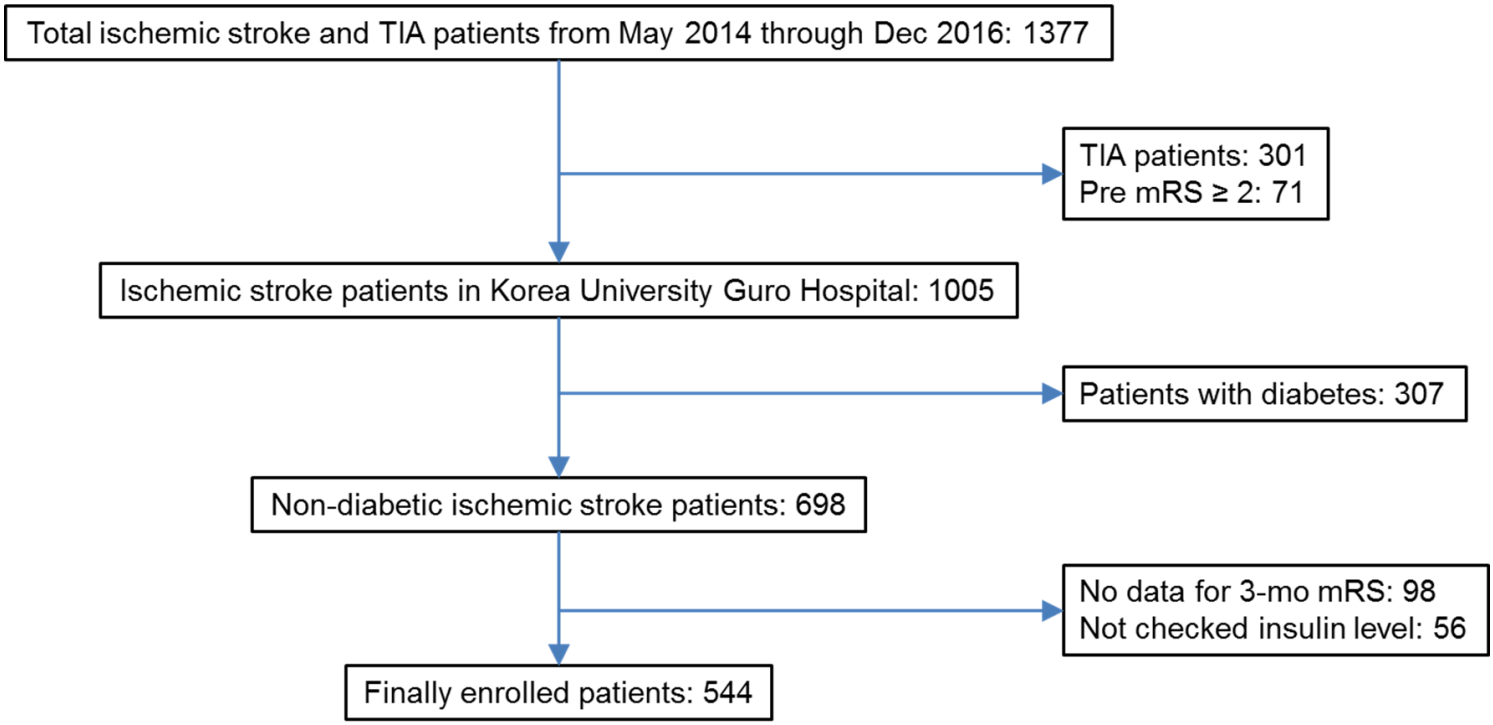

Figure 1

Flowchart of the enrolled patients in the study.

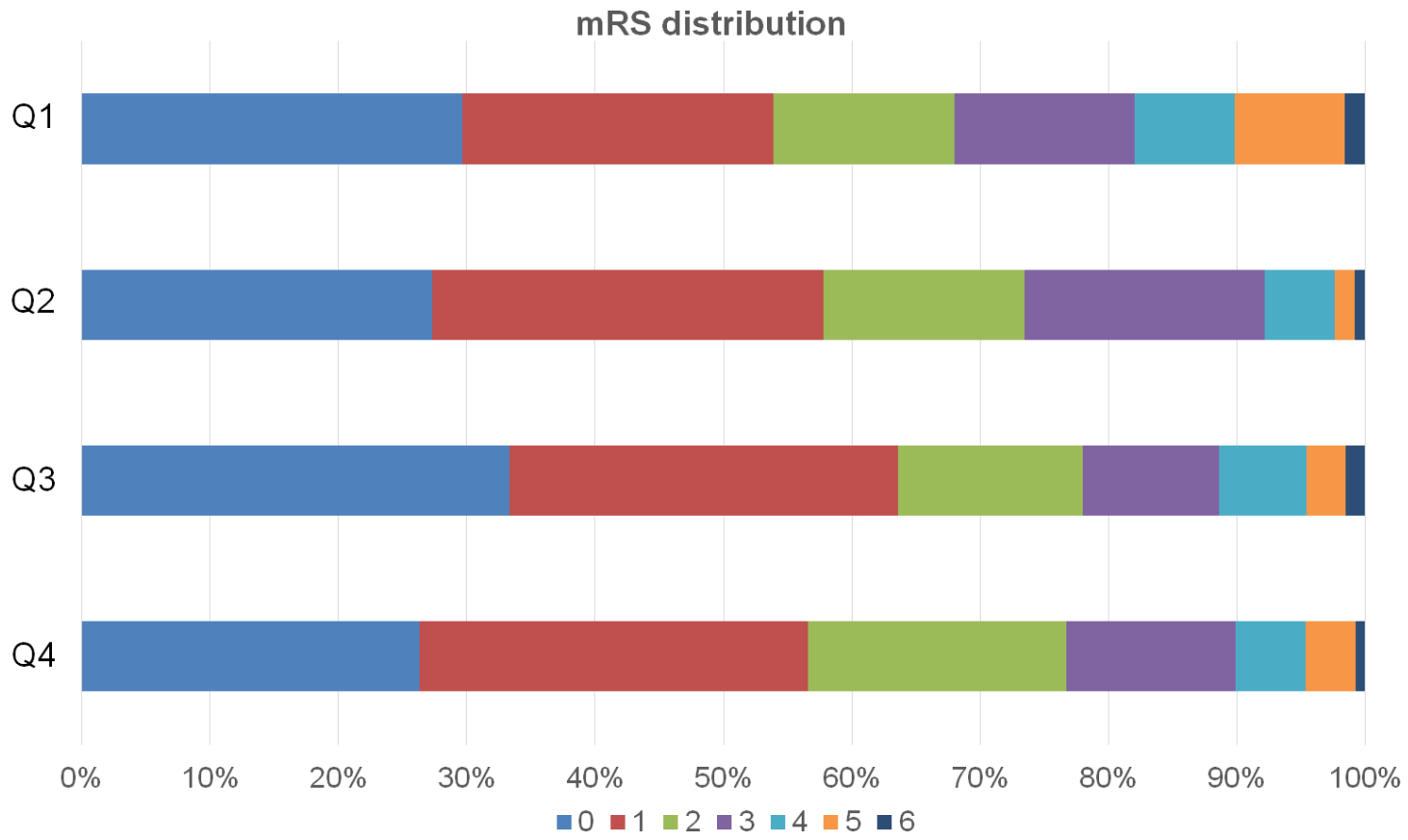

Figure 2

Modified Rankin Scale score distribution according to log homeostasis model assessment of insulin resistance score quartiles. Modified Rankin Scale score distribution showing a tendency of higher score distributions in the highest quartile of log homeostasis model assessment of insulin resistance scores.