β-Cell Function and Clinical Outcome in Nondiabetic Patients With Acute Ischemic Stroke

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β-cell function and clinical outcome in nondiabetic patients with acute ischemic stroke

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Abstract

Background and Purpose: Little is known about how β-cell dysfunction affects clinical outcome after ischemic stroke. We examined whether β-cell function is associated with clinical outcome after acute ischemic stroke, and if so, whether insulin resistance influences this association in a prospective study of patients with acute stroke.

Methods: A total of 3590 nondiabetic patients with acute ischemic stroke (mean age, 71 years) were followed up for 3 months. β-cell function was assessed using the homeostasis model assessment for β-cell function (HOMA-β). Study outcomes were poor functional outcome (modified Rankin Scale, 3-6) and stroke recurrence at 3 months after stroke onset, and neurologic deterioration (≥2-point increase in National Institutes of Health Stroke Scale score) at discharge. Logistic regression analysis was used to evaluate the association between quintile levels of serum HOMA-β and clinical outcomes.

Results: The age- and sex-adjusted odds ratios (ORs) for poor functional outcome and neurologic deterioration increased significantly with decreasing HOMA-β levels (*P* for trend <0.001 and 0.001, respectively). These associations became more prominent after adjustment for HOMA-insulin resistance (IR), and were substantially unchanged even after further adjustment for other confounders, namely, body mass index, dyslipidemia, hypertension, estimated glomerular filtration rate, stroke subtype, National Institutes of Health Stroke Scale score on admission, and reperfusion therapy (OR [95% confidence interval] for the first vs. fifth quintile of HOMA-β: 3.30 [2.15–5.08] for poor functional outcome and 10.69 [4.99–22.90] for neurologic deterioration). Such associations were not observed for stroke recurrence. In stratified analysis for the combination of HOMA-β and HOMA-IR levels, lower HOMA-β and higher HOMA-IR levels were

independently associated with increased risks of poor functional outcome and neurologic deterioration.

Conclusions: Our findings suggest that β-cell dysfunction is significantly associated with poor short-term clinical outcome independently of insulin resistance in nondiabetic patients with acute ischemic stroke.

Non-standard Abbreviations and Acronyms.

HOMA-β indicates homeostasis assessment model β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; eGFR, estimated glomerular filtration rate; and NIHSS, National Institutes of Health Stroke Scale.

Introduction

Each year, more than 14 million persons around the world experience an ischemic stroke.[1] Because the current global focus is on the improvement of prognosis in patients with ischemic stroke, the pathophysiological factors leading to unfavorable clinical outcome must be clarified. It is well known that deteriorating β-cell function and insulin resistance are the main pathophysiological factors of type 2 diabetes,[2] and the literature has reported that insulin resistance is associated with the development of cardiovascular disease not only in patients with diabetic mellitus[3,4] but also in nondiabetic individuals.[5] Previous reports by our group[6] and the ACROSS-China Study group[7] revealed an association between insulin resistance and short-term and long-term clinical outcome after acute ischemic stroke. However, there is scarce evidence on the association between β-cell function and clinical outcome after ischemic stroke. Only the study group in China showed that decreased β-cell function was linked to a higher risk of poor long-term clinical outcome in nondiabetic patients with ischemic stroke,[8,9] and no clinical study has investigated the association between β-cell function and short-term clinical outcome after ischemic stroke. It is well known that insulin secretion is affected by insulin resistance.[10] This fact suggests the possibility that insulin resistance could modify the association between β-cell function and clinical prognosis after ischemic stroke, but very few clinical studies have examined this question to date.

The aim of the present study was to clarify the association between β-cell function and short-term clinical outcome after acute ischemic stroke in nondiabetic patients, taking into account the influence of insulin resistance, in a hospital-based prospective study of stroke patients in Japan.

Methods

Data Availability

Anonymized data will be shared by request from any qualified investigator for purposes of replicating procedures and results.

Study Subjects

The Fukuoka Stroke Registry (FSR) is a database established by seven stroke centers in Fukuoka, Japan, and employed in a multicenter, hospital-based prospective study of patients with acute stroke. Details of the study design, methods of data collection, and harmonization of the FSR were described previously.[6,11,12] From April 2009 to March 2015, a total of 7634 patients with acute ischemic stroke who were hospitalized within 7 days after onset were consecutively registered in the FSR database. For the present analysis, we excluded 965 patients who were unable to live independently (modified Rankin Scale score of ≥3) before stroke onset, 2339 who had been diagnosed with diabetes according to the diagnostic criteria of the Japan Diabetes Society[13] before stroke onset or during hospitalization for stroke, and 740 for whom parameters of β-cell function and insulin resistance were not measured ≤14 days after stroke onset (Figure in the online-only Data Supplement). Finally, the remaining 3590 ischemic stroke patients were included in the present analysis.

Assessment of β-cell Function and Insulin Resistance

After admission, blood samples were collected in a fasting state to measure blood glucose and immunoreactive insulin levels on average 6.1 ± 3.4 (SD) days after stroke onset. The serum levels of glucose and insulin were determined using the hexokinase method and chemiluminescence enzyme immunoassay, respectively. β-cell function was assessed using homeostasis model assessment for β-cell function (HOMA-β) as

follows: fasting immunoreactive insulin (mU/L) × 360 / [fasting blood glucose (mg/dL) – 63], and insulin resistance was calculated using HOMA for insulin resistance (HOMA-IR) as follows: fasting blood glucose (mg/dL) × fasting immunoreactive insulin (mU/L) / 405.[14]

HOMA-β and HOMA-IR are not suitable for evaluating β-cell function and insulin resistance in hyperglycemic individuals.[14] Therefore, we excluded patients with diabetes from the study subjects. In nondiabetic individuals, β-cells compensate for the prevailing insulin resistance to maintain glucose homeostasis within a narrow range by increasing insulin secretion, and thus, a higher HOMA-β level represents intact insulin secretion and compensatory insulin secretion induced by higher insulin resistance.[10] A lower HOMA-β level indicates impaired β-cell function, and a higher HOMA-IR level indicates greater insulin resistance. To the best of our knowledge, normal ranges for HOMA-β levels have not been established in any ethnic groups, including Japanese. According to the criteria of the Japan Diabetes Society, the normal range of HOMA-IR in Japanese was defined as ≤1.6, and the high range was ≥2.5.[15]

Other Clinical Assessment

The body mass index was calculated as weight (kg) / (height [m])^2, and obesity was defined as a body mass index of ≥25.0 kg/m^2.[16] Waist circumference was measured midway between the top of the hip bone and the bottom of the ribs at the end of expiration. Dyslipidemia was determined as a serum total cholesterol ≥220 mg/dL, low-density lipoprotein cholesterol ≥140 mg/dL, or high-density lipoprotein cholesterol <40 mg/dL. Hypertension was defined as blood pressure ≥140/90 mmHg or a medical history of hypertension. Atrial fibrillation was diagnosed based on electrocardiographic findings or a medical history of atrial fibrillation. Estimated glomerular filtration rate

(eGFR) was calculated using the following equation proposed by the Japanese Society of Nephrology: eGFR (mL/min/1.73 m^2) = 194 × serum creatinine (mg/dL)$^{1.094}$ × age (year)$^{-0.287}$ × 0.739 (if female).[17] Previous stroke was defined as a history of hemorrhagic or ischemic stroke. Ischemic stroke was further classified into 4 subtypes—cardioembolic stroke, atherothrombotic infarction, lacunar infarction, and unclassified infarction—on the basis of the diagnostic criteria of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) Study.[18] Reperfusion therapy included intravenous thrombolysis with recombinant tissue plasminogen activator and endovascular therapy with intra-arterial thrombolysis or mechanical thrombectomy.

Study Outcomes

The main study outcomes were unfavorable post-stroke clinical course, including a poor functional outcome at 3 months after stroke onset and neurologic deterioration at discharge. The functional outcome was assessed using the modified Rankin Scale by stroke neurologists or trained and certified research nurses who were blinded to the patients' baseline variables, in person or through telephone assessment. Poor functional outcome was defined as a modified Rankin Scale score of 3–6. The neurologic severity was scaled by attending physicians using the National Institutes of Health Stroke Scale (NIHSS) score on admission and at discharge. Neurologic deterioration was defined as a ≥2-point increase in NIHSS score at discharge compared with that on admission.[6] We also assessed total stroke recurrence within 3 months after the onset of index stroke.

Statistical Analysis

HOMA-β levels were categorized into 5 groups according to quintiles (≤42.2, 42.3–59.9, 60.0–81.1, 81.2–115.1, and ≥115.2). The trends in mean (or median) values or

frequencies of risk factors across the HOMA-β quintiles were tested with linear or logistic regression analysis, respectively. Logistic regression analysis was also used to estimate odds ratios (ORs) with 95% confidence intervals (CIs) and to test trends in the risk of poor clinical outcomes according to HOMA-β levels. We used a 3-step approach to adjust for other variables: model 1 was adjusted for age and sex; model 2 was adjusted for the variables included in model 1 and HOMA-IR (log scale); and model 3 was adjusted for the variables included in model 2 and other confounding factors, namely, body mass index, dyslipidemia, hypertension, eGFR, stroke subtype (cardioembolic infarction vs. other subtypes of ischemic stroke), NIHSS score on admission, and reperfusion therapy. Because it is not precisely known how each of decreased β-cell function and insulin resistance independently influences the prognosis after stroke, we examined the influence of low HOMA-β and high HOMA-IR levels, both separately and together, on the risk of poor clinical outcome. We divided subjects into four groups according to the status of HOMA-β and HOMA-IR levels by dichotomizing HOMA-β levels with a median value (68.8) and HOMA-IR levels with the cutoff value for the high range (2.50) based on the criteria of the Japan Diabetes Society.[15] In this stratified analysis, the interaction of these variables was tested by adding a multiplicative interaction term in the relevant logistic model. The heterogeneity in the association between HOMA-β levels and risks of poor functional outcome and neurologic deterioration by subgroups of each risk factor was also tested by adding a multiplicative interaction term in the logistic model.

The SAS software package (University Edition; SAS Institute, Cary, NC) was used to perform all statistical analyses. Two-sided values of $p < 0.05$ were considered statistically significant in all analyses.

Ethical Considerations

The ethics committee of each hospital approved this study. Written informed consent was obtained from all study subjects.

Results

The average age of the patients was 71 ± 13 years, and 60.3% were men. Their baseline characteristics according to the HOMA-β levels are shown in Table 1. Patients with higher HOMA-β levels were less likely to be men. The mean (or median) values of HOMA-IR, body mass index, and waist circumference and the frequency of dyslipidemia increased with higher HOMA-β levels, while the mean (or median) values of age and NIHSS score on admission and the frequencies of atrial fibrillation, cardioembolic stroke, and reperfusion therapy decreased with higher HOMA-β levels.

At three months after stroke onset, 872 patients had poor functional outcome, and 217 patients experienced stroke recurrence. During hospitalization (median 18 days, range 1–111 days), 181 patients developed neurologic deterioration. Table 2 shows the ORs and 95% CIs for the development of poor clinical outcomes according to the HOMA-β levels. There were significant inverse associations between HOMA-β levels and age- and sex-adjusted risk of poor functional outcome and neurologic deterioration (*P* for trend <0.001 and 0.001, respectively, model 1). In order to exclude the influence of insulin resistance on these associations, we further adjusted for HOMA-IR levels (model 2). As a consequence, the risks of these poor outcomes increased more steeply with decreasing HOMA-β levels; the ORs of deteriorating outcomes in the first quintile rose four- to seven-fold after adjustment for HOMA-IR. These associations were substantially unchanged even after adjustment for other confounding factors (model 3). When poor functional outcome was further subdivided into functional dependency

(modified Rankin Scale score of 3–5) and all-cause death (modified Rankin Scale score of 6), these associations did not change substantially (Table I in the online-only Data Supplement). However, no significant association was found between HOMA-β levels and the risk of stroke recurrence (Table 2).

As shown in Figure, in the stratified analysis for the combination of HOMA-β and HOMA-IR levels, compared with those with high HOMA-β and low HOMA-IR levels, the multivariable-adjusted risk of poor functional outcome significantly increased in subjects with low HOMA-β and low HOMA-IR levels and subjects with high HOMA-β and high HOMA-IR levels. The subjects with low HOMA-β and high HOMA-IR levels had additively higher risk of poor functional outcome. A similar association was observed for neurologic deterioration.

Table 3 shows the results of subgroup analysis of the association between HOMA-β levels and the risk of poor functional outcome and neurologic deterioration by other risk factor levels. There was no evidence of heterogeneity between the two levels of each risk factor in either the risk of poor functional outcome or the risk of neurologic deterioration.

Discussion

The present findings showed that decreased levels of HOMA-β, a surrogate index of β-cell function, were clearly associated with short-term poor clinical outcome in nondiabetic patients with acute ischemic stroke. The associations were strongly affected by insulin resistance but were independent of it. Insufficient β-cell function and insulin resistance were additively associated with the increased risk of short-term poor clinical outcome.

Several clinical and epidemiological studies have reported an association between

β-cell function and cardiovascular disease,[19-21] but only one study group in China investigated the association of β-cell function with clinical outcome after stroke patients.[8,9] In one of their studies, β-cell dysfunction defined by HOMA-β was associated with poor functional outcome, mortality, and stroke recurrence within 1 year in nondiabetic patients with acute ischemic stroke. They also confirmed this association with β-cell function assessed by the disposition index,[9] which is considered to represent intact insulin secretion function.[22] These findings were in accordance with ours except with respect to stroke recurrence: in the present study, we did not find a clear association between β-cell function and risk of stroke recurrence within 3 months, probably due to the short follow-up period.

In our study, the association between decreased HOMA-β levels and poor clinical outcome became stronger after adjusting for HOMA-IR levels (model 2 in Table 2). As shown in Table 1, the median values of HOMA-IR increased with higher HOMA-β levels. This suggests that the index of HOMA-β reflects insulin secretory actions, including compensatory increase in insulin secretion induced by higher insulin resistance in nondiabetic individuals.[22,23] Therefore, the findings of our analysis with the adjustment for HOMA-IR levels might represent the influence of β-cell function on clinical prognosis of ischemic stroke after excluding the influence of insulin resistance. In our patients, lower HOMA-β and higher HOMA-IR levels were additively associated with higher risks of poor functional outcome and neurologic deterioration (Figure). These findings suggest that both β-cell dysfunction and insulin resistance are independent risk factors for poor clinical outcome after acute ischemic stroke in nondiabetic patients.

Although the precise mechanisms through which lower β-cell function increased the risk of worsening clinical outcome in our patients are unclear, possible explanations

for this association could be derived from the functions of insulin. In addition to a glucose-lowering effect, insulin has been shown to have a vasodilatory effect and to increase blood flow at the arterial and microcirculatory levels.[24] It has been reported that this vasodilatory effect of insulin is induced by prompt release of nitric oxide from the endothelium regardless of insulin resistance.[25,26] These findings suggest that decreased insulin secretion due to β-cell dysfunction may lead to impaired circulation in the ischemic penumbra in the acute phase and in damaged brain tissue in the subsequent phase of ischemic stroke. Several experimental and clinical studies indicated that insulin promotes wound healing by its multiple functions, such as the control of inflammation, increase in cell differentiation, and lipid and protein biosynthesis.[27] In the recovery period after stroke, insufficient insulin secretion may delay the repair of ischemic damage to brain tissue. In addition, it has been shown that decreased β-cell function is associated with reduced skeletal muscle mass, and insufficient insulin action can cause catabolism in muscles.[28,29] Therefore, lower β-cell function could aggravate weakness of muscles. Further investigations will be needed to elucidate other possible pathogenetic mechanisms underlying the association between deteriorating β-cell function and stroke prognosis.

The present study has several strengths. The number of subjects was large, and they were recruited from multiple stroke centers that treat patients with standardized criteria. In addition, possible confounding factors were extensively collected in all subjects and adjusted in the multivariate analysis.

However, some potential limitations of our study should be discussed. First, in our study, β-cell function was assessed by HOMA-β as a surrogate index, rather than by the standard test, i.e., the glucose clamp technique. We selected this index because it is not feasible to perform the glucose clamp technique in large clinical studies such as

ours, and the HOMA-β has been closely correlated with β-cell function determined by more definitive but complex tests.[30,31] Second, we did not use an index of insulin secretion adjusted for the prevailing insulin resistance, such as the disposition index, which is expressed as the product of measures of insulin secretion and sensitivity,[22] because it is considered theoretically inappropriate to estimate this index using HOMA values.[32] Instead, we accounted for the degree of insulin resistance in our evaluation of the influence of intact β-cell function by adjusting for insulin resistance as a confounding factor in the multivariable-adjusted model. Third, in nondiabetic individuals with low insulin resistance, HOMA-β, which is calculated from the basal state of insulin and blood glucose levels, might be a somewhat unreliable index of β-cell function, because β cells might secrete less insulin than their intrinsic secretion capacity.[33] This suggests that the group with low HOMA-β and low HOMA-IR levels in the Figure might have included healthy individuals with appropriately high insulin sensitivity, resulting in an underestimation of risk for poor clinical outcome. Fourth, there is a possibility that fasting blood glucose and insulin levels after stroke onset may not represent actual steady-state values before stroke onset due to the effects of stress-associated hormones and factors which are produced after ischemic stroke and disturb insulin action.[34] Fifth, the serum glucose and insulin levels were determined based on a single measurement after stroke. This may have introduced significant inter-subject variability and caused a misclassification of the HOMA-β level, which could have weakened the association found in this study, biasing the results toward the null hypothesis. Sixth, patients with disabilities were excluded from this study, limiting the generalizability of the results. Seventh, epidemiological studies have reported that insulin secretion in East Asian populations, including Japanese, is lower than in Caucasians,[35,36] and thus, the generalizability of the findings of our study should be

interpreted with caution. Further clinical and epidemiological studies in other ethnic groups will be needed to confirm our findings.

Conclusions

The present analysis clearly showed that insufficient β-cell function was associated with poor clinical outcome independently of insulin resistance in nondiabetic patients with acute ischemic stroke. Intensive research of both β-cell function and insulin resistance will contribute to our understanding of the pathophysiology of deteriorating clinical course in patients with ischemic stroke, and these clinical conditions might be new therapeutic targets for improving clinical outcome after ischemic stroke.

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Figure legends

Figure. Association of HOMA-β and HOMA-IR levels with poor functional outcome and neurologic deterioration.

The subjects were divided into four groups according to the status of HOMA-β and HOMA-IR levels by dichotomizing HOMA-β levels with a median value (68.8) and HOMA-IR levels with the cutoff value for the high range (2.50) based on the criteria of the Japan Diabetes Society.[15]

HOMA-β indicates homeostasis assessment model β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; OR, odds ratio; and CI, confidence interval.

*The ORs were adjusted for age, sex, body mass index, dyslipidemia, hypertension, eGFR, stroke subtype, National Institutes of Health Stroke Scale score on admission, and reperfusion therapy.

Table 1. Baseline characteristics of patients according to HOMA-β level

Characteristics	HOMA-β quintile					*P* for trend
	Q1 (≤42.2) n=718	Q2 (42.3-59.9) n=718	Q3 (60.0-81.1) n=718	Q4 (81.2-115.1) n=719	Q5 (≥115.2) n=717	
Age, mean (SD), y	74 (12)	73 (12)	71 (13)	69 (14)	67 (15)	<0.001
Men, n (%)	448 (62.4)	447 (62.3)	437 (60.9)	434 (60.4)	401 (55.9)	0.01
Fasting blood glucose, mean (SD), mg/dL	106.9 (18.7)	103.3 (16.7)	100.6 (16.5)	100.0 (16.5)	100.5 (20.8)	<0.001
Immunoreactive insulin, mean (SD), mU/L	3.71 (1.73)	5.72 (2.42)	7.26 (3.22)	9.90 (4.55)	19.67 (19.63)	<0.001
HOMA-IR, median (IQR)	0.9 (0.6-1.3)	1.3 (0.9-1.8)	1.5 (1.1-2.3)	2.1 (1.6-3.1)	3.2 (2.1-5.7)	<0.001
Body mass index, mean (SD), kg/m^2	20.0 (3.2)	22.1 (2.9)	22.8 (3.1)	23.4 (3.2)	24.8 (4.0)	<0.001
Obesity, n (%)	71 (9.9)	110 (15.3)	160 (22.3)	206 (28.7)	322 (44.9)	<0.001
Waist circumference, mean (SD), cm	78.0 (9.0)	81.0 (8.7)	83.0 (9.3)	84.4 (9.4)	88.0 (11.1)	<0.001
Dyslipidemia, n (%)	223 (31.7)	226 (32.4)	260 (37.7)	287 (40.7)	311 (45.0)	<0.001
Hypertension, n (%)	540 (75.2)	559 (77.9)	569 (79.3)	544 (75.7)	549 (76.6)	0.92
eGFR, mean (SD), ml/min/1.73m^2	68.8 (21.7)	68.6 (21.3)	66.9 (22.3)	69.3 (22.3)	68.8 (24.4)	0.75
Atrial fibrillation, n (%)	267 (37.2)	193 (26.9)	173 (24.1)	139 (19.3)	133 (18.6)	<0.001
Previous stroke, n (%)	85 (11.8)	93 (13.0)	99 (13.8)	93 (12.9)	75 (10.5)	0.48
Cardioembolic stroke, n (%)	240 (33.4)	181 (25.2)	157 (21.9)	122 (17.0)	121 (16.9)	<0.001
NIHSS score on admission, median (IQR)	3 (1-8)	3 (1-6)	2 (1-5)	2 (1-4)	2 (1-4)	<0.001
Reperfusion therapy, n (%)	92 (12.8)	79 (11.0)	68 (9.5)	62 (8.6)	41 (5.7)	<0.001
Intravenous thrombolysis, n (%)	86 (12.0)	76 (10.6)	65 (9.1)	59 (8.2)	41 (5.7)	<0.001
Endovascular therapy, n (%)	14 (2.0)	10 (1.4)	9 (1.3)	5 (0.7)	7 (1.0)	0.04

HOMA-β indicates homeostasis assessment model β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; IQR, interquartile range; eGFR, estimated glomerular filtration rate; and NIHSS, National Institutes of Health Stroke Scale.

Table 2. HOMA-β level and risk of worsening clinical outcomes

		Model 1		Model 2		Model 3	
	No. of events (%)	OR (95% CI)	*P*-Value	OR (95% CI)	*P*-Value	OR (95% CI)	*P*-Value
Poor functional outcome							
Q5 (≥115.2) n=717	126 (17.6)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Q4 (81.2-115.1) n=719	147 (20.5)	1.07 (0.81-1.42)	0.63	1.79 (1.32-2.43)	<0.001	1.47 (1.02-2.11)	0.04
Q3 (60.0-81.1) n=718	164 (22.8)	1.15 (0.87-1.51)	0.34	2.56 (1.86-3.52)	<0.001	1.91 (1.31-2.77)	<0.001
Q2 (42.3-59.9) n=718	172 (24.0)	1.08 (0.81-1.42)	0.61	2.93 (2.10-4.08)	<0.001	1.67 (1.12-2.49)	0.01
Q1 (≤42.2) n=718	263 (36.6)	1.85 (1.42-2.42)	<0.001	7.56 (5.27-10.83)	<0.001	3.30 (2.15-5.08)	<0.001
P for trend		<0.001		<0.001		<0.001	
Neurologic deterioration							
Q5 (≥115.2) n=717	20 (2.8)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Q4 (81.2-115.1) n=719	27 (3.8)	1.21 (0.68-2.21)	0.51	2.66 (1.40-5.05)	0.003	2.25 (1.16-4.39)	0.02
Q3 (60.0-81.1) n=718	35 (4.9)	1.50 (0.85-2.65)	0.16	4.75 (2.48-9.11)	<0.001	3.91 (1.98-7.68)	<0.001
Q2 (42.3-59.9) n=718	37 (5.2)	1.45 (0.83-2.55)	0.19	6.03 (3.07-11.83)	<0.001	4.52 (2.22-9.20)	<0.001
Q1 (≤42.2) n=718	62 (8.6)	2.27 (1.34-3.85)	0.002	15.93 (7.83-32.40)	<0.001	10.69 (4.99-22.90)	<0.001
P for trend		0.001		<0.001		<0.001	
Stroke recurrence							
Q5 (≥115.2) n=717	41 (5.7)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Q4 (81.2-115.1) n=719	37 (5.2)	0.88 (0.56-1.39)	0.57	0.96 (0.59-1.54)	0.85	0.94 (0.58-1.53)	0.80
Q3 (60.0-81.1) n=718	42 (5.9)	0.99 (0.64-1.55)	0.98	1.14 (0.70-1.85)	0.60	1.09 (0.66-1.80)	0.75
Q2 (42.3-59.9) n=718	44 (6.1)	1.03 (0.66-1.61)	0.90	1.22 (0.73-2.02)	0.44	1.22 (0.72-2.06)	0.47
Q1 (≤42.2) n=718	53 (7.4)	1.24 (0.81-1.91)	0.33	1.57 (0.91-2.72)	0.11	1.51 (0.84-2.71)	0.17
P for trend		0.22		0.06		0.10	

HOMA-β indicates homeostasis assessment model β-cell function; OR, odds ratio; CI, confidence interval; and HOMA-IR, homeostasis model assessment of insulin resistance.

Model 1 was adjusted for age and sex.
Model 2 was adjusted for the variables included in model 1 and HOMA-IR (log scale).
Model 3 was adjusted for the variables included in model 2 and body mass index, dyslipidemia, hypertension, eGFR, stroke subtype, National Institutes of Health Stroke Scale score on admission, and reperfusion therapy.

Table 3. Multivariable-adjusted risk of poor functional outcome and neurologic deterioration for low HOMA-β level (vs. high level) by risk factor subgroup

Risk factor level	No. of subjects	Poor functional outcome				Neurologic deterioration			
		No. of events	OR	(95% CI)	*P*-heter.	No. of events	OR	(95% CI)	*P*-heter.
HOMA-IR									
(<2.50)	2580	531	1.42	(1.07-1.88)	0.73	99	2.68	(1.42-5.04)	0.43
(≥2.50)	1010	341	1.83	(1.14-2.93)		82	2.18	(1.27-3.76)	
Age									
<75 y	2025	246	1.59	(1.07-2.37)	0.82	58	2.32	(1.18-4.56)	0.17
≥75 y	1565	626	1.57	(1.15-2.13)		123	2.93	(1.74-4.95)	
Sex									
Men	2167	420	1.27	(0.92-1.76)	0.71	97	2.41	(1.40-4.13)	0.35
Women	1423	452	1.91	(1.29-2.81)		84	2.96	(1.57-5.59)	
Body mass index									
<25.0	2721	719	1.60	(1.21-2.10)	0.18	142	3.31	(2.04-5.36)	0.06
≥25.0	869	153	1.63	(0.91-2.93)		39	2.47	(0.99-6.11)	
Dyslipidemia									
No	2179	534	1.29	(0.95-1.76)	0.18	107	3.08	(1.77-5.34)	0.25
Yes	1307	307	2.10	(1.39-3.20)		69	2.35	(1.24-4.42)	
Hypertension									
No	829	184	0.91	(0.54-1.54)	0.07	28	3.23	(1.04-10.10)	0.53
Yes	2761	688	1.77	(1.33-2.34)		153	2.61	(1.68-4.07)	
eGFR									
≥60	2397	458	1.48	(1.07-2.04)	0.94	98	2.83	(1.62-4.93)	0.85
<60	1193	414	1.56	(1.06-2.29)		83	2.48	(1.34-4.59)	
Stroke subtype									
Non cardioembolic	2769	538	1.46	(1.10-1.96)	0.80	120	2.56	(1.55-4.22)	0.18
Cardioembolic	821	334	1.70	(1.05-2.75)		61	2.68	(1.29-5.56)	
NIHSS on admission									
≤4	2561	286	1.14	(0.83-1.58)	0.13	71	2.18	(1.19-4.00)	0.06
>4	1029	586	2.56	(1.78-3.70)		110	3.50	(1.96-6.24)	
Reperfusion therapy									
No	3248	727	1.41	(1.08-1.84)	0.54	156	2.45	(1.58-3.80)	0.50
Yes	342	145	2.52	(1.26-5.05)		25	4.55	(1.34-15.46)	

HOMA-β levels were dichotomized with a median value (68.8).
OR indicates odds ratio; CI, confidence interval; *P*-heter., *P* for heterogeneity; HOMA-β, homeostasis assessment model β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance;

eGFR, estimated glomerular filtration rate; and NIHSS, National Institutes of Health Stroke Scale.
The multivariable model was adjusted for HOMA-IR (log scale), age, sex, body mass index, dyslipidemia, hypertension, eGFR, stroke subtype, National Institutes of Health Stroke Scale score on admission, and reperfusion therapy.
The variable relevant to the subgroup was excluded from each model.

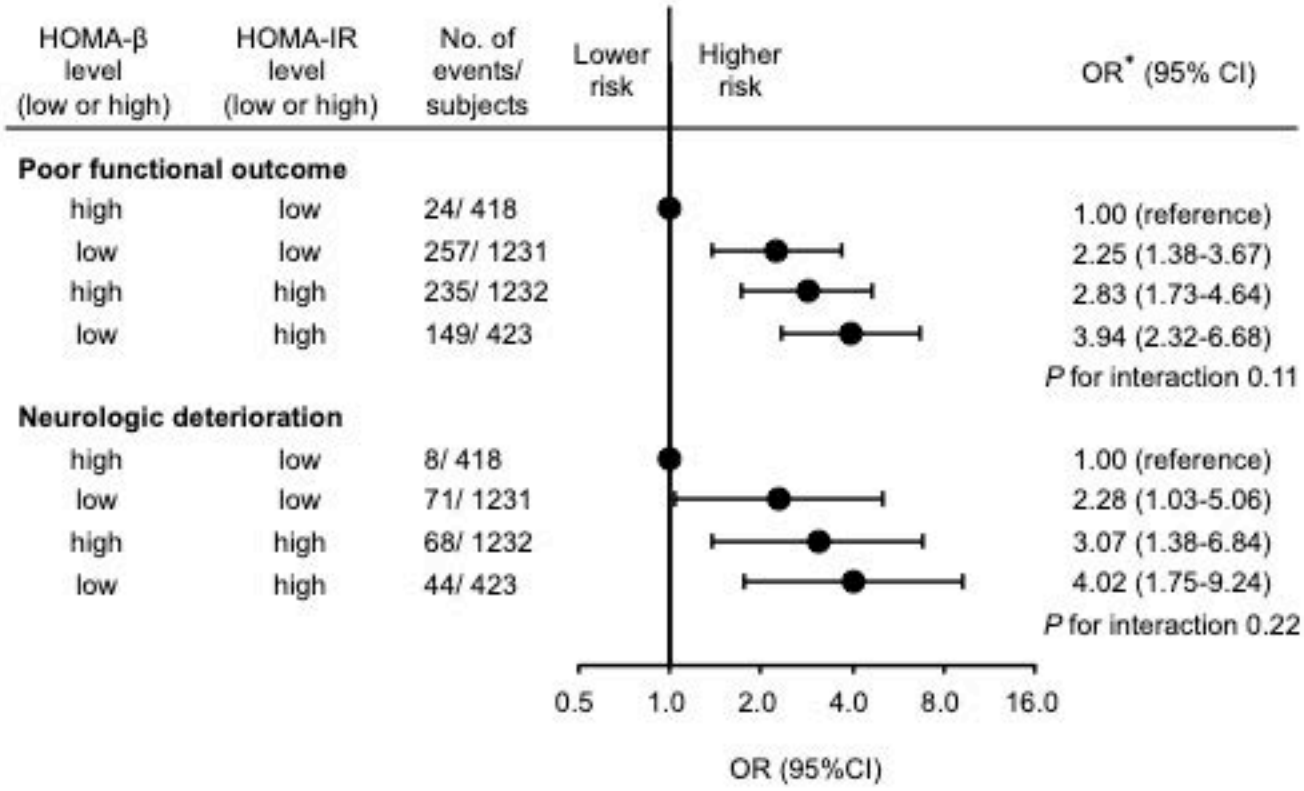

Figure. Association of HOMA-β and HOMA-IR with poor functional outcome and neurologic deterioration