C-R Relationship between Fasting Plasma Glucose and Unfavorable Outcomes in Patients of Ischemic Stroke without Diabetes

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Background: Limited data are available on the impact of fasting plasma glucose (FPG) on outcomes in nondiabetic acute ischemic stroke patients. *Methods:* The prospective, multi-center, and observational study was performed at 8 hospitals in the Liaoning Province between 2015-2016, sought to elucidate the relationship between FPG and the 6-month functional outcomes in nondiabetic acute ischemic stroke patients. The primary effect measure was the adjusted odds ratio for a shift in the direction of unfavorable outcome on the modified Rankin Scale (mRS) score at 6 months, estimated with an ordinal logistic regression, and adjusted for common prognostic factors. Finally, we employed a restricted cubic spline function of linear model to characterize concentration-response (C-R) relationships between FPG and outcomes. *Results:* A total of 1260 consecutive patients were enrolled, 48.9% of patients had FPG levels >6.1 mmol/L. A total of 282 (22.4%) patients achieved an unfavorable neurologic outcome. Patients achieving an unfavorable neurologic outcome had significantly higher levels of FPG than those achieving a favorable neurologic outcome (6.47 mmol/L versus 7.02 mmol/L). FPG was significantly related to an unfavorable neurologic outcome in nondiabetic acute ischemic stroke patients. The C-R curve showed a nonlinear relation between FPG and 6-month mRS with the nadir at 5.9 mmol/L. Moreover, the likelihood of unfavorable outcome increased by 8.5% for each 1 mmol/L increase in FPG. *Conclusions:* Early identification and prompt hyperglycemia management should be considered to improve the functional outcomes during the early poststroke stage.

Key Words: Ischemic stroke—fasting plasma glucose—diabetes—restricted cubic spline

Background

Ischemic stroke remains one of the most common causes of death and long-term disability worldwide.[1] Poststroke hyperglycemia is defined as a blood glucose level of 6.1-8.0 mmol/L, even 72 hours after the episode.[2] Poststroke hyperglycemia is potentially induced by underlying stress responses and other factors, such as subclinical diabetes and nonspecific reactions, and it is highly prevalent in patients suffering ischemic stroke, even in those without prediagnosed diabetes.[3,4] There is increasing evidence indicating that hyperglycemia aggravates neurological deterioration, resulting in enlarged infarct size, poor functional recovery, and increased mortality rates.[5-8]

As a treatable condition, there are no precise guidelines regarding the management of hyperglycemia after stroke

Abbreviation: FPG, Fasting plasma glucose; RCS, Restricted cubic spline

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currently, although identification and prompt management of hyperglycemia in the early stage of ischemic stroke is emphasized.[2] A meta-analysis reported the 30-day mortality increased to threefold in nondiabetic hyperglycemic patients compared to less than a 2-fold increase in diabetic patients.[9] However, the relatively small sample size of most studies and incidences of hemorrhagic stroke in several studies were concerning.[10-14] Moreover, previous studies reported a lack of association between hyperglycemia on admission and clinical outcomes in acute stroke patients.[15] In addition, some clinical trials failed to demonstrate the benefit of tight glycemic control after ischemic stroke.[16] Therefore, reliable and precise observational data on the relationship between glucose and ischemic stroke are still needed, especially in nondiabetic individuals.

Fasting plasma glucose (FPG) has long been considered to be a more reliable screening tool for glucose status than random glucose levels, and it could also be a stronger predictor of outcomes compared with random glucose level.[17,18] However, the concentration-response (C-R) relationship between FPG and outcomes of nondiabetic ischemic stroke remains unclear. Therefore, we generated the hypothesis that FPG levels in the early poststroke stage correlated with functional outcomes in patients of nondiabetic ischemic stroke. To test this hypothesis, we sought to elucidate the detailed relationship between FPG within 24 hours after admission and the 6-month functional outcomes in the case of nondiabetic acute ischemic stroke in the prospective study.

Methods

Patient Selection

The prospective, multi-center and observational study was performed at 8 hospitals in Dandong, Anshan, Panjin, and Liaoyang in the Liaoning Province between January 2015 and August 2016. We enrolled consecutive patients who were admitted to the hospital within 24 hours of stroke onset, and the clinical and radiological records were obtained. Ischemic stroke was diagnosed by a neurologist according to the World Health Organization recommendations and confirmed with computed tomography and/or magnetic resonance imaging,[19] it was further categorized as first-ever stroke and recurrent stroke for subsequent analysis. Recurrent stroke was defined if a period of neurological stability of ≥24 hours was demonstrated between the index stroke and the new neurological deficit, after excluding other potential causes of neurological deterioration.[20] The exclusion criteria included (1) pre-existing modified Rankin Scale (mRS) score of >2, (2) previous stroke that could hamper interpretation of clinical or radiological data, (3) other intracranial pathologies such as infection or tumor, and (4) neurological or psychiatric disease. The study protocol was approved by the institutional review board of Liaoning Provincial Center for Disease Control and Prevention, and written informed consent was obtained from all participants. If a candidate was unable to obtain informed consent because of disability, written informed consent was obtained from the appropriate legal proxy.

Clinical evaluation

Clinical information was collected and recorded carefully. Baseline evaluations were performed on admission. Demographic data, including age, sex, current smoking (consumption of ≥1 cigarette/day) and current drinking (any dose of alcohol ≥ 1time per week),[21] medical history, and comorbidities such as hypertension, diabetes, dyslipidemia, and atrial fibrillation were recorded. FPG levels were determined using the glucose oxidase method within 24 hours after admission. Diabetes mellitus was diagnosed using the recommendation of 1999 World Health Organization. mRS scores were obtained at 6-month poststroke onset by a neurologist who was blinded to the glucose results at admission (baseline). A favorable neurologic outcome was defined as an mRS score between 0 and 2, while unfavorable neurologic outcome was considered to be an mRS score between 3 and 6 at 6 months.[22]

Statistical Analysis

Statistical analyses were performed using the SPSS 17.0 software (SPSS, Inc., Chicago, IL). Descriptive data were summarized as the percentage frequency for categorical variables and as the mean ± SD for continuous variables. Continuous variables between 2 groups were analyzed with the unpaired Student *t*-test or Mann-Whitney test, and categorical data were analyzed using the Fisher exact test or chi-squared test, as appropriate. The multivariate logistic regression was performed for assessing independence associated with 6-month functional outcomes. A 2-tailed $P < .05$ was considered statistically significant.

C-R relationship was analyzed using the SAS 9.1 software (SAS, Institute, Cary, NC). We employed the restricted cubic spline function of linear model to characterize C-R relationships between FPG and outcomes. The SAS macro displays the C-R association (with a 95% confidence interval [CI]) between the principal continuous exposure of interest and the outcome. We chose FPG levels that were encoded using an restricted cubic spline function with 3 knots, located at the fifth, 50th, 95th percentiles, as previously recommended.[23]

Results

Patient Demographic and Baseline Characteristics

The study flowchart is shown in Figure 1. A total of 3086 patients with acute ischemic or hemorrhagic stroke presented to the hospital within 24 hours from the onset of stroke symptoms. A total of 1826 patients were excluded because of declined to consent, hemorrhagic

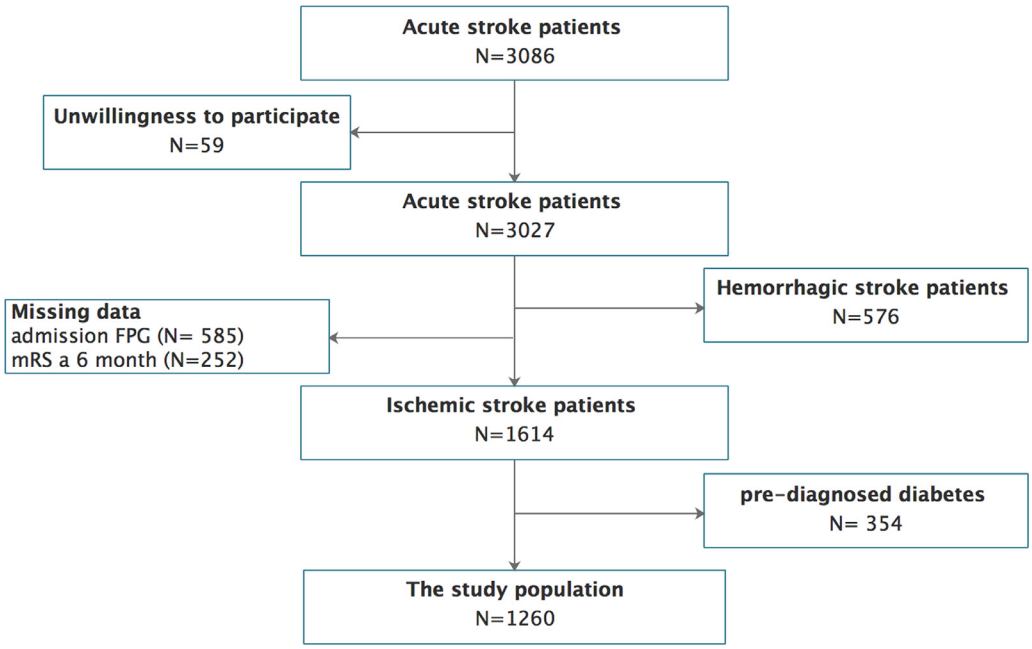

Figure 1. *Flow chart of patient selection.*

stroke, missing data including FPG and 6-month mRS, or prediagnosed diabetes. Of 1260 qualified stroke patients, 62.1% (n = 783) were first-ever stroke while 37.9% (n = 477) were recurrent stroke. Patients demographic and baseline characteristics are shown in Table 1. The median age was 69.18 years (SD: 11.12), and 576 (45.7%) were women. Figure 2 depicted the distribution of mean FPG in the whole study cohort, first-ever stroke patients, and recurrent patients. Mean FPG of the whole study population was 6.60 mmol/L (SD: 2.42); 690 patients (54.8%) had FPG levels <6.1 mmol/L, 250 patients (19.8%) had FPG levels between 6.1 mmol/L and 6.9 mmol/L, and 320 patients had FPG levels at or above 7.0 mmol/L (25.4%). The FPG levels in recurrent stroke group was slightly increased but did not reach statistical significance (6.67 ± 2.75 versus 6.55 ± 2.20, $P > 0.05$).

Risk Factors of Unfavorable Neurologic Outcome

The mean mRS score of the overall participants was 1.42 (SD 1.77, Fig 2), and the mRS score in recurrent stroke groups was higher than that in first-ever stroke group (1.29 ± 1.80 versus 1.64 ± 1.72, $P < 0.05$). The distribution of patients with scores between 0 and 6 were described in Figure 3. A total of 978 (77.6%) patients achieved a favorable neurologic outcome based on the 6-month mRS scores, while 282 (22.4%) achieved an unfavorable neurologic outcome. Patients achieving an unfavorable

Table 1. *Characteristic of patients*

	Total (N = 1260)	Unfavorable outcomes (N = 282)	Favorable outcomes (N = 978)
Female (N%)	576(45.7)	116(41.1)	460(47.0)
Age (y)	69.18 ± 11.12	73.56 ± 11.19	67.92 ± 10.78*
First-ever stroke	783(62.1)	151(19.3)	632(80.7)*
Recurrent stroke (N%)	477(37.9)	131(46.5)	346(35.4)*
Current smoking	199(25.4)	33(21.9)	166(26.3)
Current drinking	104(13.3)	17(11.3)	87(13.8)
History of TIA (N%)	286(22.7)	87(30.9)	199(20.3)*
History of hypertension (N%)	730(57.9)	155(55.0)	575(58.8)
History of myocardial infarction (N%)	25(2.0)	6(2.1)	19(1.9)
History of atrial fibrillation (N%)	26(2.1)	8(2.8)	18(1.8)
Fasting plasma glucose, mmol/L	6.60 ± 2.42	7.02 ± 3.08	6.47 ± 2.18*
Antihypertensive treatment (N, %)	815 (64.7)	147(52.3)	668(68.3)*
Lipid-lowering drugs (N%)	218 (17.3)	38(13.6)	180 (18.4)*

*$P < 0.001$.

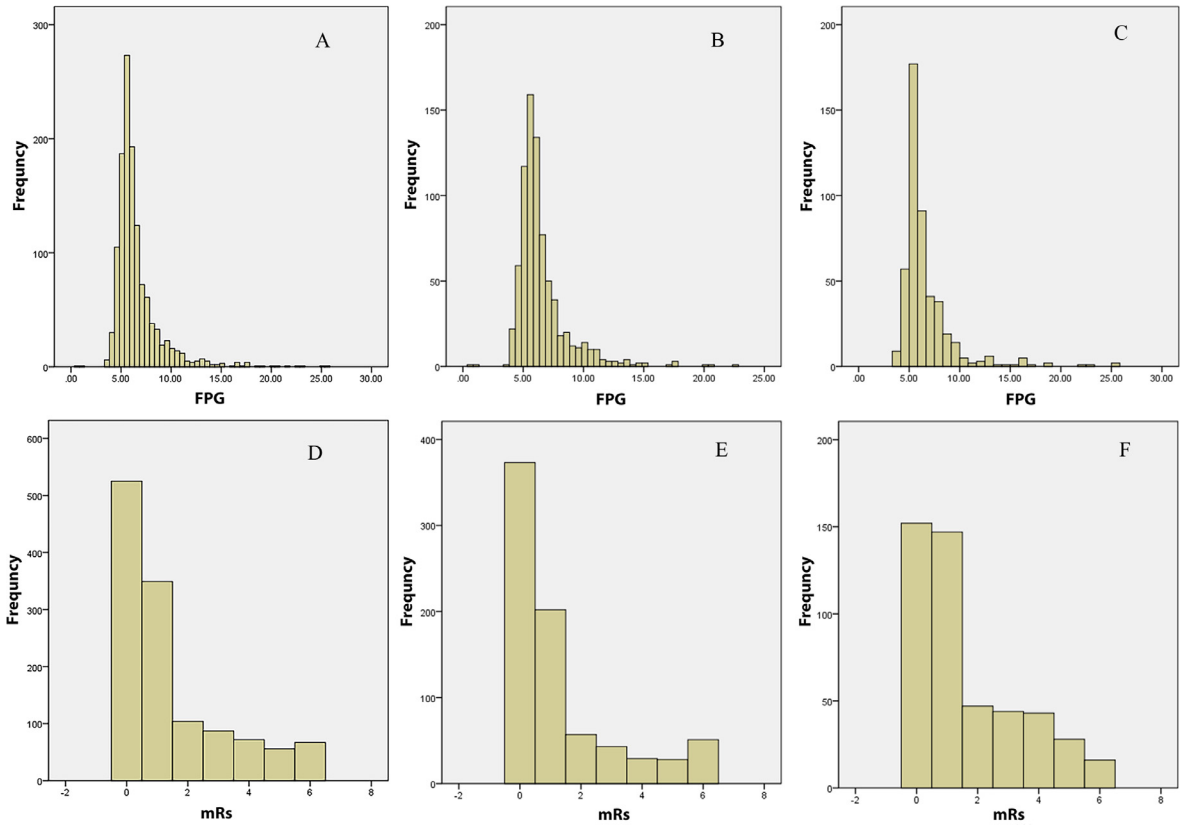

Figure 2. *Distribution of FPG levels in the overall study population (A), first-ever stroke patients (B) and recurrent stroke patients (C), and distribution of the mRS in the overall study population (D), first-ever stroke patients (E) and recurrent stroke patients (F) in 6-month. Abbreviation: FPG, fasting plasma glucose; mRs, modified Rankin scale. (Color version of figure is available online.)*

neurologic outcome had significantly higher FPG than those achieving a favorable neurologic outcome (6.47 mmol/L versus 7.02 mmol/L). By contrast, patients achieving an unfavorable neurologic outcome were older (73.56 years versus 67.92 years) and had a higher prevalence of pre-existing stroke (46.5% versus 35.4%) and transit ischemic attack (TIA) (30.9% versus 20.3%).

A multivariate logistic regression showed that FPG, age, history of TIA, hypertension, myocardial infarction, atrial fibrillation, and previous stroke were related to an unfavorable neurologic outcome, as shown in Table 2. Patients with higher FPG levels (7.0 mmol/L and above) were more likely to have unfavorable outcomes than those with normal glucose metabolism (6.0 mmol/L and below) at 6-month follow-up (aOR 1.51; 95% CI: 1.11-2.13).

C-R Relationship Between FPG and Unfavorable Neurologic Outcome

We found a nonlinear relation between the FPG (mmol/L) and 6-month mRS with the nadir at 5.9 mmol/L, as shown in Figure 4. In 657 patients (52%) with FPG $\geq$ 5.9 mmol/L, higher FPG was associated with an unfavorable neurologic outcome (1 mmol/L higher FPG; adjusted odds ratio [aOR] = 1.09 [95% CI: 1.03-1.15]). In these patients, the likelihood of an unfavorable outcome increased by 8.5% for each 1 mmol/L increase in FPG. The curves in first-ever stroke and recurrent stroke were similar with the whole study cohort.

Discussion

The major findings of the present study were as follows: (1) FPG > 6.1 mmol/L was found in 48.9% patients; and (2) higher FPG was associated with an unfavorable neurologic functional outcome at 6-months. (3) The C-R curve showed the nonlinear relationship between FPG and outcome with a nadir of 5.9 mmol/L. (4) The likelihood of an unfavorable outcome increased by 8.5% for each 1 mmol/L increase in FPG.

Hyperglycemia has been considered to be an independent predictor of larger infarct size, poor outcomes, and a higher risk of mortality in acute ischemic stroke patients,[24] as stress resulting from stroke symptom severity and large infarct size leads to high levels of cortisol and norepinephrine.[25] As a manifestation of relative insulin deficiency, hyperglycemia in the acute stroke phase is related to increased lipolysis.[24,26] Therefore, those patients tend to have hyperglycemia in the acute phase regardless of the presence of diabetes.[27]

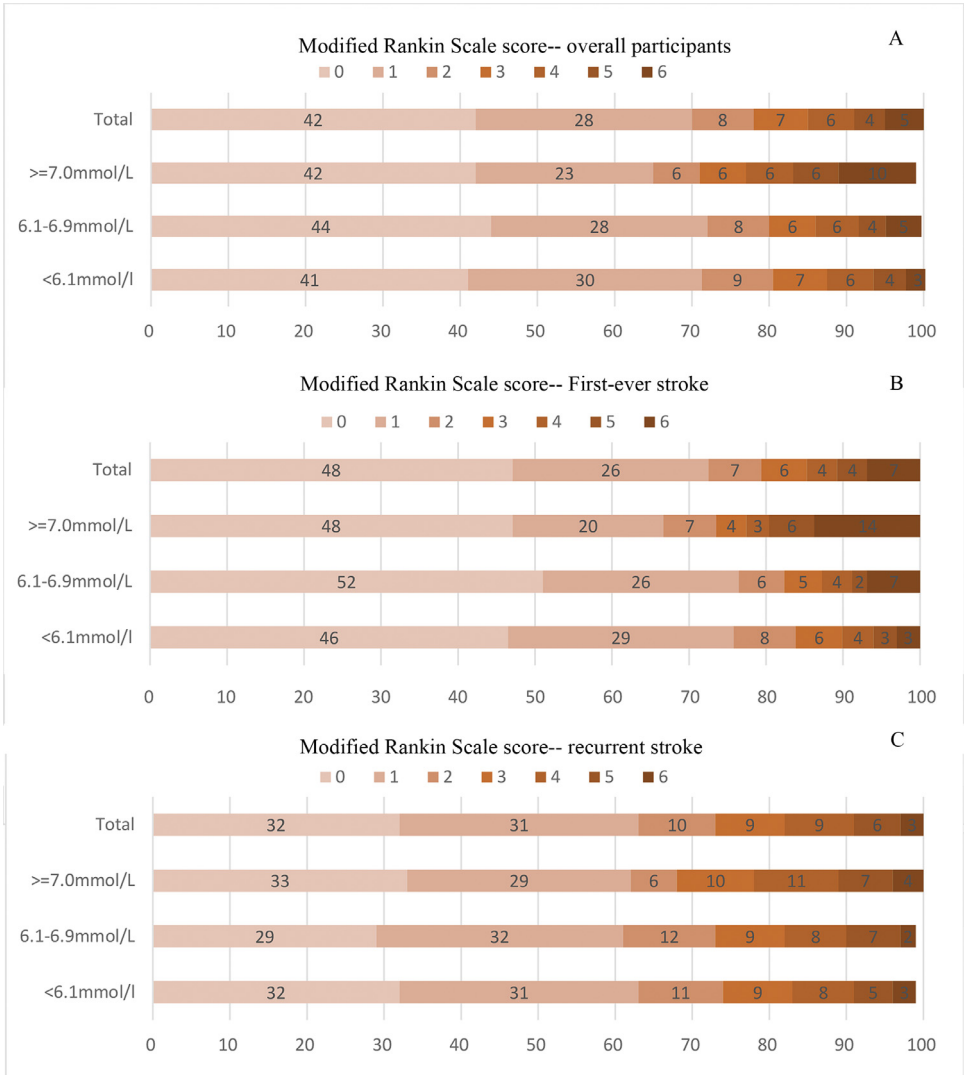

Figure 3. *The distribution of patients with mRS scores between 0 and 6 in different levels of FPG, (A) study population; (B) first-ever stroke patients and (C) recurrent stroke patients. Abbreviation: FPG, fasting plasma glucose; mRs, modified Rankin scale. (Color version of figure is available online.)*

A previous study reported that hyperglycemia is common in patients with prediagnosed diabetes.[2] The association between hyperglycemia on admission and poor outcomes in those patients is well-established. However, up to 30%-50% patients without a history of diabetes exhibited hyperglycemia after stroke. In the present study, FPG > 6.1 mmol/L was found in 48.9% nondiabetic acute ischemic stroke patients, coinciding with a previous study that demonstrated that about half of all stroke patients exhibit hyperglycemia during the first day.[2]

The FPG test requires fasting for 8 hours at least. FPG has been widely used to assess the glucose status of patients both in clinics and hospitals because of its low-cost, simplicity of use, and ease of interpretation. Additionally, it might provide a better representation of impaired glucose metabolism than glucose level on admission.[28] In the present study, we used FPG during 24 hours after admission to assess the glucose status in patients with ischemic stroke, which might be more accurate than random or admission glucose levels.

However, few data are available on the association of FPG and acute ischemic stroke patients without prediagnosed diabetes. In the present study, we found that elevated FPG was a strong predictor for neurologic functional outcome at 6-months follow-up, indicating that elevated FPG could be better at predicting unfavorable outcomes in patients without diabetes, further confirming the observations from previous study.[29]

Hyperglycemia may inhibit plasma fibrinolysis and increase the production of plasminogen activator inhibitor-1 leading to inhibitory effects on intravenous thrombolysis. Moreover, high glucose levels can impair cerebrovascular reactivity in the microvasculature, subsequently disturbing reperfusion after recanalization.[30] Furthermore, hyperglycemia may alter blood-barrier permeability and lead to blood-barrier disruption, further

Table 2. *Association of fasting glucose on admission with unfavorable outcomes*

	All participants				First ever strokes				Recurrent strokes			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	OR	95% CI	aOR	95% CI	OR	95% CI	aOR	95% CI	OR	95% CI	aOR	95% CI
Sex												
Female	1.00	-	-	-	1.00	-	1.00	-	1.00	-	-	-
Male	1.27	0.97-1.66	-	-	1.39	0.97-1.99	1.50	1.02-2.20	1.06	0.71-1.60	-	-
Age group (y)												
<60	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
60-	1.39	0.88-2.20	1.27	0.79-2.03	0.81	0.43-1.53	0.83	0.43-1.57	2.19	1.06-4.53	2.36	1.10-5.05
70-	2.07	1.33-3.24	1.93	1.22-3.05	2.20	1.25-3.85	2.31	1.30-4.10	1.84	0.87-3.87	2.19	1.00-4.80
80-	4.45	2.82-7.00	4.12	2.59-6.56	4.04	2.28-7.13	4.04	2.26-7.22	5.06	2.37-10.78	6.20	2.78-13.83
Glucose (mmol/L)												
<6.1	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	-	-
6.1-	1.03	0.72-1.48	1.03	0.71-1.50	1.05	0.65-1.69	1.03	0.63-1.70	1.08	0.62-1.87	-	-
7.0-	1.54	1.13-2.09	1.54	1.11-2.13	1.72	1.15-2.59	1.79	1.16-2.76	1.35	0.84-2.15	-	-
History of TIA												
No	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
Yes	1.75	1.30-2.35	1.82	1.30-2.55	2.17	1.30-3.62	2.06	1.19-3.56	1.23	0.82-1.84	1.52	0.98-2.35
History of hypertension												
No	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-
Yes	0.86	0.66-1.12	-	-	0.82	0.57-1.16	-	-	0.80	0.53-1.22	-	-
History of myocardial infarction												
No	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-
Yes	1.10	0.43-2.77	-	-	1.26	0.34-4.64	-	-	0.88	0.23-3.29	-	-
History of atrial fibrillation												
No	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-
Yes	1.56	0.67-3.62	-	-	1.69	0.52-5.47	-	-	1.33	0.39-4.50	-	-
Recurrent stroke												
No	1.00	-	1.00	-	-	-	-	-	-	-	-	-
Yes	1.59	1.21-2.07	1.31	0.97-1.77	-	-	-	-	-	-	-	-

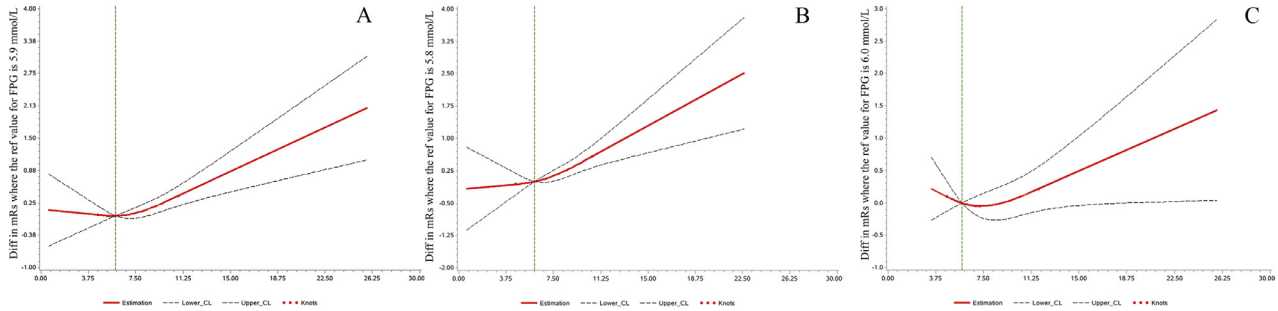

Figure 4. *Concentration-response association between the FPG (mmol/L) and 6-month Rankin score (mRS) in the overall study population (A), first-ever stroke patients (B) and recurrent stroke patients (C). Glucose values were encoded using a restrictive cubic spline(RCS) function of linear model with 3 knots located at the 5th, 50th, and 95th percentiles of FPG distribution. Y-axis values show the change of mRS between the indicated FPG values and the reference value. The dashed lines are the 95% confidence intervals. Abbreviation: FPG, fasting plasma glucose. (Color version of figure is available online.)*

aggravating brain edema formation and leading to hemorrhagic transformation.[17,30] A relatively minor increase in glucose level might produce an obvious effect on patients without diabetes as previously reported. However, whether correction of hyperglycemia during acute stroke might be beneficial for patients without diabetes remains unclear.

Previous study failed to show significant clinical benefit of hyperglycemia correction with intravenous insulin in patients with acute stroke.[31] However, in that study, only 17% were diabetic patients and 12% were intracerebral hemorrhage. Compare to the mean glucose level in the control group (6.8 mmol/L between 8 and 24 hours of treatment with saline), the difference between intervention group and control group was only 0.57 mmol/L.[31] On the other hand, greater reductions of glucose levels showed improved long-term prognosis in patients with acute myocardial infarction, although not comparable to those with acute stroke. The DIGAMI trial reported that a 2.2 mmol/L reduction of glucose level led to clinical benefits,[32] while a smaller reduction (0.9 mmol/L) did not improve clinical outcomes.[33] In the present study, we found a nonlinear relation between the FPG (mmol/L) and 6-month mRS with the nadir at 5.9 mmol/L, suggesting that a greater reduction in glucose levels might be required to improve clinical outcomes. However, hypoglycemia, resulting from a greater reduction in glucose levels in nondiabetic patients, is likely much more challenging and risky. Therefore, further dedication and prospective clinical trials are still required on the management of hyperglycemia in those patients.

This study also had some limitations. First, FPG was collected within 24 hours after admission, we did not use the glucose levels on other time course. In the present study, we focused on the acute glucose change after stroke, since early identification and management of hyperglycemia were recommended. Second, we didn't obtain the mRS score after admission, lack of any measure of stroke severity was a significant flow. However, current guideline recommended early identification and prompt management of hyperglycemia after stroke no matter the severity of stroke.[34] In the present study, we aimed to delineate the relationship between FPG and the functional outcome in nondiabetic acute ischemic stroke patients, which may lead to specific therapeutic strategies. Lastly, the diagnosis of nondiabetes was made by double-checking of the patient's history, symptoms, and manifestations, those efforts could greatly minimize the possibility of unrecognized diabetes. Therefore, we considered our results represented an accurate and precise assessment with a relatively large population with dedicated analysis.

Conclusions

The present study has important clinical implications. We found that higher FPG levels within 24 hours after admission are significantly related to higher rates of unfavorable neurologic outcomes in nondiabetic patients with acute ischemic stroke. The C-R curve showed a nonlinear relationship between FPG and an unfavorable outcome with a nadir of 5.9 mmol/L. In addition, the likelihood of an unfavorable outcome increased by 8.5% for each 1 mmol/L increase in FPG in those patients, indicating that early tight glucose lowering therapy may improve functional outcomes in nondiabetic acute ischemic stroke patients.

Ethics approval and consent to participate

The study protocol was approved by the institutional review board of Liaoning Provincial Center for Disease Control and Prevention, and written informed consents were obtained from all participants.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during this study are available from the corresponding author on reasonable request.

Competing interests

The authors declared they have no competing interests.

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Authors' contributions

Y.S. and L.X. was responsible for the concept and design of the study. L.X. was responsible for the study coordination and conduct. L.X. and S.L. contributed to the drafting of the manuscript. Y.T., H.Y. and L.J. analyzed the data. K.C., F.Y., Y.L. and J.L. interpreted the data. All authors read and approved the final manuscript.

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