Hyperglycemia is associated with poor in-hospital outcome in elderly patients with acute ischemic stroke

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Abstract
Fasting hyperglycemia is associated with poor neurologic outcome in acute ischemic stroke (AIS), but its relationship with in-hospital outcome in elderly patients remains largely unknown. To assess the association of in-hospital outcome with fasting plasma glucose (FPG) levels at admission in individuals with AIS.

This retrospective propensity score-matched case-control study included patients aged over 60 years suffering from AIS and who were admitted to the emergency department from November 2013 to October 2016. Subjects were grouped into the poor-outcome and good-outcome groups based on mortality and intensive care unit (ICU) admission. The poor- and good-outcome groups comprised 74 and 1927 cases, respectively, before propensity score matching (PSM), and 74 and 296 cases, respectively, after PSM. Univariable logistic regression analysis showed that initial FPG after admission was associated with poor in-hospital outcome. Multivariable logistic regression analysis showed that initial FPG after admission was an independent predictor of poor in-hospital outcome (odds ratio = 1.11, 95% confidence interval: 1.037–1.188, \(P = .003\)).

This study used PSM and strongly suggests that FPG is an independent predictive factor of poor in-hospital outcome in elderly patients with AIS. High initial FPG levels after admission may predict poor in-hospital outcome. Prospective studies are needed to confirm these findings.

Abbreviations: AIS = acute ischemic stroke, ALT = alanine aminotransferase, CI = confidence interval, CKD = chronic kidney disease, FPG = fasting plasma glucose, GFR = glomerular filtration rate, GOG = good-outcome group, HbA1c = hemoglobin A1c, HDL-C = high-density lipoprotein, ICU = intensive care unit, LDL-C = low-density lipoprotein cholesterol, NIHSS = National Institutes of Health Stroke Scale, OR = odds ratio, POG = poor-outcome group, PSM = propensity score matching, TC = total cholesterol, TG = triglyceride, UKPDS = United Kingdom Prospective Diabetes Study.

Keywords: acute ischemic stroke, fasting plasma glucose, in-hospital outcome prognosis, propensity score matching

1. Introduction
Stroke is one of the leading causes of death[10] and probably the greatest reason for adult permanent disability worldwide.[11] It occurs more frequently in the elderly, with one-third of the ischemic stroke cases occurring in individuals 80 years and above.[12–4] Recently, the incidence and burden of stroke in China have increased rapidly, as in other developing countries. Indeed, about 2 million people of all ages suffer a new stroke every year, with 15 million stroke-related deaths occurring each year.[11]

It is widely accepted that hyperglycemia is associated with increased incidence of stroke in rural China.[5] Therefore, minimizing glucose fluctuations and reducing hemoglobin A1c (HbA1c) levels could help prevent ischemic stroke.[6] Meanwhile, it was found that stroke patients have higher fasting plasma glucose (FPG) levels compared with their nonstroke counterparts.[7] A study revealed the detrimental effects of hyperglycemia on morbidity and mortality in patients diagnosed with acute ischemic stroke (AIS), both with or without diabetes.[9] In addition, multivariable logistic regression analysis indicated that FPG is associated with mortality in stroke.[10] Nevertheless, the association between FPG and in-hospital mortality remains largely undetermined. This study focused on in-hospital outcome to assess its association with FPG levels at admission in AIS patients.

2. Materials and methods
2.1. Patients
This retrospective propensity score-matched case-control study enrolled all patients with ischemic stroke admitted to the emergency department of Xuanwu Hospital from November 2013 to October 2016. The inclusion criteria were: age ≥60 years; AIS diagnosis by computed tomography or magnetic resonance imaging; and complete clinical information. The
patients who received thrombolytic therapy were excluded. The eligible patients were divided into 2 groups: poor-outcome (POG; individuals admitted in the intensive care unit [ICU] and/or died in the hospital) and good-outcome (GOG; patients never admitted in the ICU who were discharged from the hospital). The ethics committee of Xuanwu Hospital approved the study and waived the requirement for obtaining informed consent. All procedures were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

2.2. Treatment
All patients received aspirin, clopidogrel, statins, and symptomatic treatment. Those with diabetes maintained their original hypoglycemic regimens. When 2-hour postprandial blood glucose levels were higher than 20 mmol/L, an insulin pump was used at 0.1 IU/kg/h until blood glucose fell to 15 mmol/L.

2.3. Measurements
The FPG and HbA1c were measured the first morning upon admission after at least 8 hours of fasting. Hypertension was defined as systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg, or current use of antihypertensive drugs.[11,12] Diabetes was defined as HbA1c ≥6.5% or current use of antidiabetic drugs. FPG was not considered in the present study for the diagnosis of diabetes because of the metabolic disturbances associated with AIS. Since HbA1c represents the long-term glycomic burden, it was considered as more reliable for the diagnosis of diabetes, as per the Chinese guidelines.[14,15]

Initial stroke severity was evaluated on the 1st day of admission according to the National Institute of Health Stroke Scale (NIHSS).[16] Chronic kidney disease (CKD) was classified according to the KDOQI 2002 guideline[17] as follows: CKD 1, renal injury with glomerular filtration rate (GFR) ≥90 mL/min · 1.73 m²; CKD 2, 60 ≤ GFR < 90 mL/min · 1.73 m²; CKD 3, 30 ≤ GFR < 60 mL/min · 1.73 m²; CKD 4, 15 ≤ GFR < 30 mL/min · 1.73 m²; and CKD 5, GFR < 15 mL/min · 1.73 m²). Hypoproteinemia was defined as albumin < 3.5 g/dL.[18] Alanine aminotransferase (ALT), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were detected the first morning following admission. HbA1c was measured using Variant II Turbo (Bio-Rad Laboratories, Philadelphia, PA). The measurements of all other metabolites were performed on a Hitachi 7600 automatic biochemical analyzer (Hitachi High-Technology, Tokyo, Japan).

2.4. Grouping
Since poor outcome cases were rare in the present study (3.4%), we included 1 patient in the POG matched to 4 patients in the GOG by propensity score matching (PSM) using the R software. The propensity score was estimated in a multivariable logistic regression model. Age, sex, ALT, CKD stage, and NIHSS score are associated with outcome in AIS, and hence included in the PSM model.[16,17,19-21]

2.5. Statistical analysis
Continuous data with nonnormal distribution were presented as median (range), and assessed by the Mann–Whitney U test. The distribution of categorical variables was evaluated by the Chi-squared test. Parameters with \( P < .1 \) in univariable logistic regression analyses were included in a multivariable logistic regression analysis. SPSS 22.0 (IBM, Armonk, NY) was used for all statistical analyses. \( P < .05 \) was considered statistically significant.

3. Results

3.1. Patient baseline characteristics
A total of 2001 subjects fulfilled the eligibility criteria, including 74 and 1927 in the POG and GOG before PSM, respectively. After PSM, there were 74 POG and 296 GOG patients. No significant differences were found in baseline features, including age, sex, ALT, CKD, and NIHSS score between the 2 groups after PSM. Nevertheless, FPG was higher in the POG (mean, 7.32 mmol/L; range, 3.67–22.44 mmol/L) compared with the GOG (mean, 6.44 mmol/L; range, 3.57–22.33 mmol/L; \( P = .005 \)). The baseline characteristics are summarized in Table 1.

3.2. Factors affecting in-hospital outcome and NIHSS score before matching
Univariable logistic regression analysis before PSM suggested that age, CKD, malignant tumor, gout history, ALT, TC, HDL-C, LDL-C, and FPG were the potential influencing factors for in-hospital outcome (\( P < .1 \)). The results of multivariable analysis showed that CKD (odds ratio [OR] = 8.105, 95% confidence interval [CI]: 4.241–15.489, \( P < .001 \)), malignant tumors (OR = 5.334, 95% CI: 2.124–13.398, \( P < .001 \)), gout history (OR = 4.141, 95% CI: 1.041–16.477, \( P = .044 \)), TG (OR = 0.527, 95% CI: 0.32–0.869, \( P = .012 \)), and FPG (OR = 1.199, 95% CI: 1.118–1.285, \( P < .001 \)) were found to independently affect in-hospital outcome in patients with AIS (Table 2). Further subgroup analyses were performed based on age. Among patients aged 60 to 75 years, CKD (OR = 14.788, 95% CI: 6.824–32.046, \( P < .001 \)), HDL-C (OR = 2.889, 95% CI: 1.044–7.999, \( P = .041 \)), and FPG (OR = 1.206, 95% CI: 1.097–1.325, \( P < .001 \)) are the independent factors associated with the in-hospital outcomes (Supplementary Table S1, http://links.lww.com/MD/D157). Among patients aged >75 years, malignant tumor (OR = 7.999, 95% CI: 2.283–28.002, \( P = .001 \)) is the independent factor associated with the in-hospital outcomes (Supplementary Table S2, http://links.lww.com/MD/D157).

3.3. FPG upon admission independently predicts poor in-hospital outcome in AIS
Univariable logistic regression analysis was performed after PSM to identify potential influencing factors for in-hospital outcome. As shown in Table 3, malignant tumor, gout history, hypoproteinemia, and FPG were found to affect in-hospital outcome in patients with AIS (\( P < .1 \)). Next, multivariable logistic regression analysis was performed to locate the independent factors, which showed that FPG upon admission was an independent predictor of poor in-hospital outcome (OR = 1.11, 95% CI: 1.037–1.188; \( P = .003 \)).

4. Discussion
This study included AIS patients grouped according to poor or good in-hospital outcomes after age, sex, ALT, CKD stage, and
NIHSS score were brought into a PSM model, and suggests that FPG is an independent predictive factor of poor in-hospital outcome.

Diabetes is considered one of the most important risk factors for poor outcome after stroke,\cite{22,23} not only because of high blood glucose levels but also their fluctuation.\cite{6} Even in healthy people without a history of diabetes, elevated levels of postprandial plasma glucose have been found to be a predictor of stroke mortality.\cite{24} Therefore, strict glycemic control during hospitalization might improve prognosis after stroke. However, this may be controversial as the benefit of tight glycemic control in different population of critically ill patients in the ICU, not just stroke cases, remains debatable.\cite{25} While most studies agree that hyperglycemia is a risk for ICU patients, the major risk of strict glycemic control is increased hypoglycemia, which offsets the benefit of any intervention.\cite{26} Similarly, hyperglycemic patients undergoing surgery have worse outcome compared with other individuals, but tight glycemic control does not appear to change this outcome.\cite{27} Therefore, current opinion suggests that effective continuous monitoring systems are needed to ensure that safe levels of glucose are maintained.\cite{28} Hyperglycemia in patients after stroke is sometimes caused by stress\cite{23} and associated with changes in body composition because of aging, obesity, and sedentary behavior.\cite{26}

Until now, FPG has not been reported as a predictor of in-hospital outcome in patients with stroke. In this study, we found that FPG was valuable in predicting in-hospital outcome in such patients. It should be noted that the adjusted OR was close to 1

| Variables | OR (95% CI) | P | OR (95% CI) | P |
|-----------|-------------|---|-------------|---|
| Age       | 1.048 (1.016, 1.08) | .003 | 1.031 (1.006, 1.068) | .086 |
| Sex       | 1.365 (0.854, 2.245) | .187 |                |     |
| Hypertension | 1.093 (0.637, 1.877) | .747 |                |     |
| Diabetes  | 1.308 (0.822, 2.084) | .258 |                |     |
| CKD       | 9.03 (5.002, 16.014) | <.001 | 8.105 (4.241, 15.489) | <.001 |
| Malignant tumor | 4.578 (1.966, 10.552) | .001 | 5.334 (2.124, 13.398) | <.001 |
| Gout history | 3.215 (0.948, 10.897) | .001 | 4.141 (1.041, 16.477) | .044 |
| Hypoproteinemia | 0.681 (0.002, 5.028) | .706 |                |     |
| ALT       | 1.008 (1.002, 1.014) | .010 | 1.007 (1.008, 1.017) | .004 |
| TG        | 0.692 (0.467, 1.025) | .066 | 0.527 (0.32, 0.869) | .012 |
| TC        | 1.239 (0.993, 1.546) | .056 | 1.184 (0.519, 2.701) | .688 |
| HDL-C     | 2.05 (1.079, 3.896) | .028 | 1.484 (0.586, 3.76) | .405 |
| LDL-C     | 1.311 (1.009, 1.703) | .043 | 1.203 (0.522, 2.769) | .665 |
| FPG       | 1.198 (1.13, 1.27) | <.001 | 1.199 (1.118, 1.285) | <.001 |
| HDa1c     | 1.023 (0.87, 1.204) | .762 |                |     |

ALT = alanine aminotransferase, CKD = chronic kidney disease, FPG = fasting plasma glucose, HDa1c = hemoglobin A1c, HDL-C = high-density lipoprotein, LDL-C = low-density lipoprotein cholesterol, NIHSS = National Institutes of Health Stroke Score, TC = total cholesterol, TG = triglyceride.
As well as other factors that might affect FPG while dealing with on the above data, clinicians should consider treatment methods for vascular events, including stroke, compared with standard care. Intensive glucose control results in fewer major cardiovascular events.[30] In addition, many studies have confirmed that a 1% reduction in HbA1c is associated with a 12% reduction in risk of death or major cardiovascular events.[29] Hyperglycemia is an indicator of severe stroke; while it cannot increase cerebral blood flow, it promotes further ischemia in the brain.[28] Hyperglycemia is associated with severe stroke and poor clinical outcomes; therefore, blood glucose monitoring and management are essential tools for healthcare professionals.[29] The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that a 1% reduction in HbA1c is associated with a 12% stroke occurrence.[30] In addition, many studies have confirmed that intensive glucose control results in fewer major cardiovascular events, including stroke, compared with standard therapy.[31–33] Although FPG independently predicted in-hospital outcome, HbA1c was not associated with this parameter in the present study. On the contrary, a recent report demonstrated that elevated HbA1c is an independent predictor of 1-year all-cause mortality after acute 1st-ever ischemic stroke.[34]

On a clinical perspective, the results may suggest that paying more attention to the patients with diabetes to avoid overt hyperglycemia while avoiding hypoglycemic events could lead to improved AIS outcome. In the nondiabetic patients, blood glucose levels should be monitored to detect any hyperglycemia that could be related to stress or stroke-associated metabolic disturbance. The compensatory and self-recovery abilities of younger AIS patients are better than that of elderly AIS patients.[33] Hyperglycemia and hypoglycemia affect elderly AIS patients more deeply than younger AIS patients.[35]

The present study has some limitations. First, it was a retrospective and single-center study, with PSM, and may not comprehensively represent the clinical situation. In addition, the sample size was relatively small. Furthermore, only in-hospital outcome (mortality and ICU admission) was assessed, with no long-term outcome analysis due to lack of follow-up data. Future larger prospective studies should address these shortcomings, especially assessing the degree of disability using modified Rankin scale in these patients, by extending follow-up duration.

Overall, this study showed that FPG after admission is an independent predictor of in-hospital outcome in stroke patients. An initial high level of FPG after admission may predict poor in-hospital outcome. Prospective studies are needed to confirm these findings.

### Author contributions

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### Table 3

Logistic regression analysis for in-hospital outcome after matching.

| Variables | Univariable logistic regression | Multivariable logistic regression |
|-----------|---------------------------------|----------------------------------|
|           | OR (95% CI)         | P       | OR (95% CI)         | P       |
| Age       | 0.988 (0.954–1.022) | .472   | 0.994 (0.833–1.204) | .561   |
| Sex       | 0.786 (0.464–1.332) | .370   | 1.187 (0.949–1.494) | .241   |
| Hypertension | 1.075 (1.059–1.942) | .811   | 1.022 (1.000–1.045) | .003   |
| Diabetes  | 1.245 (0.746–2.076) | .401   | 1.085 (0.996–1.188) | .061   |
| CKD       | 1.304 (0.721–2.357) | .380   | 1.33 (1.31–1.36) | .060   |
| Malignant tumor | 2.473 (0.938–6.519) | .067   | 2.612 (0.956–7.137) | .061   |
| Gout history | 4.127 (0.816–20.877) | .087   | 4.641 (0.886–24.32) | .069   |
| Hyperproteinaemia | 0.179 (0.024–1.356) | .096   | 0.14 (0.018–1.085) | .600   |
| ALT       | 1.003 (0.997–1.01)  | .518   |                   |        |
| TG        | 0.623 (0.556–1.222) | .335   |                   |        |
| TC        | 1.16 (0.901–1.404)  | .251   |                   |        |
| HDL-C     | 1.703 (0.871–3.329) | .120   |                   |        |
| LDL-C     | 1.24 (0.928–1.658)  | .146   |                   |        |
| FPG       | 1.084 (1.015–1.157) | .015   | 1.11 (1.037–1.188) | .003   |
| HbA1c     | 0.994 (0.853–1.167) | .949   |                   |        |

ALT = alanine aminotransferase, CKD = chronic kidney disease, FPG = fasting plasma glucose, HbA1c = hemoglobin A1C, HDL-C = high-density lipoprotein, LDL-C = low-density lipoprotein cholesterol, NIHSS = National Institutes of Health Stroke Scale, TC = total cholesterol, TG = triglyceride.
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