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Association between fasting blood glucose levels and outcomes and mortality in acute ischemic stroke patients with diabetes mellitus: an observational study in Wuhan, China

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ABSTRACT

Objective To evaluate the predictive power of an acute high blood glucose level on unfavorable outcomes and mortality in diabetes mellitus(DM) patients after acute ischemic stroke (AIS).

Study design A population-based, retrospective observational study. The clinical data were collected. At the time of admission, the NHISS score was used to assess stroke severity and the fasting blood glucose(FBG) level was determined. The modified Rankin scale (mRS) was used to assess functional outcome at 90 days, as follows: 3-6, an unfavorable outcome; and 6, death.

Setting The study was conducted in Wuhan, China.

Participants A total of 568 AIS patients with DM and 353 AIS patients without DM as a control group were included.

Results The FBG levels of AIS patients with DM were significantly higher as compared to AIS patients without DM [7.37 mmol/L (IQR, 5.99 – 10.10 mmol /L) vs. 6.19 mmol/L (5.38-7.20 mmol / L); P < 0.0001]. An elevated FBG level at the time of admission was associated with an increased NHISS score (r=0.417, P <0.0001) in the study group. Multivariate logistic regression analysis of confounding factors showed that a high FBG level at the time of admission was independently predictive of an unfavorable outcome 90 days after admission [odds ratio (OR), 1.249 (1.137-1.371) ; P<0.0001] and mortality [OR, 1.096 (1.012-1.187) ; P <0.05].

Conclusions High fasting blood glucose levels are associated with unfavorable outcomes and mortality after acute ischemic stroke in Chinese patients with DM. Fasting blood glucose levels on admission can be used as a useful predictor of short-term outcomes, facilitating the management of AIS patients with DM.

Strengths and limitations of this study

- There are only a few studies have evaluated the association between FBG and outcome of AIS patients with DM. The strength of the study is to evaluate the predictive effect of the FBG level at admission as an acute blood glucose index on the outcome.
- The study included AIS patients without DM as a control group and compared data including FBG at admission generated from both groups.
- The study routinely incorporated a wide range of factors that may influence functional outcomes to correct the effects of confounding factors.
- This was a single-center study with a limited sample size, female and male patients were not balanced in absolute numbers in the study.

INTRODUCTION

Diabetes mellitus(DM) is recognized as an important risk factor for ischemic stroke.[1 2] Previous epidemiologic investigations have confirmed that patients with DM have a high disability rate and risk of in-hospital death after an acute ischemic stroke (AIS).[3 4] A recent study involving a Chinese population included 10,331 patients with DM who were confirmed to have an AIS and shown to be at high risk for in-hospital death.[5] Indeed, assessment of functional outcome and mortality risk among AIS patients with diabetes is a common concern for both patients and clinicians.

Acute hyperglycemia is common in AIS patients with and without DM.[6] Many studies have shown that acute hyperglycemia at the time of admission is associated with AIS infarct volume [7] and can independently predict functional outcome and risk of death; [8-10] however, there is a lack of studies focusing on DM patients and hyperglycemia at the time of admission has controversial predictive value with respect to functional outcomes. It has been reported that high blood glucose levels in DM patients have no significant predictive value for functional outcomes and risk of death;[11] Moreover, two recent studies have confirmed that high blood glucose levels are predictive of functional outcomes in diabetic and non-diabetic patients complicated by cerebral infarction.[12 13] Therefore, it is necessary to clarify the correlation between acute blood glucose levels and functional outcomes in DM patients which can facilitate accurate prediction of prognosis and provide theoretical support for the development of glycemic control strategies after an ischemic stroke.

Because fasting blood glucose(FBG) can minimize the effects of diet,[14] the FBG level is considered a more reliable blood glucose level detection tool than random blood glucose levels.[15] Compared to random blood glucose levels, a fasting glucose level provides a stronger predictor of functional outcomes.[16 17]

In conclusion, this study aimed to investigate Chinese acute ischemic stroke patients with DM and to determine the correlation between the FBG level at the time of admission and functional outcomes as well as the risk of death.

METHODS

Patients and Study Design

This retrospective observational study collected information involving AIS patients with DM who were admitted to the Department of Neurology of the Renmin Hospital of Wuhan University from January 2018 to June 2019. The diagnostic criteria for acute cerebral infarction are in accordance with World Health Organization standards.[18] Patient with DM is defined as patients with a history of DM before admission or those taking drugs or insulin for hypoglycemic treatment. Patients must meet the below criteria: 1. onset within 24 hours; 2. $\geq$ 18 years of age; and 3. in the case of a recurrent cerebral infarction, a modified Rankin Scale (mRs) $\leq$ 2.[19] Patients with psychoses, severe bone joint diseases, and other neurologic diseases that affect functional outcomes were excluded from the study.

In this study, the same basic information and clinical data of AIS patients without DM admitted to the same hospital from January to June 2018 were also collected as a control group. The study was approved by the Ethics Committee of the Renmin Hospital of Wuhan University. Informed consent was signed for all patients participating in the study.

Clinical Variables and Neuroimaging

All patients completed diagnostic testing after admission, including routine serologic testing, neuroimaging, intracranial and extravascular studies, and a cardiac examination. The clinical data were routinely collected at the time of admission included gender, age, BMI, notation of vascular risk factors (including hypertension, DM, coronary heart disease, atrial fibrillation, hypercholesterolemia, stroke history, and smoking history), and systolic/diastolic blood pressure. The severity of stroke at the time admission was assessed using the National Institutes of Health Stroke Scale (NIHSS).[20] Reperfusion therapy included IV thrombolysis with rtPA and endovascular therapy with intra-arterial thrombolysis or mechanical thrombectomy. The causes of stroke were grouped according to the Trial of Org 10172 in Acute Stroke

Treatment (TOAST),[21] as follows: large-vessel occlusive; small-vessel occlusive; cardioembolic; and other and unknown. The patients underwent a CT scan and/or MRI examination within 24-48 h after admission. The diagnosis of cerebral infarction was based on the CT scan and/or MRI imaging findings.

End Points and Follow-up

The mRs score at 90 days was used as an indicator of functional outcomes, as follows: ≤ 2, good outcome; 3-6, unfavorable outcome; and 6, death. Two specially-trained neurologic nurses were responsible for assessing functional outcomes of AIS patients by calling patients or their family members once a month.

Laboratory Testing

To minimize the impact of diet on the blood glucose level, FBG levels were used as an indicator of the acute blood glucose level.[14 15] Blood samples were collected at approximately 7:30 am on the first day after admission after fasting for at least 8 hours. Glycosylated hemoglobin (HbA1c) was tested using standard test methods.

Statistical Analysis

Data following normal distribution were described using the mean ± standard deviation. Data following a non-normal distribution were described using the median (quartiles). Categorical variables were described using a percentage. The Mann–Whitney U test was used to compare the non-normal distribution between two groups. The relationship between two continuous variables was analyzed by the Spearman correlation. We used univariate logistic regression to analyze the relationship between gender, age, BMI, vascular risk factors, systolic/diastolic blood pressure, NIHISS score, stroke TOAST classification, HbA1c, the FBG level, and outcomes of acute cerebral infarction at 90 days and death. Factors giving a P<0.1 were re-analyzed using multivariate regression analysis to determine the correlation between the FBG level and functional outcomes of cerebral infarction, as well as death. The results are expressed by ORs and 95% CIs. Moreover, we performed quartiles based on FBG levels as follows: quartile 1 (FBG ≤ 6.00 mmol/L); quartile 2 (FBG 6.01-7.37 mmol/L); quartile 3 (7.38-10.10 mmol/L); and quartile 4 (FBG ≥ 10.11 mmol/L). Kaplan–Meier survival curves were used to analyze the value of the FBG level for predicting death. SPSS (version 25.0; SPSS, Inc., Chicago, IL, USA) was used for statistical analysis and a $P < 0.05$ indicates a significant difference.

Patient and public involvement

No patients were involved with design, data provision, analysis and publication of the study.

RESULTS

Baseline Characteristics of the Study Population

A total of 568 AIS patients with DM including 377 males and 191 females, were enrolled in this study and all were followed up. The median age of the patients was 65 years (IQR, 55-74 years), and the mean BMI was 24.10 ± 2.96 kg/m^2. The median NIHSS score at the time of admission was 4 (IQR, 2-10). 32 of 568 AIS patients have received reperfusion therapy, including 28 patients with IV rtPA thrombolysis and 7 patients with endovascular treatment. There were 226 patients (39.8%) with unfavorable outcomes, including 58 deaths (10.2%). Of the 58 deaths in this study, 36 (62.1%) died of increased intracranial pressure, 10 (17.2%) died of cardiac diseases such as heart failure, myocardial infarction or arrhythmia, and 12 (20.7%) died of other causes such as severe pneumonia, stress ulcer bleeding and pulmonary embolism. Moreover, 14 (24.1%) had symptomatic intracerebral hemorrhages among the 58 deaths. In the control group, 353 AIS patients without DM were enrolled. The baseline data of all patients at the time of admission are shown in Table 1.

Main Results

The FBG levels of the study group (AIS patients with DM) were significantly higher than the control group (AIS patients without DM) [7.37 mmol/L (IQR, 5.99 – 10.10 mmol /L) vs. 6.19 mmol/L (5.38-7.20 mmol / L; Z = -9.127, P < 0.0001; Figure 1]. The NHISS scores of AIS patients with DM at the time of admission increased with elevation of the FBG levels. There was a moderately significant positive correlation between the NHISS score and the FBG level (r=0.417, P<0.0001). The results are shown in Figure 2. The results also showed that FBG levels had no significant correlation with other risk factors, including smoking, hypertension, coronary heart disease, hypercholesterolemia history, a history of stroke (P>0.05).

FBG level and functional outcome at 90 days

The FBG levels of 226 patients with unfavorable functional outcomes at 90 days were significantly higher than patients with favorable functional outcomes [9.64 mmol/L (IQR, 7.40 – 12.60 mmol /L vs. 6.56 mmol/L (IQR, 5.64 – 7.86 mmol /L; Z=- 11.176, P < 0.0001; Figure 3]. Univariate regression analysis showed that unfavorable functional outcomes were significantly correlated with age, male gender, atrial fibrillation, coronary heart disease, NHISS score, small-vessel occlusive, HbA1c, and the FBG level (P<0.05). Multivariate logistic regression analysis was performed on outcome-indicating factors. The results showed that age (OR, 1.023; 95% CI, 1.001-1.046; P = 0.037), NHISS score (OR, 1.422; 95% CI, 1.308-1.545; P < 0.0001), small-vessel occlusive (OR, 0.237; 95% CI, 0.061-0.929; P = 0.039), and FBG level (OR, 1.249; 95% CI, 1.137-1.371; P < 0.0001) were independent predictive factors of functional outcome for AIS patients with DM (Table 2).

FBG levels and mortality at 90 days

The FBG levels of 58 non-surviving patients at 90 days were significantly higher than surviving patients [10.41 mmol/L (IQR, 8.14 – 15.29 mmol /L vs. 7.10 mmol/L (IQR, 5.88 – 9.65 mmol /L; Z=-6.851, P < 0.0001; Figure 4]. Univariate regression analysis of non-surviving patients showed that atrial fibrillation, coronary heart disease, NHISS score, small-vessel occlusive disease, HbA1c, and FBG level were significantly associated with death (P<0.05). Multivariate logistic regression analysis was performed on functional outcome-indicating factors and the results showed that atrial fibrillation (OR, 2.851; 95% CI, 1.159-7.012; P = 0.023), NHISS score (OR, 1.133; 95% CI, 1.076-1.192; P < 0.0001), small-vessel occlusive (OR, 0.087; 95% CI, 0.011-0.669; P = 0.019), HbA1c (OR, 1.486; 95% CI, 1.227-1.779; P < 0.0001), and FBG levels (OR, 1.096; 95% CI, 1.012-1.187; P=0.025; Table 2) were independent predictive factors of death for AIS patients with DM .

We used Kaplan- Meier curves to compare the quartiles of FBG levels and time-to-death after admission. The results showed that the risk of death in the two highest quartile groups (FBG 7.38-10.10 mmol/L and ≥ 10.11 mmol/L groups) was significantly higher than the two lowest quartile groups (FBG ≤ 6.00 mmol/L and 6.01-7.37 mmol/L groups; P <0.0001; Figure 5).

DISCUSSION

We evaluated the FBG levels at the time of admission as an indicator of functional outcome and risk of death among Chinese AIS patients combined with DM. This study showed that FBG levels increased with elevated NHISS scores at the time of admission. Moreover, after adjustment for potential influencing factors, the FBG level at the time of admission was an independent predictor for functional outcome and mortality in AIS patients with DM.

Acute stroke may be accompanied by neuroendocrine disorders, as well as inflammation, resulting in an acute blood glucose elevation.[22] Previous studies focusing on acute blood glucose elevations generally used fasting or random blood glucose levels at the time of admission an indicator of acute blood glucose. A meta-analysis involving 32 studies showed that acute stroke patients with acute high blood glucose levels are a widespread finding, and the proportion of high blood glucose levels in acute stroke patients with and without DM reached 8%-63% and 39%-83%, respectively.[6] A number of studies have shown that high blood glucose levels at the time of admission are closely related to the functional outcome of patients with AIS.[9 10 23 24] Masrur et al. [9] studied 1408 AIS patients who received intravenous thrombolysis and showed that an acute high blood glucose level at the time of admission increased the risk of unfavorable functional outcomes and death. Snarska et al. [10] and Zhao et al.[25] observed AIS patients and reported that a high blood glucose level at the time of admission was significantly associated with an unfavorable functional outcome and risk of in-hospital death. Moreover, several previous studies involving AIS patients without DM showed that high blood glucose levels were also closely related to unfavorable functional outcomes and risk of death.[24 26]

Because the focus of previous studies has been on AIS patients only or AIS patients without DM, acute blood glucose levels at the time of admission among AIS patients with DM has not been adequately addressed, and thus the predictive value for unfavorable functional outcomes or mortality has not been established.[12 13 24 26-28] Yao et al.[24] and Hu et al.[28] showed that in AIS patients without DM, high FBG levels predicted unfavorable functional outcomes and death, but had insignificant predictive value for AIS patients with DM. Tsuga et al.[12] and Sung et al.[13] performed subgroup analysis on AIS patients with and without DM and showed that acute blood glucose levels in both groups had predictive power for functional outcomes. Recently a meta-analysis incorporated 13 studies that showed that there was no statistical difference in prognostic indicators between AIS patients with and without DM.[29] In this study, we used baseline FBG levels at the time of admission as a marker for the acute blood glucose level. The results revealed additional evidence for the predictive value of high acute blood glucose levels on functional outcomes and high risk of death in AIS patients with DM.

The mechanism underlying the predictive value of high blood glucose levels at the time of admission on functional outcome and mortality is not fully understood; however, the correlation between a high blood glucose level after AIS and the severity of stroke and unfavorable functional outcomes may be summarized as follows. First, a high blood glucose level can affect the balance between the coagulation and fibrinolytic systems, resulting in impaired recanalization.[30 31] Second, a high blood glucose level may affect endothelium-derived nitric oxide-mediated vasodilation, thereby reducing intracranial blood flow and reperfusion at the infarct site.[32 33] In *vitro* studies have shown that nitric oxide synthase 3 gene expression and nitric oxide production are reduced in hyperglycemic conditions.[34 35] Clinical studies have shown that cerebral infarction tissue reperfusion is decreased and infarct volume is increased in patients with high blood glucose levels. [36-38] Third, a high blood glucose level may generate oxidative stress, leading to neuroendocrine disorders and inflammatory reactions, [39 40] blood-brain barrier disruption,[41] and eventually reperfusion injury. [37 42] Two clinical studies have shown that ischemic stroke patients with acute high blood glucose levels are at increased risk for hemorrhagic transformation, [43] and cerebral hemorrhage in patients with thrombolysis leads to unfavorable functional outcomes.[44] It has been suggested that high blood glucose levels may increase the risk of vascular reperfusion injury. Fourth, patients with DM generally have insufficient insulin secretion or insulin resistance, and therefore anaerobic glycolysis may increase in patients with high blood glucose levels,[45 46] resulting in brain tissue lactic acid accumulation and internal environment disorders that aggravate brain tissue damage.[47] All of these pathologic changes together cause severe stroke and secondary functional outcomes and death.

Strengths and limitations

This study had the following highlights. First, Only a few studies have evaluated the association between FBG levels and outcomes of AIS patients with DM. Because the FBG levels were not affected by diet, the results better reveal blood

glucose levels as a function of stress, this study used FBG at admission as an acute blood glucose index. Second, this study included AIS patients without DM as a control group and compared data including FBG at admission generated from both groups. Finally, this study routinely incorporated a wide range of factors that may influence functional outcomes to correct the effects of confounding factors.

This study also had limitations. First, this was a single-center study with a limited sample size. Additional prospective multicenter studies are needed. Moreover, female and male patients were not balanced in absolute numbers in the study. Combined with previous research results,[48] we analyzed the possible reason of gender imbalance that male patients with DM had a higher incidence of AIS.

CONCLUSIONS

In conclusion, our results suggest that high FBG levels are associated with unfavorable outcomes and mortality of AIS patients with DM. In the Chinese population, high FBG levels can be used as a useful predictor of short-term outcomes, facilitating the management of AIS patients with DM.

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Contributors TY analyzed and interpreted the results and wrote this manuscript text. TY, YQZ, JS, BP, LX, and QC had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. YT, YQZ, and ZCL designed the study. All authors reviewed and approved the manuscript.

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Competing interests None declared.

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Table 1 Baseline characteristics of patients with AIS		
Demographic characteristics	DM Patients	Non-DM Patients
N	568	353
Age(years), median (IQR)	65(55-74)	68(59-75)
Male gender, n (%)	377（66.4□	220（62.3□
Vascular risk factors, n (%)		
Hypertension	398(70.1□	209（59.2□
Atrial fibrillation	78(13.7□	52（14.7□
Hypercholesterolemia	182（32.0□	128（36.3□
Coronary heart disease	75（13.2□	37（10.5□
Previous TIA or stroke	89（15.7□	51（14.4□
Active smoking	205（36.1□	130（36.8□
Clinical findings		
BMI (kg/m^2), mean± SD	24.10±2.96	23.22±3.15
Systolic blood pressure (mmHg), median (IQR)	148(130-166)	139(122-156)
Diastolic blood pressure (mmHg), median (IQR)	83(75-93)	78(70-89)
TOAST classification, n (%)		
Large-vessel occlusive	177(31.2)	137(38.8)
Small-vessel occlusive	318(56.0)	170(48.2)
Cardioembolic	56(9.9)	38(10.8)
Other and Unknown	17(3.0)	8(2.3)
HbA1c (%), median (IQR)	6.6(5.8-8.3)	-
NIHSS at admission, median (IQR)	4(2-10)	5(3-11)
Reperfusion therapy, n (%)	32(5.6)	26(7.4)
Unfavorable outcome at 3 months, n (%)	226(39.8)	133(37.7)
Mortality at 3 months, n (%)	58(10.2)	43(12.2)

AIS acute ischemic stroke; IQR interquartile range; TIA transient ischemic attack; BMI body mass index; SD standard deviation; TOAST Trial of Org 10172 in Acute Stroke Treatment; HbA1c hemoglobin A1c; NIHSS National Institutes of Health Stroke Scale.

Table 2 Univariate and multivariate logistic regression analyses for unfavorable outcome and mortality

Parameter	Univariate analysis			Multivariate analysis		
	OR	95 % CI[a]	*P* value	OR	95 % CI[a]	*P* value
Predictor: Unfavorable functional outcome						
Age	1.025	1.011-1.039	<0.0001	1.023	1.001-1.046	0.037
Male gender	0.633	0.445-0.902	0.011	0.715	0.400-1.280	0.259
Hypertension	0.921	0.639-1.328	0.659			
Atrial fibrillation	2.190	1.350-3.552	0.001	1.985	0.799-5.057	0.151
Hypercholesterolemia	0.891	0.620-1.279	0.530			
Coronary heart disease	1.886	1.157-3.075	0.011	1.031	0.466-2.280	0.940
Previous TIA or stroke	1.286	0.815-2.029	0.280			
Active Smoking	1.080	0.762-1.532	0.664			
BMI	0.965	0.912-1.022	0.226			
Systolic blood pressure	1.000	0.994-1.007	0.966			
Diastolic blood pressure	0.999	0.988-1.010	0.875			
Reperfusion therapy	0.903	0.432-1.885	0.785			
NIHSS at admission	1.577	1.464-1.700	<0.0001	1.422	1.308-1.545	<0.0001
Large-vessel occlusive [b]	1.120	0.375-3.346	0.839			
Small-vessel occlusive [b]	0.065	0.022-0.194	<0.0001	0.237	0.061-0.929	0.039
Cardioembolic [b]	1.250	0.374-4.715	0.717			
HbA1c (%)	1.111	1.006-1.228	0.038	0.843	0.707-1.005	0.056
Fasting blood glucose	1.380	1.287-1.478	<0.0001	1.249	1.137-1.371	<0.0001
Predictor: Mortality						
Age	1.013	0.991-1.035	0.238			
Male gender	0.690	0.396-1.201	0.189			
Hypertension	1.136	0.619-2.082	0.681			
Atrial fibrillation	4.954	2.723-9.015	<0.0001	2.851	1.159-7.012	0.023
Hypercholesterolemia	0.867	0.478-1.572	0.638			
Coronary heart disease	2.087	1.066-4.087	0.032	1.614	0.669-3.896	0.287
Previous TIA or stroke	1.296	0.644-2.609	0.467			
Active Smoking	1.502	0.868-2.600	0.146			
BMI	0.956	0.872-1.048	0.337			
Systolic blood pressure	0.992	0.981-1.003	0.135			
Diastolic blood pressure	0.995	0.977-1.013	0.596			
NIHSS at admission	1.209	1.159-1.262	<0.0001	1.133	1.076-1.192	<0.0001
Large-vessel occlusive	0.888	0.274-2.882	0.884			
Reperfusion therapy	1.275	0.431-3.773	0.661			
Small-vessel occlusive	0.021	0.003-0.123	<0.0001	0.087	0.011-0.669	0.019
Cardioembolic	1.083	0.303-3.870	0.902			
HbA1c (%)	1.545	1.335-1.787	0.000	1.486	1.227-1.779	0.000
Fasting blood glucose	1.229	1.153-1.309	<0.0001	1.096	1.012-1.187	0.025

OR odds ratio; CI confidence interval; TIA transient ischemic attack; BMI body mass index; NIHSS National Institutes of Health Stroke Scale

[a] Note that the odds ratio corresponds to a unit increase in the explanatory variable

[b] Other and unknown ischemic stroke subtype as the reference

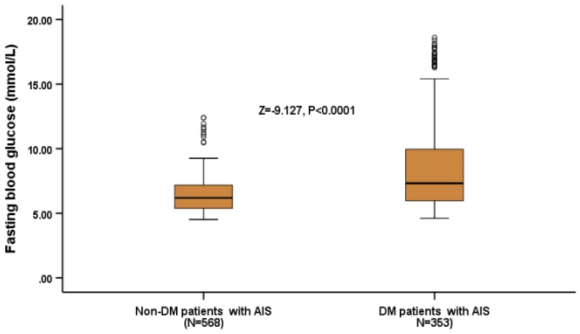
Fig. 1 Distribution of fasting blood glucose levels in non-T2DM patients and T2DM patients with AIS. All data are the median and interquartile range (IQR). Mann–Whitney U-test (Z=-9.127, P<0.0001)

Fig. 2. The correlation between fasting blood glucose levels and the National Institutes of Health Stroke Scale (NIHSS); Spearman's analysis (r=0.417, P<0.0001)

Fig. 3. Distribution of fasting blood glucose levels in patients with favorable and unfavorable outcomes. All data are the median and interquartile range (IQR). Mann–Whitney U-test (Z=-11.176, P<0.0001)

Fig. 4. Distribution of fasting blood glucose levels in survivors and non-survivors. All data are the median and interquartile range (IQR). Mann–Whitney U-test (Z=-6.851, P<0.0001)

Fig. 5. Kaplan–Meier survival based on fasting blood glucose (FBG) quartiles. Time-to-death was analyzed by Kaplan–Meier curves based on FBG quartiles. Patients in the lower two quartiles (FBG ≤6.00 mmol/L and 6.00<FBG≤7.37 mmol/L) had a lower risk of mortality compared to patients with FBG levels in the higher two quartiles (FBG>10.10 mmol/L and 7.37<FBG≤10.10 mmol/L, P<0.0001).



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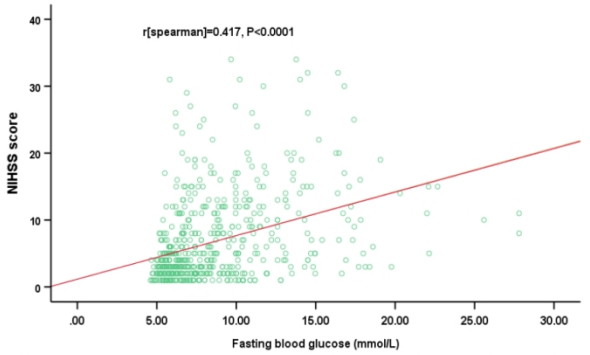

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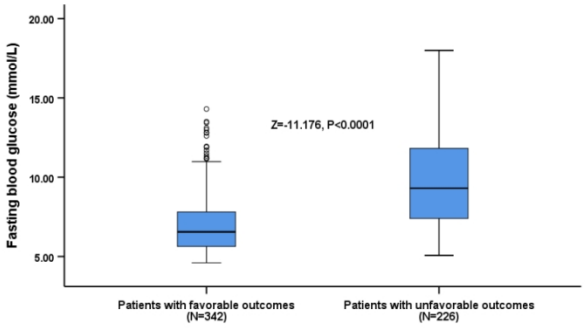

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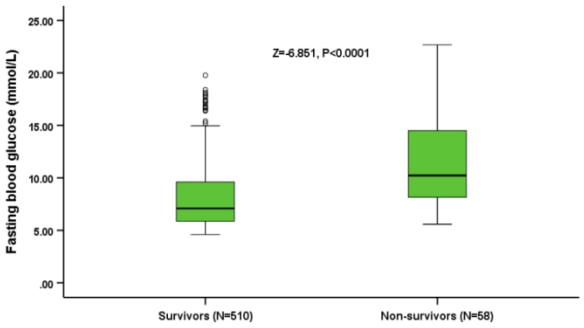

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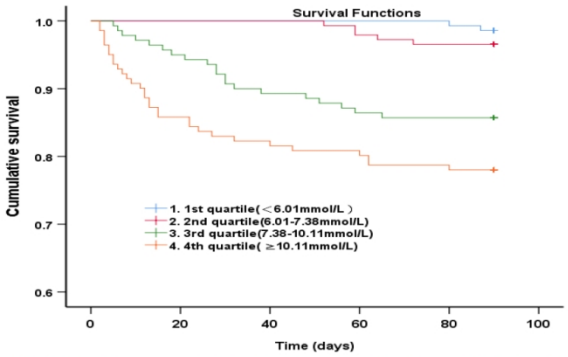

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3, 4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	3
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4
		(*b*) Describe any methods used to examine subgroups and interactions	4
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	4
		(b) Indicate number of participants with missing data for each variable of interest	4
		(c) Summarise follow-up time (eg, average and total amount)	4
Outcome data	15*	Report numbers of outcome events or summary measures over time	4, 5

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5
		(*b*) Report category boundaries when continuous variables were categorized	5
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	5
Discussion			
Key results	18	Summarise key results with reference to study objectives	6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	6
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	6
Generalisability	21	Discuss the generalisability (external validity) of the study results	6
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	7

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Association between fasting blood glucose and outcomes and mortality in acute ischemic stroke patients with diabetes mellitus: a retrospective observational study in Wuhan, China

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Association between fasting blood glucose and outcomes and mortality in acute ischemic stroke patients with diabetes mellitus: a retrospective observational study in Wuhan, China

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ABSTRACT

Objective To evaluate the predictive value of fasting blood glucose (FBG) on unfavorable outcomes and mortality in diabetes mellitus (DM) patients after acute ischemic stroke (AIS).

Study design A population-based, retrospective observational study was conducted. Clinical data were routinely collected, including sex, age, BMI, vascular risk factors, and systolic/diastolic blood pressure. National Institute of Health Stroke Scale (NIHSS) score was used to assess stroke severity on admission. FBG was determined on the first day after fasting for at least 8 hours. The modified Rankin Scale (mRS) was used to assess functional outcome at 90 days: 3-6, unfavorable outcome; 6, death.

Setting Renmin Hospital of Wuhan University, Wuhan, China.

Participants AIS patients with DM who were consecutively admitted within 24 hours of onset from January 2018 to June 2019.

Results For the 568 patients, the median age was 65 years [interquartile range (IQR), 55-74]. There were 377 (66.4%) men. The median FBG values were 7.37 mmol/L (IQR, 5.99-10.10 mmol /L), and the median glycosylated hemoglobin (HbA1c) values were 6.6 (IQR, 5.8-8.3). Multivariable logistic regression analysis of confounding factors showed that FBG at the time of admission was an independent predictor of unfavorable outcome [odds ratio (OR), 1.25 (1.14-1.37); P<0.0001] and mortality [OR, 1.096 (1.01-1.19) ; P <0.05] at 90 days after onset. Time to death was analyzed by Kaplan–Meier curves based on FBG quartiles. The risk of death in the two highest quartile groups (FBG, 7.38-10.10 mmol/L; FBG, ≥ 10.11 mmol/L) was significantly higher than that in the two lowest quartile groups (FBG, ≤6.00 mmol/L; FBG, 6.01-7.37 mmol/L) (P <0.0001).

Conclusions Higher FBG levels are associated with unfavorable outcomes and mortality in Chinese AIS patients with DM. Our data contribute to the knowledge regarding the relationship between FBG and outcome in AIS with DM.

Strengths and limitations of this study

- This study evaluated the predictive value of FBG at admission with regard to short-term outcome. Previous studies focusing on this evaluation are rare.
- Complete follow-up was achieved in this study.
- The study used routinely collected clinical data and practical statistical methods to correct the effects of confounding factors.
- This study was conducted in a single center with a limited sample size.
- Data of random blood glucose as a possible meaningful predictor were not fully available in this retrospective study.

INTRODUCTION

Diabetes mellitus (DM) is recognized as an important risk factor for ischemic stroke.[1 2] Previous epidemiologic investigations have confirmed that patients with DM have a high disability rate and a high risk of in-hospital death after an acute ischemic stroke (AIS).[3 4] A recent study involving a Chinese population included 10,331 patients with DM who were confirmed to have an AIS showed a high risk for in-hospital death.[5] Indeed, assessment of functional outcome and mortality risk among AIS patients with diabetes is a common concern for both patients and clinicians.

Hyperglycemia is common in AIS patients with and without DM.[6] Many studies have shown that hyperglycemia at the time of admission is associated with AIS infarct volume.[7] This condition can also predict functional outcome and risk of death.[8-10] However, few studies have focused on DM patients with hyperglycemia at the time of admission. Studies have shown that high blood glucose levels in DM patients have no significant predictive value for functional outcomes and risk of death.[11] Moreover, two recent studies have confirmed that high blood glucose levels are predictive of functional outcomes in diabetic and non-diabetic patients complicated by cerebral infarction.[12 13] Therefore, the correlation between blood glucose levels and functional outcomes in DM patients should be defined so that clinicians can provide accurate prognosis and eventually develop glycemic control strategies after an ischemic stroke.

Because fasting blood glucose (FBG) can minimize the effects of diet,[14] the FBG level is considered a more reliable blood glucose level detection tool than random blood glucose levels.[15] Compared to random blood glucose levels, FBG level provides a stronger predictor of functional outcomes.[16 17]

Hence, this study aimed to investigate the predictive value of FBG on functional outcomes and mortality in Chinese AIS patients with DM.

METHODS

Patients and Study Design

This retrospective observational study collected information involving AIS patients with DM who were admitted to the Department of Neurology of the Renmin Hospital of Wuhan University from January 2018 to June 2019. The diagnostic criteria for acute cerebral infarction are in accordance with World Health Organization standards.[18] Patients with DM were defined as patients with a history of DM before admission according to their medical records or those who received drugs or insulin for hypoglycemic treatment after admission. Patients must meet the following criteria: onset was within 24 h; age $\geq$ 18 years; and, in the case of a recurrent cerebral infarction, a modified Rankin Scale (mRS) $\leq$ 2.[19] Patients with psychoses, severe bone joint diseases, and other neurologic diseases that affect functional outcomes were excluded from the study.

The study was approved by the Ethics Committee of the Renmin Hospital of Wuhan University. Signed informed consent was obtained for all patients participating in the study.

Clinical Variables and Neuroimaging

All patients completed diagnostic testing after admission, including routine serologic testing, neuroimaging, intracranial and extravascular studies, and a cardiac examination. Clinical data were routinely collected at the time of admission, included gender, age, BMI, notation of vascular risk factors (including hypertension, DM, coronary heart disease, atrial fibrillation, hypercholesterolemia,

stroke history, and smoking history), and systolic/diastolic blood pressure. The severity of stroke at the time of admission was assessed using the National Institutes of Health Stroke Scale (NIHSS).[20] Reperfusion therapy included IV thrombolysis with rtPA and endovascular therapy with intra-arterial thrombolysis or mechanical thrombectomy. The causes of stroke were grouped according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST),[21] as follows: large-vessel occlusive; small-vessel occlusive; cardioembolic; and other and unknown. Patients underwent a CT scan and/or MRI examination within 24-48 h after admission. The diagnosis of cerebral infarction was based on these images.

End Points and Follow-up

The mRsS score at 90 days was used as an indicator of functional outcomes, as follows: ≤ 2, good outcome; 3-6, unfavorable outcome; and 6, death. Two specially trained neurologic nurses were responsible for assessing functional outcomes of AIS patients by calling patients or their family members once a month.

Laboratory Testing

To minimize the impact of diet on the blood glucose level, FBG levels were used as a reliable glycemic index. Blood samples were collected at approximately 7:30 am on the first day after admission after fasting for at least 8 hours. Glycosylated hemoglobin (HbA1c) was tested using standard test methods.

Statistical Analysis

Data following normal distribution were described using the mean ± standard deviation. Data following a non-normal distribution were described using the median (quartiles). Categorical variables were described using a percentage. The Mann–Whitney U test was used to compare the non-normal distribution between two groups. The relationship between two continuous variables was analyzed by the Spearman correlation. We used univariable logistic regression to analyze the relationship between gender, age, BMI, vascular risk factors, systolic/diastolic blood pressure, NIHSS score, stroke TOAST classification, HbA1c, the FBG level, and outcomes of acute cerebral infarction at 90 days and death. Factors giving a $P<0.1$ were re-analyzed using multivariable regression analysis to determine the correlation between the FBG level and functional outcomes of cerebral infarction, as well as death. The results are expressed by ORs and 95%CIs. Moreover, we performed quartiles based on FBG levels as follows: quartile 1 (FBG ≤ 6.00 mmol/L); quartile 2 (FBG, 6.01-7.37 mmol/L); quartile 3 (FBG, 7.38-10.10 mmol/L); and quartile 4 (FBG ≥ 10.11 mmol/L). Kaplan–Meier survival curves were used to analyze the value of the FBG level for predicting death. SPSS (version 25.0; SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. A $P < 0.05$ indicates a significant difference.

Patient and public involvement

No patients were involved with design, data provision, analysis, or publication of the study.

RESULTS

Baseline Characteristics of the Study Population

A total of 568 AIS patients with DM, including 377 males and 191 females, were enrolled in this study and all were followed up. The median age of the patients was 65 years (IQR, 55-74 years), and the mean BMI was 24.10 ± 2.96 kg/m^2. The median NIHSS score at the time of admission was 4 (IQR, 2-10). A total of 32 of 568 AIS patients received reperfusion therapy, including 28 patients with IV rtPA thrombolysis and 7 patients with endovascular treatment. A total of 226 patients (39.8%) had unfavorable outcomes, including 58 deaths (10.2%). Of the 58 deaths in this study, 36 (62.1%) died of increased intracranial pressure; 10 (17.2%) died of cardiac diseases such as heart failure, myocardial infarction, or arrhythmia; and 12 (20.7%) died of other causes such as severe pneumonia, stress ulcer bleeding, or pulmonary embolism. Moreover, 14 (24.1%) had symptomatic intracerebral hemorrhages. The baseline data of all patients at the time of admission are shown in Table 1.

Main Results

The median FBG values were 7.37 mmol/L(IQR, 5.99-10.10 mmol /L). The NIHSS scores of AIS patients with DM at the time of admission increased with elevation of the FBG levels. A moderately significant positive correlation was found between the NIHSS score and the FBG level (r = 0.417, P<0.0001). The results are shown in Figure 1. The results also showed that FBG levels had no significant correlation with other risk factors, including smoking, hypertension, coronary heart disease, hypercholesterolemia history, or a history of stroke (P>0.05).

FBG level and functional outcome at 90 days

FBG levels of 226 patients with unfavorable functional outcomes at 90 days [9.64 mmol/L (IQR, 7.40-12.60 mmol /L)] were significantly higher than patients with favorable functional outcomes vs. [6.56 mmol/L (IQR, 5.64-7.86 mmol /L); Z = -11.176; P < 0.0001; Figure 2]. Univariable regression analysis showed that unfavorable functional outcomes were significantly correlated with age, male gender, atrial fibrillation, coronary heart disease, NIHSSNIHSS score, small-vessel occlusion, HbA1c, and FBG level (P<0.05). Multivariable logistic regression analysis was performed on outcome-indicating factors. The results showed that age (OR, 1.02; 95%CI, 1.00-1.05; P = 0.037), NIHSSNIHSS score (OR, 1.42; 95%CI, 1.31-1.55; P < 0.0001), small-vessel occlusion (OR, 0.24; 95%CI, 0.06-0.93; P = 0.039), and FBG level (OR, 1.25; 95%CI, 1.14-1.37; P < 0.0001) were independent predictive factors of functional outcome for AIS patients with DM (Table 2).

FBG levels and mortality at 90 days

The FBG levels of 58 nonsurviving patients at 90 days were significantly higher than surviving patients [10.41 mmol/L (IQR, 8.14-15.29 mmol /L vs. 7.10 mmol/L (IQR, 5.88-9.65 mmol /L); Z = -6.851, P < 0.0001; Figure 3]. Univariable regression analysis of nonsurviving patients showed that atrial fibrillation, coronary heart disease, NIHSS score, small-vessel occlusive disease, HbA1c, and FBG level were significantly associated with death (P<0.05). Multivariable logistic regression analysis was performed on functional-outcome-indicating factors and the results showed that atrial fibrillation (OR, 2.85; 95%CI, 1.16-7.01; P = 0.023), NIHSS score (OR, 1.13; 95%CI, 1.08-1.19; P < 0.0001), small-vessel occlusive ((OR, 0.087; 95%CI, 0.01-0.67; P = 0.019), HbA1c ((OR, 1.49;

95%CI, 1.23-1.78; P < 0.0001), and FBG levels ((OR, 1.10; 95%CI, 1.01-1.19; P=0.025; Table 2) were independent predictive factors of death for AIS patients with DM.

We used Kaplan-Meier curves to compare the quartiles of FBG levels and time to death after admission. The results showed that the risk of death in the two highest quartile groups (FBG, 7.38-10.10 mmol/L; and FBG, ≥10.11 mmol/L) was significantly higher than the two lowest quartile groups (FBG, ≤6.00 mmol/L; and FBG, 6.01-7.37 mmol/L; P <0.0001; Figure 4).

DISCUSSION

In this retrospective study, we found that higher fasting blood glucose levels are associated with unfavorable outcomes and mortality in Chinese AIS patients with DM. Moreover, higher FBG was associated with higher NIHSS score on admission.

Acute stroke may be accompanied by neuroendocrine disorders and inflammation, resulting in an acute blood glucose elevation.[22] Previous studies focusing on acute blood glucose elevations generally used fasting or random blood glucose levels at the time of admission as an indicator of acute blood glucose. A meta-analysis involving 32 studies showed that acute stroke patients often had high blood glucose levels, and the proportion of high blood glucose levels in acute stroke patients with and without DM reached 8%-63% and 39%-83%, respectively.[6] A number of studies have shown that high blood glucose levels at the time of admission are closely related to the functional outcome of patients with AIS.[9 10 23 24] Masrur et al.[9] studied 1408 AIS patients who received intravenous thrombolysis and showed that high blood glucose levels at the time of admission increased the risk of unfavorable functional outcomes and death. Snarska et al. [10] and Zhao et al.[25] reported that a high blood glucose level in AIS patients at the time of admission was significantly associated with an unfavorable functional outcome and risk of in-hospital death. Moreover, several previous studies involving AIS patients without DM showed that high blood glucose levels were also closely related to unfavorable functional outcomes and risk of death.[24 26]

Because the focus of previous studies was on AIS patients only or AIS patients without DM, acute blood glucose levels at the time of admission among AIS patients with DM were not adequately addressed; thus, the predictive value for unfavorable functional outcomes or mortality has not been established.[12 13 26-28] Yao et al.[24] and Hu et al.[28] showed that in AIS patients without DM, high FBG levels predicted unfavorable functional outcomes and death; however, similar levels for AIS patients with DM had an insignificant predictive value. Tsuga et al.[12] and Sung et al.[13] performed subgroup analysis on AIS patients with and without DM and showed that acute blood glucose levels in both groups had predictive power for functional outcomes. Recently, a meta-analysis incorporated 13 studies and showed no statistical difference existed in prognostic indicators between AIS patients with and without DM.[29] In this study, we used baseline FBG levels at the time of admission as a marker for the acute blood glucose level. The results revealed additional evidence for the predictive value of high acute blood glucose levels on functional outcomes and high risk of death in AIS patients with DM.

The mechanism underlying the predictive value of high blood glucose levels at the time of admission on functional outcome and mortality is not fully understood; however, the correlation between a high blood glucose level after AIS and the severity of stroke and unfavorable functional outcomes may be summarized as follows. First, a high blood glucose level can affect the balance

between the coagulation and fibrinolytic systems, resulting in impaired recanalization.[30 31] Second, a high blood glucose level may affect endothelium-derived nitric-oxide-mediated vasodilation, thereby reducing intracranial blood flow and reperfusion at the infarct site.[32 33] In vitro studies have shown that nitric oxide synthase 3 gene expression and nitric oxide production are reduced in hyperglycemic conditions.[34 35] Clinical studies have shown that cerebral infarction tissue reperfusion is decreased and infarct volume is increased in patients with high blood glucose levels.[36-38] Third, a high blood glucose level may generate oxidative stress, leading to neuroendocrine disorders and inflammatory reactions,[39 40] blood-brain barrier disruption,[41] and eventually reperfusion injury.[37 42] Two clinical studies have shown that ischemic stroke patients with acute high blood glucose levels are at increased risk for hemorrhagic transformation,[43] and cerebral hemorrhage in patients with thrombolysis leads to unfavorable functional outcomes.[44] High blood glucose levels may increase the risk of vascular reperfusion injury. Fourth, patients with DM generally have insufficient insulin secretion or insulin resistance; therefore, anaerobic glycolysis may increase in patients with high blood glucose levels,[45 46] resulting in brain tissue lactic acid accumulation and internal environment disorders that aggravate brain tissue damage.[47] All of these pathologic changes together cause severe stroke and secondary functional outcomes and death.

Strengths and limitations

This study had the following highlights. First, quite a few studies have evaluated the association between blood glucose level and outcomes of AIS patients without DM; however, to the best of our knowledge, no studies have evaluated these conditions in patients with DM[24 26]. Furthermore, complete follow-up of all patients was achieved in this study. Third, this study used routinely collected clinical data such as gender, age, BMI, vascular risk factors, NIHSS score, systolic/diastolic blood pressure, and reperfusion therapy. Also, practical statistical methods were used to correct the effects of confounding factors.

This study also had limitations. First, a single center was used and sample size was limited. Second, data of random blood glucose as a possible meaningful predictor were not fully available in this retrospective study. Therefore, we cannot investigate the predictive value of random blood glucose compared with FBG.

CONCLUSIONS

In conclusion, higher fasting blood glucose levels are associated with unfavorable outcomes and mortality in Chinese AIS patients with DM. Our data contribute to the knowledge for clinicians about the relation between FBG and outcome in AIS with DM.

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Contributors TY analyzed and interpreted the results and wrote this manuscript text. TY, YQZ, JS, BP, LX, and QC had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. YT, YQZ, and ZCL designed the study. All authors reviewed and approved the manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

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Data availability statement Data are available upon reasonable request from corresponding author.

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Table 1 Baseline characteristics of patients with AIS

Demographic characteristics	DM Patients
N	568
Age(years), median (IQR)	65(55-74)
Male gender, n (%)	377（66.4）
Vascular risk factors, n (%)	
Hypertension	398(70.1）
Atrial fibrillation	78(13.7）
Hypercholesterolemia	182（32.0）
Coronary heart disease	75（13.2）
Previous TIA or stroke	89（15.7）
Active smoking	205（36.1）
Clinical findings	
BMI (kg/m^2), mean± SD	24.10±2.96
Systolic blood pressure (mmHg), median (IQR)	148(130-166)
Diastolic blood pressure (mmHg), median (IQR)	83(75-93)
TOAST classification, n (%)	
Large-vessel occlusive	177(31.2)
Small-vessel occlusive	318(56.0)
Cardioembolic	56(9.9)
Other and Unknown	17(3.0)
HbA1c (%), median (IQR)	6.6(5.8-8.3)
FBG (mmol/L), median (IQR)	7.37(5.99-10.10)
NIHSS at admission, median (IQR)	4(2-10)
Reperfusion therapy, n (%)	32(5.6)
Unfavorable outcome at 3 months, n (%)	226(39.8)
Mortality at 3 months, n (%)	58(10.2)

AIS acute ischemic stroke; IQR interquartile range; TIA transient ischemic attack; BMI body mass index; SD standard deviation; TOAST Trial of Org 10172 in Acute Stroke Treatment; HbA1c hemoglobin A1c; FBG fasting blood glucose; NIHSS National Institutes of Health Stroke Scale.

Table 2 Univariable and multivariable logistic regression analyses for unfavorable outcome and mortality

Parameter	Univariable analysis			Multivariable analysis		
	OR	95 %CI[a]	*P* value	OR	95 %CI[a]	*P* value
Predictor: Unfavorable functional outcome						
Age	1.03	1.01-1.04	<0.0001	1.02	1.00-1.05	0.037
Male gender	0.63	0.45-0.90	0.011	0.72	0.40-1.28	0.259
Hypertension	0.92	0.64-1.33	0.659	—		
Atrial fibrillation	2.19	1.35-3.55	0.001	1.99	0.80-5.06	0.151
Hypercholesterolemia	0.89	0.62-1.28	0.530	—		
Coronary heart disease	1.89	1.16-3.08	0.011	1.03	0.47-2.28	0.940
Previous TIA or stroke	1.29	0.82-2.03	0.280	—		
Active Smoking	1.08	0.76-1.53	0.664	—		
BMI	0.97	0.912-1.02	0.226	—		
Systolic blood pressure	1.00	1.00-1.01	0.966	—		
Diastolic blood pressure	1.00	1.00-1.01	0.875	—		
Reperfusion therapy	0.90	0.43-1.89	0.785	—		
NIHSS at admission	1.58	1.46-1.70	<0.0001	1.42	1.31-1.55	<0.0001
Large-vessel occlusive	1.12	0.38-3.35	0.839	—		
Small-vessel occlusive	0.07	0.02-0.19	<0.0001	0.24	0.06-0.93	0.039
Cardioembolic [b]	1.25	0.37-4.72	0.717	—		
HbA1c (%)	1.11	1.01-1.23	0.038	0.84	0.71-1.01	0.056
Fasting blood glucose	1.38	1.29-1.48	<0.0001	1.25	1.14-1.37	<0.0001
Predictor: Mortality						
Age	1.01	1.00-1.04	0.238	—		
Male gender	0.69	0.40-1.20	0.189	—		
Hypertension	1.13	0.62-2.09	0.681	—		
Atrial fibrillation	4.95	2.72-9.02	<0.0001	2.85	1.16-7.01	0.023
Hypercholesterolemia	0.87	0.48-1.57	0.638	—		
Coronary heart disease	2.09	1.07-4.09	0.032	1.61	0.67-3.90	0.287
Previous TIA or stroke	1.296	0.64-2.61	0.467	—		
Active Smoking	1.50	0.87-2.60	0.146	—		
BMI	0.96	0.87-1.05	0.337	—		
Systolic blood pressure	0.99	0.98-1.00	0.135	—		
Diastolic blood pressure	1.00	0.98-1.01	0.596	—		
NIHSS at admission	1.21	1.16-1.26	<0.0001	1.13	1.08-1.19	<0.0001
Large-vessel occlusive	0.89	0.27-2.88	0.884	—		
Reperfusion therapy	1.28	0.43-3.77	0.661	—		
Small-vessel occlusive	0.02	0.00-0.12	<0.0001	0.09	0.01-0.67	0.019
Cardioembolic	1.08	0.30-3.87	0.902	—		
HbA1c (%)	1.55	1.34-1.79	0.000	1.49	1.23-1.78	0.000
Fasting blood glucose	1.23	1.15-1.31	<0.0001	1.10	1.01-1.19	0.025

OR odds ratio; CI confidence interval; TIA transient ischemic attack; BMI body mass index; NIHSS National Institutes of Health Stroke Scale

[a] Note that the odds ratio corresponds to a unit increase in the explanatory variable

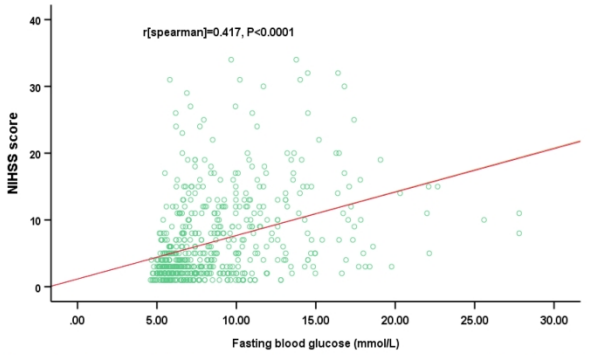
[b] Other and unknown ischemic stroke subtype as the reference

Figure 1 The correlation between fasting blood glucose levels and the National Institutes of Health Stroke Scale (NIHSS); Spearman's analysis (r=0.417, P<0.0001)

Figure 2 Distribution of fasting blood glucose levels in patients with favorable and unfavorable outcomes. All data are the median and interquartile range (IQR). Mann–Whitney U-test (Z=-11.176, P<0.0001)

Figure 3 Distribution of fasting blood glucose levels in survivors and non-survivors. All data are the median and interquartile range (IQR). Mann–Whitney U-test (Z=-6.851, P<0.0001)

Figure 4 Kaplan–Meier survival based on fasting blood glucose (FBG) quartiles. Time-to-death was analyzed by Kaplan–Meier curves based on FBG quartiles. Patients in the lower two quartiles (FBG ≤6.00 mmol/L and 6.00<FBG≤7.37 mmol/L) had a lower risk of mortality compared to patients with FBG levels in the higher two quartiles (FBG>10.10 mmol/L and 7.37<FBG≤10.10 mmol/L, P<0.0001).



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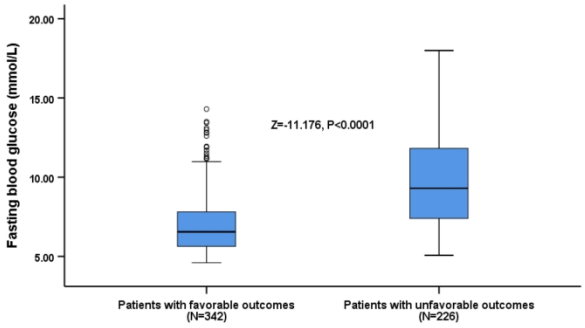

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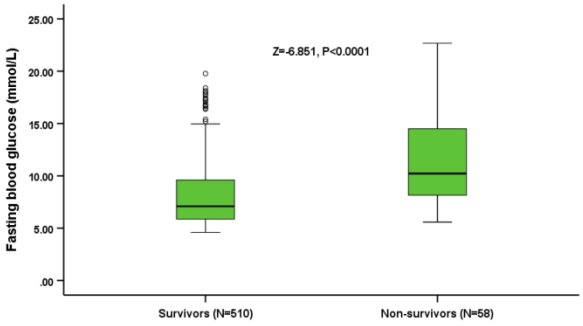

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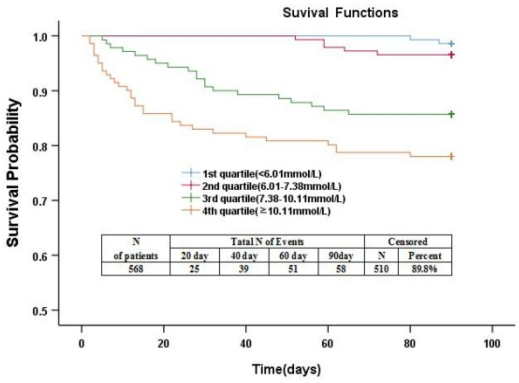

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209x296mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3, 4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	3
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4
		(*b*) Describe any methods used to examine subgroups and interactions	4
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	4
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	4
Outcome data	15*	Report numbers of outcome events or summary measures over time	4, 5

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5
		(*b*) Report category boundaries when continuous variables were categorized	5
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	5，6
Discussion			
Key results	18	Summarise key results with reference to study objectives	6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7
Generalisability	21	Discuss the generalisability (external validity) of the study results	7
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	8

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Association between fasting blood glucose and outcomes and mortality in acute ischemic stroke patients with diabetes mellitus: a retrospective observational study in Wuhan, China

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Association between fasting blood glucose and outcomes and mortality in acute ischemic stroke patients with diabetes mellitus: a retrospective observational study in Wuhan, China

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ABSTRACT

Objective To evaluate the predictive value of fasting blood glucose (FBG) on unfavorable outcomes and mortality in diabetes mellitus (DM) patients after acute ischemic stroke (AIS).

Study design A hospital-based observational cohort study was conducted. Clinical data, including sex, age, BMI, vascular risk factors, and systolic/diastolic blood pressure, were routinely collected. National Institute of Health Stroke Scale (NIHSS) score was used to assess stroke severity on admission. FBG was determined on the first day after fasting for at least 8 hours. The modified Rankin Scale (mRS) was used to assess functional outcome at 90 days: 3-6, unfavorable outcome; 6, death.

Setting Renmin Hospital of Wuhan University, Wuhan, China.

Participants AIS patients with DM who were consecutively admitted within 24 hours of onset from January 2018 to June 2019.

Results For the 568 patients, the median age was 65 years [interquartile range (IQR), 55-74]. There were 377 (66.4%) men. The median FBG values were 7.37 mmol/L (IQR, 5.99-10.10 mmol /L), and the median glycosylated hemoglobin (HbA1c) values were 6.6 (IQR, 5.8-8.3). Multivariable logistic and Cox regression analysis of confounding factors showed that FBG at the time of admission was an independent predictor of unfavorable outcome [odds ratio (OR), 1.25 (1.14-1.37); P<0.0001] and mortality [hazard ratio (HR), 1.10 (1.03-1.15) ; P <0.05] at 90 days after onset. Time to death was analyzed by Kaplan–Meier curves based on FBG quartiles. The risk of death in the two highest quartile groups (FBG, 7.38-10.10 mmol/L; FBG, ≥ 10.11 mmol/L) was significantly higher than that in the two lowest quartile groups (FBG, ≤6.00 mmol/L; FBG, 6.01-7.37 mmol/L) (P <0.0001).

Conclusions Higher FBG levels are associated with unfavorable outcomes and mortality in Chinese AIS patients with DM. Our data contribute to the knowledge regarding the relationship between FBG and outcome in AIS with DM.

Strengths and limitations of this study

- This study evaluated the predictive value of FBG at admission with regard to short-term outcome. Previous studies focusing on this evaluation are rare.
- Complete follow-up was achieved in this study.
- The study used routinely collected clinical data and practical statistical methods to correct the effects of confounding factors.
- This study was conducted in a single center with a limited sample size.
- Data of random blood glucose as a possible meaningful predictor were not fully available in this retrospective study.

INTRODUCTION

Diabetes mellitus (DM) is recognized as an important risk factor for ischemic stroke.[1 2] Previous epidemiologic investigations have confirmed that patients with DM have a high disability rate and a high risk of in-hospital death after an acute ischemic stroke (AIS).[3 4] A recent study involving a Chinese population included 10,331 patients with DM who were confirmed to have an AIS showed a high risk for in-hospital death.[5] Indeed, assessment of functional outcome and mortality risk among AIS patients with diabetes is a common concern for both patients and clinicians.

Hyperglycemia is common in AIS patients with and without DM.[6] Many studies have shown that hyperglycemia at the time of admission is associated with AIS infarct volume.[7] This condition can also predict functional outcome and risk of death.[8-10] However, few studies have focused on DM patients with hyperglycemia at the time of admission. Studies have shown that high blood glucose levels in DM patients have no significant predictive value for functional outcomes and risk of death.[11] Moreover, two recent studies have confirmed that high blood glucose levels are predictive of functional outcomes in diabetic and non-diabetic patients complicated by cerebral infarction.[12 13] Therefore, the correlation between blood glucose levels and functional outcomes in DM patients should be defined so that clinicians can provide accurate prognosis and eventually develop glycemic control strategies after an ischemic stroke.

Because fasting blood glucose (FBG) can minimize the effects of diet,[14] the FBG level is considered a more reliable blood glucose level detection tool than random blood glucose levels.[15] Compared to random blood glucose levels, FBG level provides a stronger predictor of functional outcomes.[16 17]

Hence, this study aimed to investigate the predictive value of FBG on functional outcomes and mortality in Chinese AIS patients with DM.

METHODS

Patients and Study Design

This retrospective observational study collected information involving AIS patients with DM who were admitted to the Department of Neurology of the Renmin Hospital of Wuhan University from January 2018 to June 2019. The diagnostic criteria for acute cerebral infarction are in accordance with World Health Organization standards.[18] Patients with DM were defined as patients with a history of DM before admission according to their medical records or those who received drugs or insulin for hypoglycemic treatment after admission. Patients must meet the following criteria: onset was within 24 h; age $\geq$ 18 years; and, in the case of a recurrent cerebral infarction, a modified Rankin Scale (mRS) $\leq$ 2.[19] Patients with psychoses, severe bone joint diseases, and other neurologic diseases that affect functional outcomes were excluded from the study.

The study was approved by the Ethics Committee of the Renmin Hospital of Wuhan University. Signed informed consent was obtained for all patients participating in the study.

Clinical Variables and Neuroimaging

All patients completed diagnostic testing after admission, including routine serologic testing, neuroimaging, intracranial and extravascular studies, and a cardiac examination. Clinical data were routinely collected at the time of admission, included gender, age, BMI, notation of vascular risk factors (including hypertension, DM, coronary heart disease, atrial fibrillation, hypercholesterolemia,

stroke history, and smoking history), and systolic/diastolic blood pressure. The severity of stroke at the time of admission was assessed using the National Institutes of Health Stroke Scale (NIHSS).[20] Reperfusion therapy included IV thrombolysis with rtPA and endovascular therapy with intra-arterial thrombolysis or mechanical thrombectomy. The causes of stroke were grouped according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST),[21] as follows: large-vessel occlusive; small-vessel occlusive; cardioembolic; and other and unknown. Patients underwent a CT scan and/or MRI examination within 24-48 h after admission. The diagnosis of cerebral infarction was based on these images.

End Points and Follow-up

The mRsS score at 90 days was used as an indicator of functional outcomes, as follows: ≤ 2, good outcome; 3-6, unfavorable outcome; and 6, death. Two specially trained neurologic nurses were responsible for assessing functional outcomes of AIS patients by calling patients or their family members once a month.

Laboratory Testing

To minimize the impact of diet on the blood glucose level, FBG levels were used as a reliable glycemic index. Blood samples were collected at approximately 7:30 am on the first day after admission after fasting for at least 8 hours. Glycosylated hemoglobin (HbA1c) was tested using standard test methods.

Statistical Analysis

Data following normal distribution were described using the mean ± standard deviation. Data following a non-normal distribution were described using the median (quartiles). Categorical variables were described using a percentage. The Mann–Whitney U test was used to compare the non-normal distribution between two groups. The Pearson correlation coefficient and Spearman's rank correlation coefficient were used for liner correlation analysis.. The continuous variables proved to be linearly correlated with the outcomes were brought into the regression model. We used univariable logistic regression to analyze the relationship between factors and outcomes of acute cerebral infarction at 90 days . We used univariable Cox regression to analyze the relationship between factors and mortality of acute cerebral infarction at 90 days. Factors giving a $P<0.1$ were re-analyzed using multivariable regression analysis to determine the correlation between the FBG level and functional outcomes of cerebral infarction, as well as death. The results are expressed by ORs and 95%CIs. Moreover, we performed quartiles based on FBG levels as follows: quartile 1 (FBG ≤ 6.00 mmol/L); quartile 2 (FBG, 6.01-7.37 mmol/L); quartile 3 (FBG, 7.38-10.10 mmol/L); and quartile 4 (FBG ≥ 10.11 mmol/L). Kaplan–Meier survival curves were used to analyze the value of the FBG level for predicting death. SPSS (version 25.0; SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. A $P < 0.05$ indicates a significant difference.

Patient and public involvement

No patients were involved with design, data provision, analysis, or publication of the study.

RESULTS

Baseline Characteristics of the Study Cohort

A total of 568 AIS patients with DM, including 377 males and 191 females, were enrolled in this study and all were followed up. The median age of the patients was 65 years (IQR, 55-74 years), and the mean BMI was 24.10 ± 2.96 kg/m^2. The median NIHSS score at the time of admission was 4 (IQR, 2-10). A total of 32 of 568 AIS patients received reperfusion therapy, including 28 patients with IV rtPA thrombolysis and 7 patients with endovascular treatment. A total of 226 patients (39.8%) had unfavorable outcomes, including 58 deaths (10.2%). Of the 58 deaths in this study, 36 (62.1%) died of increased intracranial pressure; 10 (17.2%) died of cardiac diseases such as heart failure, myocardial infarction, or arrhythmia; and 12 (20.7%) died of other causes such as severe pneumonia, stress ulcer bleeding, or pulmonary embolism. Moreover, 14 (24.1%) had symptomatic intracerebral hemorrhages. The baseline data of all patients at the time of admission are shown in Table 1.

Main Results

The median FBG values were 7.37 mmol/L(IQR, 5.99-10.10 mmol /L). The NIHSS scores of AIS patients with DM at the time of admission increased with elevation of the FBG levels. A moderately significant positive correlation was found between the NIHSS score and the FBG level (r = 0.417, P<0.0001). The results are shown in Figure 1. The results also showed that FBG levels had no significant correlation with other risk factors, including smoking, hypertension, coronary heart disease, hypercholesterolemia history, or a history of stroke (P>0.05).

FBG level and functional outcome at 90 days

FBG levels of 226 patients with unfavorable functional outcomes at 90 days [9.64 mmol/L (IQR, 7.40-12.60 mmol /L)] were significantly higher than patients with favorable functional outcomes [6.56 mmol/L (IQR, 5.64-7.86 mmol /L); Z = -11.176; P < 0.0001; Figure 2]. Univariable regression analysis showed that unfavorable functional outcomes were significantly correlated with age, male gender, atrial fibrillation, coronary heart disease, NIHSSNIHSS score, small-vessel occlusion, HbA1c, and FBG level (P<0.05). Multivariable logistic regression analysis was performed on outcome-indicating factors. The results showed that age (OR, 1.02; 95%CI, 1.00-1.05; P = 0.037), NIHSSNIHSS score (OR, 1.42; 95%CI, 1.31-1.55; P < 0.0001), small-vessel occlusion (OR, 0.24; 95%CI, 0.06-0.93; P = 0.039), and FBG level (OR, 1.25; 95%CI, 1.14-1.37; P < 0.0001) were independent predictive factors of functional outcome for AIS patients with DM (Table 2).

FBG levels and mortality at 90 days

The FBG levels of 58 nonsurviving patients at 90 days were significantly higher than surviving patients [10.41 mmol/L (IQR, 8.14-15.29 mmol /L vs. 7.10 mmol/L (IQR, 5.88-9.65 mmol /L); Z = -6.851, P < 0.0001; Figure 3]. Univariable Cox regression analysis of nonsurviving patients showed that atrial fibrillation, coronary heart disease, NIHSS score, small-vessel occlusive disease, HbA1c, and FBG level were significantly associated with death (P<0.05). Multivariable Cox regression analysis was performed on functional-outcome-indicating factors and the results showed that atrial fibrillation [hazard ratio (HR), 2.17; 95%CI, 1.20-3.93; P = 0.011), NIHSS score (HR, 1.11; 95%CI,

1.08-1.15; P < 0.0001), small-vessel occlusive (HR. 0.07; 95%CI, 0.12-0.38; P = 0.002), HbA1c (HR, 1.32; 95%CI, 1.15-1.51; P < 0.0001), and FBG levels (HR, 1.10; 95%CI, 1.03-1.15; P=0.004; Table 3) were independent predictive factors of death for AIS patients with DM.

We used Kaplan-Meier curves to compare the quartiles of FBG levels and time to death after admission. The results showed that the risk of death in the two highest quartile groups (FBG, 7.38-10.10 mmol/L; and FBG, ≥10.11 mmol/L) was significantly higher than the two lowest quartile groups (FBG, ≤6.00 mmol/L; and FBG, 6.01-7.37 mmol/L; P <0.0001; Figure 4).

DISCUSSION

In this retrospective study, we found that higher fasting blood glucose levels are associated with unfavorable outcomes and mortality in Chinese AIS patients with DM. Moreover, higher FBG was associated with higher NIHSS score on admission.

Acute stroke may be accompanied by neuroendocrine disorders and inflammation, resulting in an acute blood glucose elevation.[22] Previous studies focusing on acute blood glucose elevations generally used fasting or random blood glucose levels at the time of admission as an indicator of acute blood glucose. A meta-analysis involving 32 studies showed that acute stroke patients often had high blood glucose levels, and the proportion of high blood glucose levels in acute stroke patients with and without DM reached 8%-63% and 39%-83%, respectively.[6] A number of studies have shown that high blood glucose levels at the time of admission are closely related to the functional outcome of patients with AIS.[9 10 23 24] Masrur et al.[9] studied 1408 AIS patients who received intravenous thrombolysis and showed that high blood glucose levels at the time of admission increased the risk of unfavorable functional outcomes and death. Snarska et al. [10] and Zhao et al.[25] reported that a high blood glucose level in AIS patients at the time of admission was significantly associated with an unfavorable functional outcome and risk of in-hospital death. Moreover, several previous studies involving AIS patients without DM showed that high blood glucose levels were also closely related to unfavorable functional outcomes and risk of death.[24 26]

Because the focus of previous studies was on AIS patients only or AIS patients without DM, acute blood glucose levels at the time of admission among AIS patients with DM were not adequately addressed; thus, the predictive value for unfavorable functional outcomes or mortality has not been established.[12 13 26-28] Yao et al.[24] and Hu et al.[28] showed that in AIS patients without DM, high FBG levels predicted unfavorable functional outcomes and death; however, similar levels for AIS patients with DM had an insignificant predictive value. Tsuga et al.[12] and Sung et al.[13] performed subgroup analysis on AIS patients with and without DM and showed that acute blood glucose levels in both groups had predictive power for functional outcomes. Recently, a meta-analysis incorporated 13 studies and showed no statistical difference existed in prognostic indicators between AIS patients with and without DM.[29] In this study, we used baseline FBG levels at the time of admission as a marker for the acute blood glucose level. The results revealed additional evidence for the predictive value of high acute blood glucose levels on functional outcomes and high risk of death in AIS patients with DM.

The mechanism underlying the predictive value of high blood glucose levels at the time of admission on functional outcome and mortality is not fully understood; however, the correlation between a high blood glucose level after AIS and the severity of stroke and unfavorable functional

outcomes may be summarized as follows. First, a high blood glucose level can affect the balance between the coagulation and fibrinolytic systems, resulting in impaired recanalization.[30 31] Second, a high blood glucose level may affect endothelium-derived nitric-oxide-mediated vasodilation, thereby reducing intracranial blood flow and reperfusion at the infarct site.[32 33] In vitro studies have shown that nitric oxide synthase 3 gene expression and nitric oxide production are reduced in hyperglycemic conditions.[34 35] Clinical studies have shown that cerebral infarction tissue reperfusion is decreased and infarct volume is increased in patients with high blood glucose levels.[36-38] Third, a high blood glucose level may generate oxidative stress, leading to neuroendocrine disorders and inflammatory reactions,[39 40] blood-brain barrier disruption,[41] and eventually reperfusion injury.[37 42] Two clinical studies have shown that ischemic stroke patients with acute high blood glucose levels are at increased risk for hemorrhagic transformation,[43] and cerebral hemorrhage in patients with thrombolysis leads to unfavorable functional outcomes.[44] High blood glucose levels may increase the risk of vascular reperfusion injury. Fourth, patients with DM generally have insufficient insulin secretion or insulin resistance; therefore, anaerobic glycolysis may increase in patients with high blood glucose levels,[45 46] resulting in brain tissue lactic acid accumulation and internal environment disorders that aggravate brain tissue damage.[47] All of these pathologic changes together cause severe stroke and secondary functional outcomes and death.

Strengths and limitations

This study had the following highlights. First, quite a few studies have evaluated the association between blood glucose level and outcomes of AIS patients without DM; however, to the best of our knowledge, no studies have evaluated these conditions in patients with DM[24 26]. Furthermore, complete follow-up of all patients was achieved in this study. Third, this study used routinely collected clinical data such as gender, age, BMI, vascular risk factors, NIHSS score, systolic/diastolic blood pressure, and reperfusion therapy. Additionally, practical statistical methods were used to correct the effects of confounding factors.

This study also had limitations. First, a single center was used and sample size was limited. Second, data of random blood glucose as a possible meaningful predictor were not fully available in this retrospective study. Therefore, we cannot investigate the predictive value of random blood glucose compared with FBG.

CONCLUSIONS

In conclusion, higher fasting blood glucose levels are associated with unfavorable outcomes and mortality in Chinese AIS patients with DM. Our data contribute to the knowledge for clinicians about the relation between FBG and outcome in AIS with DM.

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Contributors TY analyzed and interpreted the results and wrote this manuscript text. TY, YQZ, JS, BP, LX, and QC had full access to all of the data in the study and took responsibility for the integrity of the data and accuracy of the data analysis. TY, YQZ, and ZCL designed the study. All authors reviewed and approved the manuscript.

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Table 1 Baseline characteristics of patients with AIS

Demographic characteristics	DM Patients
N	568
Age(years), median (IQR)	65(55-74)
Male gender, n (%)	377（66.4）
Vascular risk factors, n (%)	
Hypertension	398(70.1）
Atrial fibrillation	78(13.7）
Hypercholesterolemia	182（32.0）
Coronary heart disease	75（13.2）
Previous TIA or stroke	89（15.7）
Active smoking	205（36.1）
Clinical findings	
BMI (kg/m^2), mean± SD	24.10±2.96
Systolic blood pressure (mmHg), median (IQR)	148(130-166)
Diastolic blood pressure (mmHg), median (IQR)	83(75-93)
TOAST classification, n (%)	
Large-vessel occlusive	177(31.2)
Small-vessel occlusive	318(56.0)
Cardioembolic	56(9.9)
Other and Unknown	17(3.0)
HbA1c (%), median (IQR)	6.6(5.8-8.3)
FBG (mmol/L), median (IQR)	7.37(5.99-10.10)
NIHSS at admission, median (IQR)	4(2-10)
Reperfusion therapy, n (%)	32(5.6)
Unfavorable outcome at 3 months, n (%)	226(39.8)
Mortality at 3 months, n (%)	58(10.2)

AIS acute ischemic stroke; IQR interquartile range; TIA transient ischemic attack; BMI body mass index; SD standard deviation; TOAST Trial of Org 10172 in Acute Stroke Treatment; HbA1c hemoglobin A1c; FBG fasting blood glucose; NIHSS National Institutes of Health Stroke Scale.

Table 2 Univariable and multivariable logistic regression analyses for unfavorable outcome

Parameter	Univariable analysis			Multivariable analysis		
	OR	95 %CI[a]	*P* value	OR	95 %CI[a]	*P* value
Age	1.03	1.01-1.04	<0.0001	1.02	1.00-1.05	0.037
Male gender	0.63	0.45-0.90	0.011	0.72	0.40-1.28	0.259
Hypertension	0.92	0.64-1.33	0.659	—		
Atrial fibrillation	2.19	1.35-3.55	0.001	1.99	0.80-5.06	0.151
Hypercholesterolemia	0.89	0.62-1.28	0.530	—		
Coronary heart disease	1.89	1.16-3.08	0.011	1.03	0.47-2.28	0.940
Previous TIA or stroke	1.29	0.82-2.03	0.280	—		
Active Smoking	1.08	0.76-1.53	0.664	—		
BMI	0.97	0.912-1.02	0.226	—		
Systolic blood pressure	1.00	1.00-1.01	0.966	—		
Diastolic blood pressure	1.00	1.00-1.01	0.875	—		
Reperfusion therapy	0.90	0.43-1.89	0.785	—		
NIHSS at admission	1.58	1.46-1.70	<0.0001	1.42	1.31-1.55	<0.0001
Large-vessel occlusive	1.12	0.38-3.35	0.839	—		
Small-vessel occlusive	0.07	0.02-0.19	<0.0001	0.24	0.06-0.93	0.039
Cardioembolic [b]	1.25	0.37-4.72	0.717	—		
HbA1c (%)	1.11	1.01-1.23	0.038	0.84	0.71-1.01	0.056
Fasting blood glucose	1.38	1.29-1.48	<0.0001	1.25	1.14-1.37	<0.0001

OR odds ratio; CI confidence interval; TIA transient ischemic attack; BMI body mass index; NIHSS National Institutes of Health Stroke Scale

[a] Note that the odds ratio corresponds to a unit increase in the explanatory variable

[b] Other and unknown ischemic stroke subtype as the reference

Table 3 Univariable and multivariable Cox regression analyses for mortality

Parameter	Univariable analysis			Multivariable analysis		
	HR	95 %CI[a]	*P* value	HR	95 %CI[a]	*P* value
Age	1.01	1.00-1.03	0.252	—		
Male gender	0.70	0.42-1.20	0.186	—		
Hypertension	1.13	0.63-2.00	0.684	—		
Atrial fibrillation	4.36	2.56-7.41	<0.0001	2.17	1.20-3.93	0.011
Hypercholesterolemia	0.88	0.50-1.56	0.670	—		
Coronary heart disease	1.97	1.06-3.65	0.031	1.44	0.76-2.71	0.262
Previous TIA or stroke	1.25	0.65-2.42	0.499	—		
Active Smoking	1.48	0.88-2.49	0.135	—		
BMI	0.96	0.88-1.04	0.301	—		
Systolic blood pressure	0.99	0.98-1.00	0.135	—		
Diastolic blood pressure	1.00	0.98-1.01	0.620	—		
Reperfusion therapy	1.27	0.46-3.75	0.659	—		
NIHSS at admission	1.20	1.14-1.20	<0.0001	1.11	1.08-1.15	<0.0001
Large-vessel occlusive	0.88	0.31-2.46	0.802	—		
Small-vessel occlusive	0.02	0.00-0.13	<0.0001	0.07	0.12-0.38	0.002
Cardioembolic	1.05	0.35-3.19	0.933	—		
HbA1c (%)	1.46	1.30-1.65	<0.0001	1.32	1.15-1.51	<0.0001
Fasting blood glucose	1.17	1.12-1.22	<0.0001	1.10	1.03-1.15	0.004

OR odds ratio; CI confidence interval; TIA transient ischemic attack; BMI body mass index; NIHSS National Institutes of Health Stroke Scale

[a] Note that the odds ratio corresponds to a unit increase in the explanatory variable

[b] Other and unknown ischemic stroke subtype as the reference

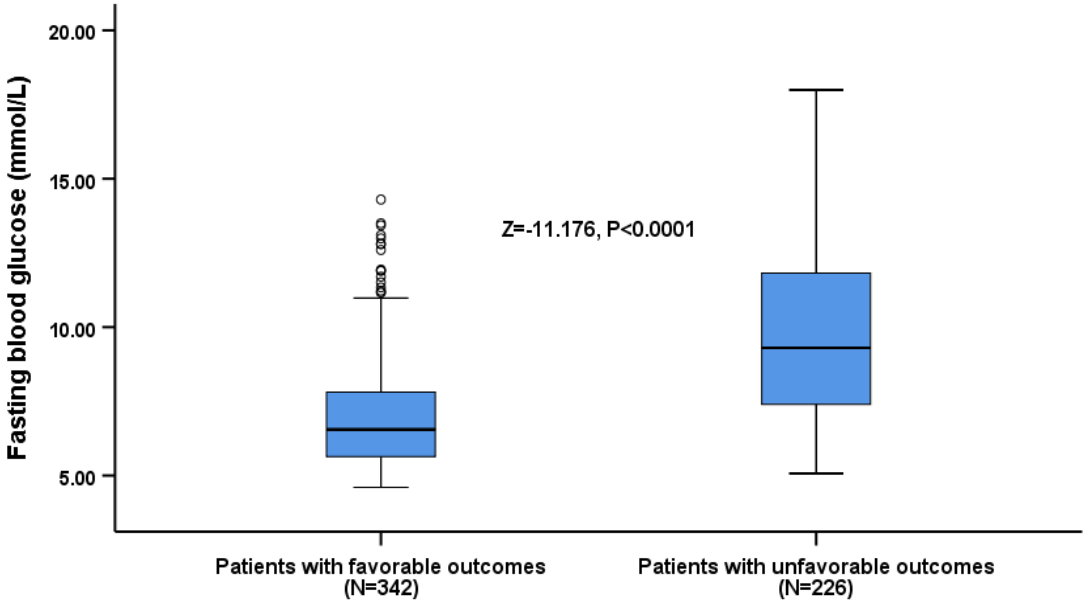
Figure 1 The correlation between fasting blood glucose levels and the National Institutes of Health Stroke Scale (NIHSS); Spearman's analysis (r=0.417, P<0.0001)

Figure 2 Distribution of fasting blood glucose levels in patients with favorable and unfavorable outcomes. All data are the median and interquartile range (IQR). Mann–Whitney U-test (Z=-11.176, P<0.0001)

Figure 3 Distribution of fasting blood glucose levels in survivors and non-survivors. All data are the median and interquartile range (IQR). Mann–Whitney U-test (Z=-6.851, P<0.0001)

Figure 4 Kaplan–Meier survival based on fasting blood glucose (FBG) quartiles. Time-to-death was analyzed by Kaplan–Meier curves based on FBG quartiles. Patients in the lower two quartiles (FBG ≤6.00 mmol/L and 6.00<FBG≤7.37 mmol/L) had a lower risk of mortality compared to patients with FBG levels in the higher two quartiles (FBG>10.10 mmol/L and 7.37<FBG≤10.10 mmol/L, P<0.0001).

Figure 1 The correlation between fasting blood glucose levels and the National Institutes of Health Stroke Scale (NIHSS); Spearman's analysis (r=0.417, P<0.0001).



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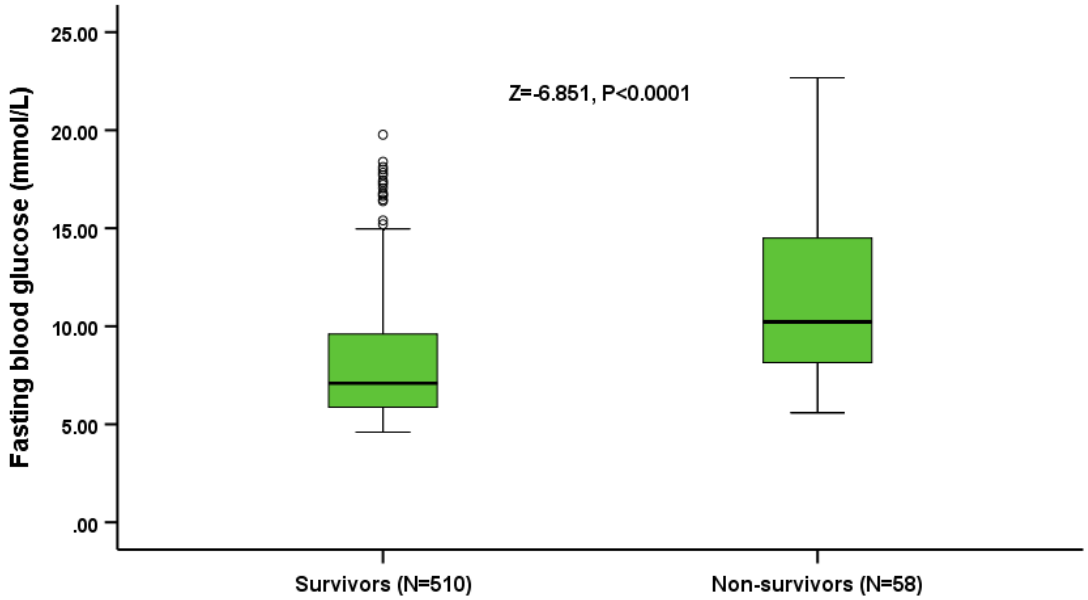

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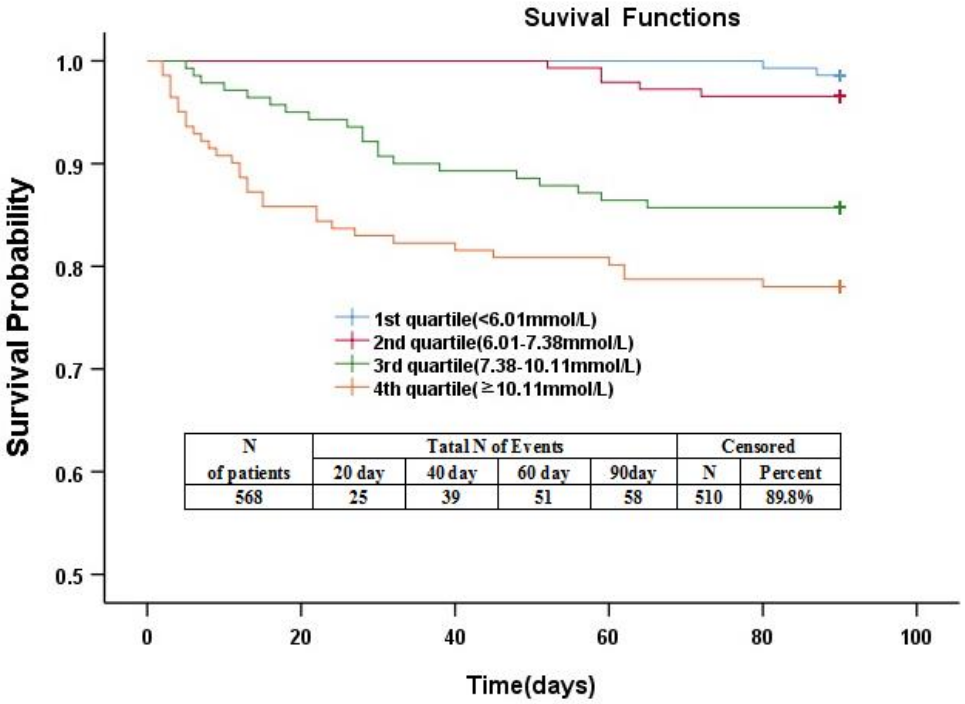

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3, 4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	3
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4
		(*b*) Describe any methods used to examine subgroups and interactions	4
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	4
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	4
Outcome data	15*	Report numbers of outcome events or summary measures over time	4, 5

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5
		(*b*) Report category boundaries when continuous variables were categorized	5
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	5，6
Discussion			
Key results	18	Summarise key results with reference to study objectives	6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7
Generalisability	21	Discuss the generalisability (external validity) of the study results	7
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	8

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.