




BMJ Open Association between fasting blood glucose and outcomes and mortality in acute ischaemic 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 unfavourable outcomes and mortality in diabetes mellitus (DM) patients after acute ischaemic stroke (AIS).

Study design A hospital-based observational cohort study was conducted. Clinical data, including sex, age, body mass index, vascular risk factors and systolic/diastolic blood pressure, were routinely collected. National Institutes of Health Stroke Scale 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 was used to assess functional outcome at 90 days: 3–6, unfavourable outcome and 6, death.

Setting Renmin Hospital of Wuhan University, Wuhan, China.

Participants Patients who had AIS 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 (IQR, 55–74 years). 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 glycated haemoglobin (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 unfavourable outcome (OR, 1.25 (1.14–1.37); $p < 0.0001$) and mortality (HR, 1.10 (1.03–1.15); $p < 0.05$) at 90 days after onset. Time to death was analysed 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 unfavourable outcomes and mortality in Chinese patients who had AIS with DM. Our data contribute to the knowledge regarding the relationship between FBG and prognosis in patients with DM who had AIS.

INTRODUCTION

Diabetes mellitus (DM) is recognised as an important risk factor for ischaemic stroke.^{1 2}

Strengths and limitations of this study

- This study evaluated the predictive value of fasting blood glucose 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 centre with a limited sample size.
- The data of random blood glucose as a possible meaningful predictor were not fully available in this retrospective study.

Previous epidemiological investigations have confirmed that patients with DM have a high disability rate and a high risk of in-hospital death after an acute ischaemic 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 patients who had AIS with diabetes is a common concern for both patients and clinicians.

Hyperglycaemia is common in patients who had AIS with and without DM.⁶ Many studies have shown that hyperglycaemia 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 hyperglycaemia 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 glycaemic control strategies after an ischaemic stroke.

Because fasting blood glucose (FBG) can minimise 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 with 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 patients who had AIS with DM.

METHODS

Patients and study design

This retrospective observational study collected information involving patients who had AIS 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 WHO's 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 hypoglycaemic treatment after admission. Patients must meet the following criteria: onset was within 24 hours; age ≥ 18 years and, in the case of a recurrent cerebral infarction, a modified Rankin Scale (mRS) score of ≤ 2 .¹⁹ Patients with psychoses, severe bone joint diseases and other neurological diseases that affect functional outcomes were excluded from the study.

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 extracranial studies and a cardiac examination. Clinical data were routinely collected at the time of admission, included gender, age, body mass index (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 intravenous thrombolysis with recombinant tissue plasminogen activator (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 an MRI examination within 24–48 hours after admission. The diagnosis of cerebral infarction was based on these images.

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, unfavourable outcome and 6, death. Two specially trained neurologic nurses were responsible for assessing functional outcomes of patients who had AIS by calling patients or their family members once a month.

Laboratory testing

To minimise the impact of diet on the blood glucose level, FBG levels were used as a reliable glycaemic index. Blood samples were collected at approximately 07:30 on the first day after admission after fasting for at least 8 hours. Glycated haemoglobin (HbA1c) was tested using standard test methods.

Statistical analysis

The data following normal distribution were described using the mean \pm SD. The 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 linear correlation analysis. The continuous variables proved to be linearly correlated with the outcomes and were brought into the regression model. We used univariable logistic regression to analyse the relationship between factors and outcomes of acute cerebral infarction at 90 days. We used univariable Cox regression to analyse the relationship between factors and mortality of acute cerebral infarction at 90 days. Factors giving a $p < 0.1$ were re-analysed 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 analyse the value of the FBG level for predicting death. SPSS V.25.0 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 patients who had AIS with DM, including 377 men and 191 women, were enrolled in this study

Table 1 Baseline characteristics of patients who had 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 (mm Hg), median (IQR)	148 (130–166)
Diastolic blood pressure (mm Hg), 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 score at admission, median (IQR)	4 (2–10)
Reperfusion therapy, n (%)	32 (5.6)
Unfavourable outcome at 3 months, n (%)	226 (39.8)
Mortality at 3 months, n (%)	58 (10.2)

AIS, acute ischaemic stroke; BMI, body mass index; DM, diabetes mellitus; FBG, fasting blood glucose; HbA1c, glycated haemoglobin; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischaemic attack; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

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/m². The median NIHSS score at the time of admission was 4 (IQR, 2–10). A total of 32 of 568 patients who had AIS received reperfusion therapy, including 28 patients with intravenous rtPA thrombolysis and 7 patients with endovascular treatment. A total of 226 patients (39.8%) had unfavourable 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 haemorrhages. The baseline data of all patients at the time of admission are shown in [table 1](#).

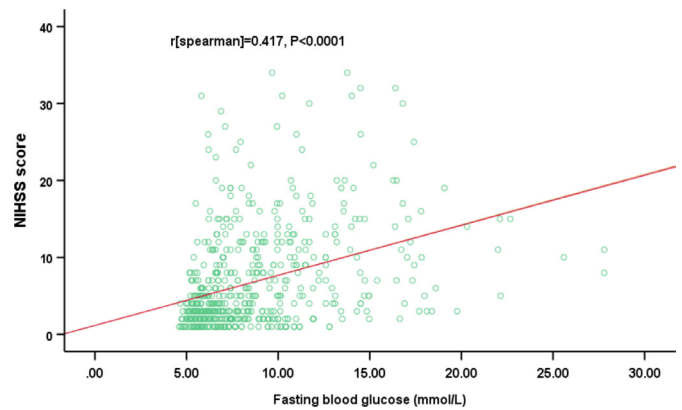


Figure 1 The correlation between fasting blood glucose levels and the National Institutes of Health Stroke Scale (NIHSS) scores; Spearman's analysis ($r=0.417$, $p<0.0001$).

Main results

The median FBG values were 7.37 mmol/L (IQR, 5.99–10.10 mmol/L). The NIHSS scores of patients who had AIS 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 unfavourable functional outcomes at 90 days (9.64 mmol/L (IQR, 7.40–12.60 mmol/L)) were significantly higher than patients with favourable 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 unfavourable functional outcomes were significantly correlated with age, male gender, atrial fibrillation, coronary heart disease, NIHSS 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

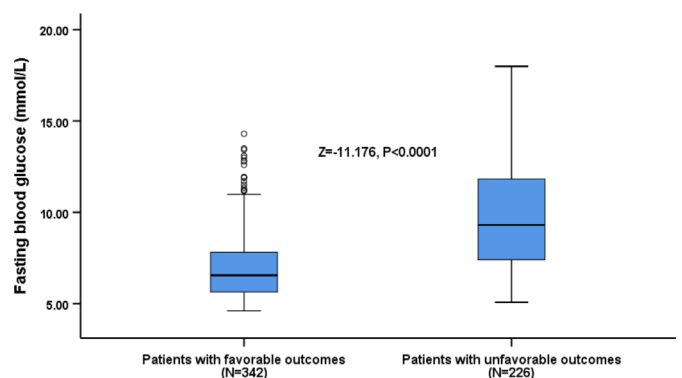


Figure 2 Distribution of fasting blood glucose levels in patients with favourable and unfavourable outcomes. All data are the median and IQR. Mann-Whitney U test ($Z=-11.176$, $p<0.0001$).

Table 2 Univariable and multivariable logistic regression analyses for unfavourable outcomes

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

*Note that the OR corresponds to a unit increase in the explanatory variable.

†Other and unknown ischaemic stroke subtype as the reference.

BMI, body mass index; FBG, fasting blood glucose; HbA1c, glycated haemoglobin; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischaemic attack.

(OR, 1.02; 95% CI 1.00 to 1.05; $p=0.037$), NIHSS score (OR, 1.42; 95% CI 1.31 to 1.55; $p<0.0001$), small-vessel occlusion (OR, 0.24; 95% CI 0.06 to 0.93; $p=0.039$) and FBG level (OR, 1.25; 95% CI 1.14 to 1.37; $p<0.0001$) were independent predictive factors of functional outcome for patients who had AIS 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

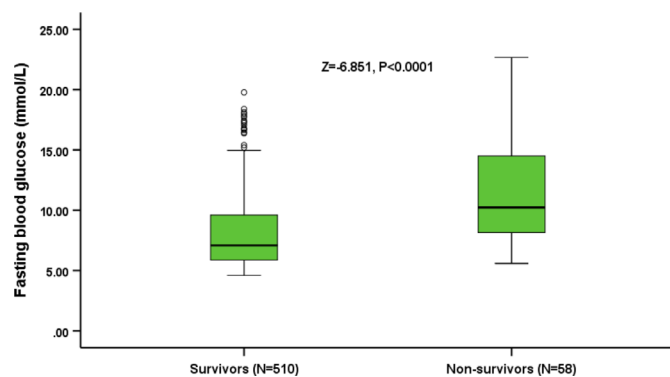


Figure 3 Distribution of fasting blood glucose levels in survivors and non-survivors. All data are the median and IQR. Mann-Whitney U test ($Z=-6.851$, $p<0.0001$).

(IQR, 5.88–9.65 mmol/L); $Z=-6.851$, $p<0.0001$; figure 3). Univariable Cox regression analysis of non-surviving 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 (HR, 2.17; 95% CI 1.20 to 3.93; $p=0.011$), NIHSS score (HR, 1.11; 95% CI 1.08 to 1.15; $p<0.0001$), small-vessel occlusion (HR, 0.07; 95% CI 0.12 to 0.38; $p=0.002$), HbA1c (HR, 1.32; 95% CI 1.15 to 1.51; $p<0.0001$) and FBG levels (HR, 1.10; 95% CI 1.03 to 1.15; $p=0.004$; table 3) were independent predictive factors of death for patients who had AIS 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; FBG, ≥ 10.11 mmol/L) was significantly higher than the two lowest quartile groups (FBG, ≤ 6.00 mmol/L; FBG, 6.01–7.37 mmol/L; $p<0.0001$; figure 4).

DISCUSSION

In this retrospective study, we found that higher FBG levels are associated with unfavourable outcomes and

Table 3 Univariable and multivariable Cox regression analyses for mortality

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

*Note that the hazard ratio corresponds to a unit increase in the explanatory variable.

†Other and unknown ischaemic stroke subtype as the reference.

BMI, body mass index; FBG, fasting blood glucose; HbA1c, glycated haemoglobin; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischaemic attack.

mortality in Chinese patients who had AIS with DM. Moreover, higher FBG was associated with higher NIHSS score on admission.

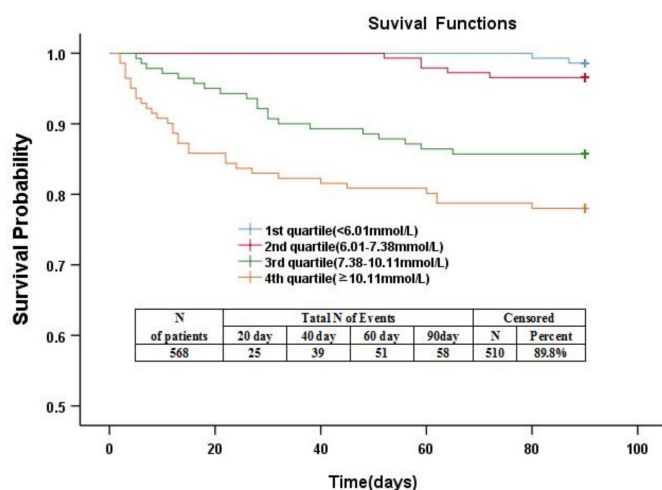


Figure 4 Kaplan-Meier survival based on fasting blood glucose (FBG) quartiles. Time to death was analysed by Kaplan-Meier curves based on FBG quartiles. Patients in the lower two quartiles (FBG, ≤ 6.00 mmol/L; FBG, 6.01–7.37 mmol/L) had a lower risk of mortality compared with patients with FBG levels in the higher two quartiles (FBG, >10.10 mmol/L; FBG, 7.38–10.10 mmol/L; $p < 0.0001$).

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 patients who had AIS, who received intravenous thrombolysis and showed that high blood glucose levels at the time of admission increased the risk of unfavourable functional outcomes and death. Snarska *et al*¹⁰ and Zhao *et al*²⁵ reported that a high blood glucose level in patients who had AIS at the time of admission was significantly associated with an unfavourable functional outcome and risk of in-hospital death. Moreover, several previous studies involving patients who had AIS without DM showed that high blood glucose levels were also closely related to unfavourable functional outcomes and risk of death.^{24 26}



Because the focus of previous studies was on patients who had AIS only or patients who had AIS without DM, acute blood glucose levels at the time of admission among patients who had AIS with DM were not adequately addressed; thus, the predictive value for unfavourable functional outcomes or mortality has not been established.^{12 13 26–28} Yao *et al*²⁴ and Hu *et al*²⁸ showed that in patients who had AIS without DM, high FBG levels predicted unfavourable functional outcomes and death; however, similar levels for patients who had AIS with DM had an insignificant predictive value. Zsuga *et al*¹² and Sung *et al*¹³ performed subgroup analysis on patients who had AIS 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 patients who had AIS 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 patients who had AIS 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 unfavourable functional outcomes may be summarised as follows. First, a high blood glucose level can affect the balance between the coagulation and fibrinolytic systems, resulting in impaired recanalisation.^{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 hyperglycaemic 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 disruption⁴¹ and eventually reperfusion injury.^{37 42} Two clinical studies have shown that ischaemic stroke patients with acute high blood glucose levels are at increased risk for haemorrhagic transformation,⁴³ and cerebral haemorrhage in patients with thrombolysis leads to unfavourable 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 pathological 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 patients who had AIS 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 centre was used and sample size was limited. Second, the 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 FBG levels are associated with unfavourable outcomes and mortality in Chinese patients who had AIS with DM. Our data contribute to the knowledge regarding the relationship between FBG and prognosis in patients with DM who had AIS.

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Contributors TY analysed and interpreted the results and wrote this manuscript text. TY, YZ, 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. TY, YZ and ZL 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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Provenance and peer review Not commissioned; externally peer reviewed.

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

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