

# Fasting blood glucose-to-glycated hemoglobin ratio and all-cause mortality among Chinese in-hospital patients with acute stroke: a 12-month follow-up study

**Zhong-ming Cai**

The First Affiliated Hospital of Wenzhou Medical University

**Man-man Zhang**

The First Affiliated Hospital of Wenzhou Medical University

**Ren-qian Feng**

The First Affiliated Hospital of Wenzhou Medical University

**Xu-dong Zhou**

Pingyang People's Hospital

**Hao-man Chen**

The First Affiliated Hospital of Wenzhou Medical University

**Zhi-peng Liu**

The First Affiliated Hospital of Wenzhou Medical University

**Yan-zhi Wu**

The First Affiliated Hospital of Wenzhou Medical University

**Qun-li Lin**

Yongjia People's Hospital

**Sheng-lie Ye**

The First Affiliated Hospital of Wenzhou Medical University

**Cheng-wei Liao**

The First Affiliated Hospital of Wenzhou Medical University

**Xue-rong Huang**

Ruian People's Hospital

**Le-qiu Sun**

Wenzhou Medical University Affiliated Yueqing Hospital

**Bo Yang**

Wenzhou Medical University

**Bei-lei Zhu** (✉ [doczbl@163.com](mailto:doczbl@163.com))

The First Affiliated Hospital of Wenzhou Medical University

## Research Article

**Keywords:** Acute stroke, all-cause mortality, stress hyperglycemia, fasting blood glucose, glycated hemoglobin

**Posted Date:** April 14th, 2022

**DOI:** <https://doi.org/10.21203/rs.3.rs-1544464/v1>

**License:**  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

---

# Abstract

## Background

Stroke is a leading cause of death and functional impairment in older people. To assess the prospective association between fasting blood glucose-to-glycated hemoglobin ratio and all-cause mortality and poor prognosis in stroke patients.

## Methods

A total of 941 Chinese inpatients with acute stroke (mean age of 65.7) were consecutively enrolled in the prospective clinical study and followed up for 12 months after discharge. Stress hyperglycemia was measured using the ratio of fasting blood glucose (FBG, mmol/L)/glycated hemoglobin (HbA1c, %). The primary outcome was all-cause mortality, and secondary outcomes were poor prognosis defined as infectious complications, a National Institutes of Health Stroke Scale (NIHSS) score  $\geq 6$ , a Barthel Index score  $\leq 60$ , or a modified Rankin Scale (mRS) score of 3–6, presented as multivariate-adjusted odds ratios (ORs) with 95% confidence intervals (CIs) across the quartiles of the FBG/HbA1c ratio.

## Results

There were 35 (4.1%) all-cause deaths at 3 months and 85 (11.4%) at 12 months. The inpatients with the highest quartile of the FBG/HbA1c ratio had a higher risk of all-cause death at 3 months (adjusted OR: 5.14, 95% CI: 1.06–24.90) and 12 months (adjusted OR: 2.58, 95% CI: 1.14–5.83) and a higher risk of infectious complications (adjusted OR 2.52, 95% CI 1.33–4.76) and dysfunction (adjusted OR 1.87, 95% CI 1.13–3.10) during hospitalization than inpatients with the lowest quartile.

## Conclusions

Stress hyperglycemia, measured by the FBG/HbA1c ratio, was associated with an increased risk of adverse outcomes, including all-cause death, infectious complications, and dysfunction after stroke.

## Background

Stress hyperglycemia, a relatively transient increase in blood glucose levels secondary to neurohormonal derangements and inflammation[1], is associated with increased morbidity and mortality in in-patients hospitalized for myocardial infarction[2], congestive cardiac failure[3], and other critical illnesses[4].

Stress hyperglycemia may occur in a high proportion of patients with stroke[5]. During period of acute stroke, an increase in blood glucose levels was detected induced by the release of stress hormones after the stress stimulating the hypothalamus-pituitary-adrenal axis and the sympathetic nervous system[6]. Previous studies have shown that stress hyperglycemia appears to be a marker of an increased risk of

short-term mortality and poor functional outcomes after stroke[6–8]. However, these studies were performed in selected patient populations, focusing on patients with acute ischemic stroke[6, 9] or further extending to the large vessel occlusion subtype[7]. Additionally, the prognosis was measured only during the hospital stay[9] or at three months after discharge[6, 7]. Furthermore, although specific guidelines for the definition of stress hyperglycemia have not been developed, most previous studies have been based on absolute, rather than relative increases in fasting or randomized blood glucose levels[8, 9].

Due to successful standardization, the glycosylated hemoglobin (HbA1c) concentration has been proposed to be a valuable diagnostic tool for monitoring long-term glycemic control[10]. Additionally, transient changes in blood glucose levels generally do not affect HbA1c concentration[11]. Recent studies have shown that relative hyperglycemia, defined as the fasting blood glucose (FBG)/HbA1c ratio[12] or as admission glucose divided by the estimated average glucose level derived from HbA1c[13], might be a better predictor of outcomes of critical illness than absolute glucose indicators. Therefore, it can be hypothesized that the FBG-to-HbA1c ratio could reflect stress hyperglycemia considering the background glucose level prior to the stroke event[12, 13].

Infectious complications, including pneumonia, urinary tract infection (UTI), gastrointestinal infection, infectious fever etc. are the third most common stroke complications[14], affecting a large number of stroke populations[15]. Infection has been shown to be an independent predictor of neurological functional deterioration[16] and stroke readmission rates[17], leading to a substantial economic burden upon stroke care[18]. Stress hyperglycemia results in impaired host defenses, increasing the risk for infection after stroke[19], which may contribute to adverse outcomes jointly in stroke patients.

We designed this study to prospectively explore the association between stress hyperglycemia, measured by the FBG/HbA1c ratio, and all-cause mortality and poor prognosis after acute stroke. Furthermore, we assessed whether infectious complications may play an important role in the pathway from stress hyperglycemia to mid- and long-term all-cause death.

## Methods

The patient data collection and assessment of outcomes were described as our previous studies[20, 21].

## Patients

Five major medical institutions in Wenzhou (the First Affiliated Hospital of Wenzhou Medical University, Yueqing People's Hospital, Ruian People's Hospital, Yongjia People's Hospital, and Pingyang People's Hospital) participated in this multicenter, prospective study. Patients who were admitted to the hospital within one week after the sudden onset of stroke between October 1 and December 31, 2018, were included in the data pool. Only patients with complete data on FBG and HbA1c upon admission were enrolled in this study. Stroke, including ischemic stroke and hemorrhagic stroke, was diagnosed according to the World Health Organization criteria [22] and confirmed by brain computed tomography or magnetic resonance imaging.

## Data Collection

We collected data on patient demographics, medical history, neurological functional assessment, risk of malnutrition assessment and medical treatment during hospitalization. The baseline data were collected by the same professionally trained investigator within 48 hours after admission. Whether the patient had a history of atrial fibrillation, coronary heart disease or stroke was determined on the basis of statements from the patient or their relatives and confirmed by a review of the patient's past medical history.

Hypertension and diabetes were assessed according to the 2010 Chinese guidelines for the management of hypertension[23] and the 2018 American Diabetes Association Standards of Medical Care in Diabetes[24], respectively. Hyperlipemia was diagnosed when one of the following criteria was met: total cholesterol level  $\geq 6.2$  mmol/L, low-density lipoprotein cholesterol level  $\geq 4.1$  mmol/L, triglyceride level  $\geq 2.3$  mmol/L or high-density lipoprotein cholesterol level  $< 1.0$  mmol/L. The severity of stroke was assessed with the National Institutes of Health Stroke Scale (NIHSS)[25]. The Barthel index was used to assess the patient's level of independence in activities of daily living (ADL)[26]. According to the Nutritional Risk Screening 2002, which considers impaired nutritional status, the severity of the disease and age, a total score of  $\geq 3$  points indicates that the patient is at risk of malnutrition[27]. Nutrition support was defined as enteral nutrition or intravenous nutrition support during hospitalization.

## Assessment of Stress Hyperglycemia

Fasting venous blood samples were drawn within 48 hours after admission during the morning hours after an overnight fast to measure FBG and HbA1c. All measurements were performed by laboratory personnel blinded to the study samples, study group assignments, and outcomes.

Stress hyperglycemia was estimated with the FBG/HbA1c ratio. We used the following formula to calculate the FBG/HbA1c ratio:  $\text{FBG/HbA1c ratio} = \text{FBG (mmol/L)}/\text{HbA1c (\%)}$ . According to the quartiles of the FBG/HbA1c ratio, the patients were further categorized into four equal groups ( $Q1-Q4$ ,  $Q1 \leq 0.81$ ,  $0.82 \leq Q2 < 0.91$ ,  $0.92 \leq Q3 < 1.1.06$ ,  $Q4 \geq 1.07$ ). The FBG/HbA1c ratio was used to quantify the extent of acute elevation of plasma glucose compared with the background plasma glucose levels.

## Outcome Assessment

The outcomes were assessed at three time points after stroke: within 48 hours after discharge (infectious complications, NIHSS score and dysfunction), at three months after discharge (all-cause death and functional outcomes) and at 12 months after discharge (all-cause death and functional outcomes). Infectious complications were defined as pneumonia, UTI, gastrointestinal infection, sepsis, infective fever, and other infections of hospitalization. Dysfunction was defined as a Barthel Index value  $\leq 60$ . Functional outcomes were measured with the modified Rankin Scale (mRS). Poor functional outcomes were defined as a mRS score of 3–6. We followed up with the patients by telephone at the end of 3 and 12 months after discharge. Patients who could not be contacted by telephone after discharge were considered to be lost to follow-up.

## Statistical Analysis

Categorical variables are presented as frequencies and percentages, while continuous variables are presented as the mean with standard deviation (SD) or median with interquartile range (IQR) when data were not normally distributed. Outliers were detected using residual examination. Categorical variables were analyzed using the chi-square test or Fisher's exact test. Normally distributed continuous variables were analyzed using ANOVA. Continuous variables that were not normally distributed were analyzed with the Mann–Whitney U test and Kruskal–Wallis test.

The relationship between the quartiles of the FBG/HbA1c ratio and outcomes after stroke were evaluated by multivariable logistic regression models with the lowest quartile as the reference. Collinearity was checked before establishing each regression models. The tolerance  $\geq 0.1$  and the variance inflation factor  $< 10$  were considered to be the absence of collinearity. The ratio of outcome events per independent variable were  $\geq 10$ . For the regression analyses with infectious complications as outcomes, we adjusted for the following factors: sex, age, NIHSS score, diabetes, previous stroke, alcohol abuse, risk of malnutrition, length of hospital stay, and nutrition support. For the regression analyses with other in-hospital outcomes, we adjusted for sex, age, NIHSS score, atrial fibrillation, hypertension, diabetes, coronary heart disease, hyperlipemia, previous stroke, history of smoking, and history of alcohol consumption. For the regression analyses with mortality and functional outcomes at 3 and 12 months after discharge, we adjusted for sex, age, NIHSS score, atrial fibrillation, hypertension, diabetes, coronary heart disease, hyperlipemia, previous stroke, history of smoking, history of alcohol consumption, and infectious complications of hospitalization. We performed a sensitivity analysis restricted to patients without a history of diabetes, as previous studies have suggested that this group of patients has a worse outcome when presenting with hyperglycemia [28].

Infection of hospitalization was significantly associated with the short-term risk of recurrent stroke [29]. To assess infectious complications as an intermediate in the pathway from stress hyperglycemia to mid- and long-term all-cause death, we also adjusted for infectious complications (both as an individual variable and as an interaction variable with stress hyperglycemia quartiles) in the multivariate regression models with all-cause mortality at 3 and 12 months.

To investigate the association between stress hyperglycemia and all-cause mortality at 12 months after stroke in relation to each variable, we performed subgroup analyses of the following adjusted variables: sex, age ( $< 75$  or  $\geq 75$ ), NIHSS score ( $< 6$  or  $\geq 6$ ), diabetes, hypertension, infectious complications, and stroke type (ischemic or hemorrhagic).

Data were analyzed by SPSS 22.0 software (SPSS, Inc., Chicago, IL), and a 2-sided  $P$  value  $< 0.05$  was considered to indicate statistical significance.

## Results

Among 941 stroke patients, 846 were successfully followed up with 3 months after discharge, and 743 of these patients remained in contact at 12 months (Fig. 1). Therefore, we performed most analyses with 846 patients, and the 12-month analysis was restricted to 743 patients. Of the 846 stroke patients, 522

(61.7%) were male, and the mean age was  $65.7 \pm 12.6$  years. The mean and median FBG/HbA1c ratios were 0.98 (SD, 0.34) and 0.91 (IQR, 0.81–1.06), respectively. The median of admission NIHSS score was 3 (IQR, 1–7). (Table 1) shows the baseline characteristics of the patients by quartiles of the FBG/HbA1c ratio.

Table 1  
Baseline characteristics

	FBG/HbA1c				p Value
	Q1 (n = 214)	Q2 (n = 212)	Q3 (n = 210)	Q4 (n = 210)	
Patient characteristics					
Female sex, n (%)	61 (28.5)	95 (44.8)	79 (37.6)	89 (42.4)	0.003
Age, mean (SD), years	66.3 (11.8)	66.1 (13.1)	64.8 (12.8)	65.5 (12.6)	0.624
NIHSS, median (IQR)	3 (1–5)	2 (1–5)	3 (1–6.5)	4 (1–9.5)	< 0.001
Barthel Index, median (IQR)	75 (45–95)	75 (45–95)	60 (30–92.5)	45 (20–75)	< 0.001
Risk of malnutrition, n (%)	91 (42.7)	87 (41.0)	85 (40.5)	99 (47.5)	0.503
Nutrition support, n (%)	11 (5.1)	11 (5.2)	26 (12.4)	49 (23.3)	< 0.001
Alcohol abuse, n (%)	34 (15.9)	25 (11.8)	30 (14.3)	24 (11.4)	0.482
Length of hospital stay, median (IQR), days	10 (8–13)	9 (7–13)	10 (7–14)	12 (8–17)	< 0.001
Cardiovascular risk factors, n (%)					
Atrial fibrillation	18 (8.4)	12 (5.7)	11 (5.2)	21 (10.0)	0.187
Hypertension	151 (70.6)	143 (67.5)	159 (75.7)	160 (76.2)	0.131
Diabetes mellitus	65 (30.4)	42 (19.8)	65 (31.0)	97 (46.2)	< 0.001
Coronary heart disease	14 (6.5)	6 (2.8)	8 (3.8)	9 (4.3)	0.286
Hyperlipemia	89 (41.6)	111 (52.4)	105 (50.0)	109 (51.9)	0.092
Previous stroke	58 (27.1)	39 (18.4)	38 (18.1)	33 (15.7)	0.018
History of smoking	75 (35.0)	57 (26.9)	61 (29.0)	55 (26.2)	0.172
History of drinking	72 (33.6)	55 (25.9)	61 (29.0)	56 (26.7)	0.289
Blood glucose indicators					
FBG, mean (SD), mmol/L	4.88 (1.1)	5.34 (1.0)	6.28 (1.3)	9.37 (4.0)	< 0.001
Notes: Quartiles of FBG/HbA1c ratio, Q1 ≤ 0.81, 0.82 ≤ Q2 < 0.91, 0.92 ≤ Q3 < 1.1.06, Q4 ≥ 1.07.					

	FBG/HbA1c				p Value
	Q1 (n = 214)	Q2 (n = 212)	Q3 (n = 210)	Q4 (n = 210)	
HbA1C, mean (SD), %	6.75 (1.7)	6.18 (1.1)	6.41 (1.3)	6.99 (2.0)	< 0.001
FBG/HbA1C, mean (SD)	0.73 (0.09)	0.86 (0.02)	0.98 (0.04)	1.34 (0.49)	< 0.001
Notes: Quartiles of FBG/HbA1c ratio, Q1 ≤ 0.81, 0.82 ≤ Q2 < 0.91, 0.92 ≤ Q3 < 1.1.06, Q4 ≥ 1.07.					

### Stress Hyperglycemia and Primary Outcomes

(Table 2) and (Fig 2) show the 3- and 12-month all-cause mortality after stroke across quartiles of the FBG/HbA1c ratio. There were 35 (4.1%) all-cause deaths at 3 months and 85 (11.4%) at 12 months. After adjustment for sex, age, NIHSS, atrial fibrillation, hypertension, diabetes, coronary heart disease, hyperlipemia, previous smoking, history of smoking, history of drinking, and infectious complications, multivariable regression showed that patients in the highest quartile of the FBG/HbA1c ratio had an elevated risk of all-cause death at 3 months (adjusted OR: 5.14, 95% CI: 1.06–24.90) and at 12 months (adjusted OR: 2.58, 95% CI: 1.14–5.83).

Table 2 Logistic regression of all-cause death according to FBG/HbA1c quartiles.

Outcomes	FBG/HbA1c	n	Events, n (%)	Crude OR (95% CI)	Adjusted OR (95% CI) <sup>a</sup>
<b>Primary Outcomes</b>					
All-cause death at 3 months	Q1 (≤0.81)	214	2 (0.9)	Ref.	Ref.
	Q2 (0.82–0.91)	212	6 (2.8)	3.09 (0.62–15.48)	2.74 (0.52–14.48)
	Q3 (0.92–1.06)	210	10 (4.8)	5.30 (1.15–24.49)	3.75 (0.77–18.31)
	Q4 (≥1.07)	210	17 (8.1)	9.34 (2.13–40.94)	5.14 (1.06–24.90)
All-cause death at 12 months	Q1 (≤0.81)	183	11 (6.0)	Ref.	Ref.
	Q2 (0.82–0.91)	189	22 (11.6)	2.06 (0.97–4.38)	2.47 (1.09–5.58)
	Q3 (0.92–1.06)	190	17 (8.9)	1.54 (0.70–3.38)	1.31 (0.56–3.07)
	Q4 (≥1.07)	181	35 (19.3)	3.78 (1.84–7.64)	2.58 (1.14–5.83)

Notes: Quartiles of FBG/HbA1c ratio,  $Q1 \leq 0.81$ ,  $0.82 \leq Q2 < 0.91$ ,  $0.92 \leq Q3 < 1.1.06$ ,  $Q4 \geq 1.07$ .

Abbreviations: FBG, fasting blood glucose; HbA1c, glycated hemoglobin.

<sup>a</sup>Logistic regression is adjusted for sex, age, NIHSS, atrial fibrillation, hypertension, diabetes, coronary heart disease, hyperlipemia, previous stroke, history of smoking, history of drinking, and infectious complications.

### **Stress Hyperglycemia and Secondary Outcomes**

(Table 3) shows the outcomes of hospitalization across quartiles of the FBG/HbA1c ratio in the study patients. There were 140 (16.5%) infectious complications, including 102 (12.1%) instances of pneumonia and 22 (2.6%) UTIs. A total of 165 (19.5%) patients had NIHSS scores  $\geq 6$ , and 337 (39.8%) had dysfunction (Barthel index value  $\leq 60$ ) after discharge. Compared with patients in the lowest quartile, patients in the highest quartile of the FBG/HbA1c ratio had higher NIHSS scores ( $P < 0.001$ ). Compared with patients in the lowest quartile, patients in the highest quartile of the FBG/HbA1c ratio had a higher risk of infectious complications (adjusted OR 2.52, 95% CI 1.33–4.76) and dysfunction (adjusted OR 1.87, 95% CI 1.13–3.10) after adjusting for covariates. There was also a trend that patients in the highest quartile of the FBG/HbA1c ratio had a higher risk of pneumonia (adjusted OR 1.38, 95% CI 0.69–2.76) and UTI (adjusted OR 2.06, 95% CI 0.46–9.29) and a higher prevalence of NIHSS score  $\geq 6$  (adjusted OR 1.75, 95% CI 0.90–3.40) than patients in the lowest quartile.

Table 3 Logistic regression of outcomes of hospitalization according to FBG/HbA1c quartiles.

Outcomes	FBG/HbA1c	n	Events, n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Secondary outcomes: of hospitalization					
Infectious complications <sup>a</sup>	Q1 ( $\leq 0.81$ )	214	21 (9.8)	Ref.	Ref.
	Q2 (0.82–0.91)	212	23 (10.8)	1.12 (0.60–2.09)	1.08 (0.52–2.24)
	Q3 (0.92–1.06)	210	29 (13.8)	1.47 (0.81–2.68)	1.22 (0.61–2.42)
	Q4 ( $\geq 1.07$ )	210	67 (31.9)	4.31 (2.52–7.36)	2.52 (1.33–4.76)
Pneumonia <sup>a</sup>	Q1 ( $\leq 0.81$ )	214	19 (8.9)	Ref.	Ref.
	Q2 (0.82–0.91)	212	14 (6.6)	0.73 (0.35–1.49)	0.70 (0.31–1.60)
	Q3 (0.92–1.06)	210	21 (10.0)	1.14 (0.59–2.29)	0.81 (0.38–1.73)
	Q4 ( $\geq 1.07$ )	210	48 (22.9)	3.04 (1.72–5.38)	1.38 (0.69–2.76)
Urinary tract infection <sup>a</sup>	Q1 ( $\leq 0.81$ )	214	3 (1.4)	Ref.	Ref.
	Q2 (0.82–0.91)	212	6 (2.8)	2.05 (0.51–8.30)	1.08 (0.22–5.27)
	Q3 (0.92–1.06)	210	5 (2.4)	1.72 (0.41–7.27)	1.78 (0.39–8.10)
	Q4 ( $\geq 1.07$ )	210	8 (3.8)	2.78 (0.73–10.65)	2.06 (0.46–9.29)
NIHSS $\geq 6$ post discharge <sup>b</sup>	Q1 ( $\leq 0.81$ )	214	29 (14.1)	Ref.	Ref.
	Q2 (0.82–0.91)	212	30 (14.7)	1.05 (0.61–1.83)	1.22 (0.60–2.49)
	Q3 (0.92–1.06)	210	39 (19.4)	1.47 (0.87–2.49)	0.82 (0.41–1.65)
	Q4 ( $\geq 1.07$ )	210	67 (34.0)	3.15 (1.93–5.14)	1.75 (0.90–3.40)
Dysfunction post discharge (Bathel $\leq 60$ ) <sup>b</sup>	Q1 ( $\leq 0.81$ )	214	81 (31.9)	Ref.	Ref.
	Q2 (0.82–0.91)	212	88 (41.5)	1.11 (0.74–1.66)	1.08 (0.66–1.78)
	Q3 (0.92–1.06)	210	114 (51.3)	1.56 (1.04–2.32)	1.23 (0.76–2.02)

Q4 ( $\geq 1.07$ )	210	139 (66.2)	2.72 (1.82– 4.04)	1.87 (1.13– 3.10)
--------------------	-----	---------------	----------------------	----------------------

Notes: Quartiles of FBG/HbA1c ratio,  $Q1 \leq 0.81$ ,  $0.82 \leq Q2 < 0.91$ ,  $0.92 \leq Q3 < 1.1.06$ ,  $Q4 \geq 1.07$ .

Abbreviations: FBG, fasting blood glucose; HbA1c, glycated hemoglobin; NIHSS, The National Institutes of Health Stroke Scale.

<sup>a</sup>Adjusted for sex, age, NIHSS, diabetes, previous stroke, alcohol abuse, risk of malnutrition, length of hospital stay, and nutrition support

<sup>b</sup>Adjusted for sex, age, NIHSS, atrial fibrillation, hypertension, diabetes, coronary heart disease, hyperlipemia, previous stroke, history of smoking and history of drinking.

(Table 4) shows the 3- and 12-month poor functional outcomes after stroke across quartiles of the FBG/HbA1c ratio. There were 204 (24.1%) poor outcomes at 3 months and 241 (32.9%) at 12 months. There was a trend that patients in the highest quartile of the FBG/HbA1c ratio had a higher risk of poor functional outcomes at 3 months (adjusted OR 1.38, 95% CI 0.78–2.45) and 12 months (adjusted OR 1.68, 95% CI 0.98–3.28).

Table 4 Logistic regression of poor functional outcomes according to FBG/HbA1c quartiles.

Outcomes	FBG/HbA1c	n	Events, n (%)	Crude OR (95% CI)	Adjusted OR (95% CI) <sup>a</sup>
<b>Secondary Outcomes: after discharge</b>					
Poor functional outcomes (mRS of 3–6) at 3 months	Q1 ( $\leq 0.81$ )	214	32 (16.4)	Ref.	Ref.
	Q2 (0.82–0.91)	212	46 (21.7)	1.42 (0.87–2.31)	1.51 (0.86–2.66)
	Q3 (0.92–1.06)	210	50 (23.8)	1.60 (0.99–2.59)	1.19 (0.68–2.08)
	Q4 ( $\geq 1.07$ )	210	72 (34.3)	2.67 (1.68–4.23)	1.38 (0.78–2.45)
Poor functional outcomes (mRS of 3–6) at 12 months	Q1 ( $\leq 0.81$ )	183	52 (28.4)	Ref.	Ref.
	Q2 (0.82–0.91)	189	49 (25.9)	0.88 (0.56–1.39)	1.16 (0.68–1.99)
	Q3 (0.92–1.06)	190	57 (30.0)	1.08 (0.69–1.69)	0.94 (0.55–1.59)
	Q4 ( $\geq 1.07$ )	181	83 (45.9)	2.13 (1.38–3.29)	1.68 (0.98–3.28)

Notes: Quartiles of FBG/HbA1c ratio, Q1  $\leq 0.81$ ,  $0.82 \leq Q2 < 0.91$ ,  $0.92 \leq Q3 < 1.1.06$ ,  $Q4 \geq 1.07$ .

Abbreviations: FBG, fasting blood glucose; HbA1c, glycated hemoglobin.

<sup>a</sup>Logistic regression is adjusted for sex, age, NIHSS, atrial fibrillation, hypertension, diabetes, coronary heart disease, hyperlipemia, previous stroke, history of smoking, history of drinking, and infectious complications.

The sensitivity analyses excluding patients with preexisting diabetes yielded similar results (Additional File 1).

### **The role of infectious complications in the pathway from admission stress hyperglycemia to death**

To assess the role of infectious complications in the pathway from stress hyperglycemia to mid- and long-term all-cause death, we also added infectious complications as an interaction variable with stress hyperglycemia quartiles in the logistic regression model. Multivariable regression showed that adding infectious complications (both as individual variables and as an interaction variable with quartiles

of FBG/HbA1c ratio) to the models did not modify the relationships of the highest quartile of the FBG/HbA1c ratio with all-cause death at 3 months (adjusted OR 5.63, 95% CI 1.05–30.16) and at 12 months (adjusted OR 3.36, 95% CI 1.28–8.85). No statistical significance was found in the interaction of the FBG/HbA1c ratio with infectious complications in predicting all-cause mortality at 3 and 12 months ( $P = 0.516$  and  $P = 0.369$ , respectively).

### Subgroup Analysis

In the subgroup analysis of all-cause mortality at 12 months, the highest quartile of the FBG/HbA1c ratio was associated with or showed a trend toward an association with infectious complications in all subgroups (Fig 3). Compared with patients in the lowest quartile, patients in the highest quartile of the FBG/HbA1c ratio had a higher risk of infectious complications in the subgroups of NIHSS score <6 (adjusted OR 3.23, 95% CI 1.01–10.32), age  $\geq 75$  (adjusted OR 5.01, 95% CI 1.13–22.25), AIS subjects (adjusted OR 3.66, 95% CI 1.36–9.83), hypertensive subjects (adjusted OR 2.57, 95% CI 1.03–6.37), and noninfectious subjects (adjusted OR 3.45, 95% CI 1.29–9.21).

## Discussion

In this multicenter, prospective study, we explored the association between stress hyperglycemia and all-cause mortality and poor prognosis in patients with acute stroke and found that the glucose/HbA1c ratio may independently predict mid- and long-term all-cause mortality, infectious complications, and dysfunction in acute stroke patients. Although no specific guidelines have defined stress hyperglycemia, studies have revealed that relative hyperglycemia might be an enhanced predictor for outcomes of acute illness than absolute hyperglycemia [12, 13]. Studies have proven that the glucose/HbA1c ratio could work as an economical and practical indicator to precisely detect and quantify stress hyperglycemia [13].

Our current study showed that patients in the highest quartile of the FBG/HbA1c ratio had an increased risk of all-cause death at 3 months (adjusted OR: 5.14, 95% CI: 1.06–24.90) and at 12 months (adjusted OR: 2.58, 95% CI: 1.06–24.90) after adjusting for confounders, including demographic variables, stroke severity and cardiovascular risk factors. These results demonstrated the independent role of stress hyperglycemia in predicting mid- and long-term all-cause death in acute stroke patients.

One of our secondary outcomes was poor functional outcomes defined as a mRS score of  $\geq 3$ . Our results revealed that there was a trend that patients in the highest quartile of the FBG/HbA1c ratio had a higher risk of poor functional outcomes at 3 months (adjusted OR 1.38, 95% CI 0.78–2.45) and 12 months (adjusted OR 1.68, 95% CI 0.98–3.28). Since poor functional outcomes measured by the mRS might be most relevant to clinicians and patients considering further rehabilitation [30], these results suggested that stress hyperglycemia measured by the FBG/HbA1c ratio might facilitate the identification of patients with acute stroke who require early intervention to promote functional recovery.

Since a history of diabetes has been shown to be an important potential covariate in the relationship between stress hyperglycemia, complications and poor prognosis [31], sensitivity analyses excluding

patients with preexisting diabetes were performed and yielded results similar to those of the overall analysis. Among nondiabetic patients, compared with patients in the lowest quartile, patients in the highest quartile of the FBG/HbA1c ratio had a higher risk of poor functional outcomes at 3 months and 12 months, which was consistent with a previous study[31]. These results suggested that the relationship between stress hyperglycemia and long-term adverse outcomes exists regardless of the presence or absence of a history of diabetes.

Another important secondary outcome was infectious complications of hospitalization. Infection is regarded as the most frequent complication of stroke, affecting almost 30% of patients[15], and has been confirmed to be an independent risk factor for a high risk of stroke recurrence [29]. Special attention should be given to the relationship between stress hyperglycemia and the risk of infectious complications after stroke. We found that stress hyperglycemia was associated with an increased risk of infectious complications, which was consistent with a previous study[32] and added evidence on the relationship between disorders of glucose metabolism and complications in stroke patients[33, 34]. The association between hyperglycemia and infections after stroke may be explained by the fact that high blood glucose levels aggravate the already immunocompromised state of stroke patients[35, 36].

Despite the clear associations we found between stress hyperglycemia and infectious complications, we did not find evidence that the association between admission hyperglycemia and mid- and long-term all-cause death is explained or mediated by the occurrence of infectious complications. This might be explained by the relatively low incidence rate of infectious complications in our population (16.5% vs. 30% in a systematic review[15]). Overall, further designed studies should be performed to explore the role of infections in hyperglycemia and worse clinical outcomes.

In the subgroup analysis of 12-month all-cause death, compared with patients in the lowest quartile, patients in the highest quartile of the FBG/HbA1c ratio had a higher risk of all-cause death in the subgroups of NIHSS score <6, age  $\geq 75$ , hypertensive subjects, and noninfectious subjects, which demonstrated the importance of the enhanced detection of stress hyperglycemia in these populations. Since the subgroup analyses were conducted post hoc, these associations should be explored in future research.

There are several explanations for the association between stress hyperglycemia and poor prognoses of stroke. First, stress hyperglycemia may contribute to adverse outcomes in stroke patients through mechanisms such as induction of more endothelial apoptosis and greater endothelial dysfunction and oxidative stress responses [1]. Second, hyperglycemia may have direct neurotoxicity on the ischemic penumbra and cause more neurons to be injured<sup>3</sup>, which may facilitate the conversion of hypoperfused at-risk tissue into infarction and adversely affect stroke prognosis[37]. Finally, acute hyperglycemia increases brain lactate production, which may accelerate irreversible injury by enhancing glutamate release and altering intracellular calcium regulation[38, 39], thus resulting in poorer stroke outcomes.

Although clear associations of stress hyperglycemia with all-cause death were found in the present study, a recent observational study[9] and a clinical trial[40] have come to the opposite conclusion. An observational study showed that stress hyperglycemia measured by absolute fasting serum glucose levels was not directly associated with in-hospital mortality but was only a marker of stroke severity[9]. The conflicting data presented above, which highlight a controversial role for stress hyperglycemia on outcomes following stroke, may result from the discrepancy in the measurement time points (at the second day after admission) and the index for hyperglycemia (absolute but not relative increases in fasting glucose were assessed in this study). Moreover, the present study showed that after adjusting for the NIHSS score as one of the confounders in the multivariable model, the associations remained significant between stress hyperglycemia and an increased risk of all-cause death at 3 months and 12 months after stroke, respectively. The recent randomized Stroke Hyperglycemia Insulin Network Effort trial, which compared intensive glucose lowering with standard treatment in patients with stroke, found no difference in the death and favorable mRS score at 3 months[40]. However, treatment with intravenous tissue plasminogen activator therapy in 63% of the patients may suggest a selection bias for patients in this study. Thus, further well-designed randomized clinical trials with larger samples should be performed to evaluate whether improving glycemic control in stroke patients could help to achieve better outcomes.

There are several strengths in our present study. The data presented in this study likely reflect daily clinical practice, as they come from consecutive patients at 5 major hospitals in the Wenzhou region in China who were treated for stroke without the exclusion of hemorrhagic stroke patients, unlike most previous studies[6, 7, 32]. In addition, the present study prospectively designed abundant prognostic indicators. The primary outcome was all-cause mortality, and the secondary outcomes were poor prognosis defined as infectious complications, NIHSS score  $\geq 6$ , Barthel Index score  $\leq 60$ , and mRS score  $\geq 3$ . The inclusion of both short- and long-term follow-up information strengthened the reliability of our results. There are still some limitations. First, 95 patients were lost to follow-up at 3 months, and 103 were lost at 12 months after discharge, which may lead to selection bias. Moreover, there were no data available on the use of glucose-lowering medication or on follow-up glucose levels. Therefore, we were unable to assess the dynamics of hyperglycemia after stroke, although studies have suggested that persistent hyperglycemia is associated with poor functional outcomes[41].

In conclusion, stress hyperglycemia on admission measured by the FBG/HbA1c ratio was associated with an increased risk of all-cause death after stroke. Our present study suggests that the glucose/HbA1c ratio may help identify patients at increased risk of adverse outcomes, including infectious complications, dysfunction, and all-cause death. Further prospective studies or randomized trials with large sample sizes are warranted to evaluate whether improving glycemic control in stroke patients could improve outcomes.

## List Of Abbreviations

FBG, fasting blood glucose; HbA1c, glycated hemoglobin; UTI, urinary tract infection ; NIHSS, the National Institutes of Health Stroke Scale; ADL, activities of daily living; mRS, the modified Rankin Scale.

# Declarations

## Ethics approval and consent to participate

This study protocol was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University, China. Written informed consent was obtained from each patient and their family. The study conformed to the principles of the Declaration of Helsinki.

## Consent for publication

Not applicable

## Availability of data and materials

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

## Competing interests

The authors declare that they have no competing interests.

## Funding

This work was supported by the project of the science committee in Wenzhou, China (Project number: Y20190561).

## Authors' contributions

ZC analyzed the data and was a major contributor in writing the manuscript. MZ, RF, XZ, HC, ZL, YW, QL, SY, CL, XH, and LS participated in data collection and analysis. BY and BZ designed the study and revised the manuscript. All authors read and approved the final manuscript.

## Acknowledgements

Thank Dao-dao for technical support.

# References

1. Dungan K M, Braithwaite S S, Preiser J C. Stress hyperglycaemia. *Lancet*. 2009;373(9677):1798–807.
2. Capes S E, Hunt D, Malmberg K, et al. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet*. 2000;355(9206):773–8.

3. Itzhaki Ben Zadok O, Kornowski R, Goldenberg I, et al. Admission blood glucose and 10-year mortality among patients with or without pre-existing diabetes mellitus hospitalized with heart failure. *Cardiovasc Diabetol*. 2017;16(1):102.
4. Krinsley J S. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. *Mayo Clin Proc*. 2003;78(12):1471-8.
5. Melamed E. Reactive hyperglycaemia in patients with acute stroke. *J Neurol Sci*. 1976;29(2-4):267-75.
6. Pan Y, Cai X, Jing J, et al. Stress Hyperglycemia and Prognosis of Minor Ischemic Stroke and Transient Ischemic Attack: The CHANCE Study (Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events). *Stroke*. 2017;48(11):3006-11.
7. Yazawa Y, Ohira T, Itabashi R, et al. Association of Admission Hyperglycemia with Clinical Outcomes in Japanese Patients with Acute Large Vessel Occlusion Stroke: A post hoc Analysis of the Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism Japan Registry 2. *Cerebrovascular diseases (Basel, Switzerland)*. 2021;50(1):12-9.
8. Xing L, Liu S, Tian Y, et al. C-R Relationship between Fasting Plasma Glucose and Unfavorable Outcomes in Patients of Ischemic Stroke without Diabetes. *Journal of Stroke & Cerebrovascular Diseases*. 2019;28(5):1400-8.
9. Tziomalos K, Dimitriou P, Bouziana S D, et al. Stress hyperglycemia and acute ischemic stroke in-hospital outcome. *Metabolism*. 2017;67:99-105.
10. Weykamp C. HbA1c: a review of analytical and clinical aspects. *Ann Lab Med*. 2013;33(6):393-400.
11. Chehregosha H, Khamseh M E, Malek M, et al. A View Beyond HbA1c: Role of Continuous Glucose Monitoring. *Diabetes Ther*. 2019;10(3):853-63.
12. Su Y W, Hsu C Y, Guo Y W, et al. Usefulness of the plasma glucose concentration-to-HbA(1c) ratio in predicting clinical outcomes during acute illness with extreme hyperglycaemia. *Diabetes Metab*. 2017;43(1):40-7.
13. Roberts G W, Quinn S J, Valentine N, et al. Relative Hyperglycemia, a Marker of Critical Illness: Introducing the Stress Hyperglycemia Ratio. *J Clin Endocrinol Metab*. 2015;100(12):4490-7.
14. Aslanyan S, Weir C J, Diener H C, et al. Pneumonia and urinary tract infection after acute ischaemic stroke: a tertiary analysis of the GAIN International trial. *Eur J Neurol*. 2004;11(1):49-53.
15. Westendorp W F, Nederkoorn P J, Vermeij J D, et al. Post-stroke infection: a systematic review and meta-analysis. *BMC neurology*. 2011;11:110.
16. Boehme A K, Kumar A D, Dorsey A M, et al. Infections present on admission compared with hospital-acquired infections in acute ischemic stroke patients. *Journal of stroke and cerebrovascular diseases: the official journal of National Stroke Association*. 2013;22(8):e582-9.
17. Shah S V, Corado C, Bergman D, et al. Impact of Poststroke Medical Complications on 30-Day Readmission Rate. *Journal of stroke and cerebrovascular diseases: the official journal of National Stroke Association*. 2015;24(9):1969-77.

18. Berger B, Gumbinger C, Steiner T, et al. Epidemiologic features, risk factors, and outcome of sepsis in stroke patients treated on a neurologic intensive care unit. *J Crit Care*. 2014;29(2):241–8.
19. Butler S O, Btaiche I F, Alaniz C. Relationship between hyperglycemia and infection in critically ill patients. *Pharmacotherapy*. 2005;25(7):963–76.
20. Zhang M, Ye S, Huang X, et al. Comparing the prognostic significance of nutritional screening tools and ESPEN-DCM on 3-month and 12-month outcomes in stroke patients. *Clin Nutr*. 2021;40(5):3346–53.
21. Cai Z M, Wu Y Z, Chen H M, et al. Being at risk of malnutrition predicts poor outcomes at 3 months in acute ischemic stroke patients. *Eur J Clin Nutr*. 2020;74(5):796–805.
22. Stroke–1989. Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO Task Force on Stroke and other Cerebrovascular Disorders. *Stroke*. 1989;20(10):1407–31.
23. Liu L S. [2010 Chinese guidelines for the management of hypertension]. *Zhonghua Xin Xue Guan Bing Za Zhi*. 2011;39(7):579–615.
24. Chamberlain J J, Johnson E L, Leal S, et al. Cardiovascular Disease and Risk Management: Review of the American Diabetes Association Standards of Medical Care in Diabetes 2018. *Ann Intern Med*. 2018;168(9):640–50.
25. Kwah L K, Diong J. National Institutes of Health Stroke Scale (NIHSS). *J Physiother*. 2014;60(1):61.
26. Shah S, Vanclay F, Cooper B. Improving the sensitivity of the Barthel Index for stroke rehabilitation. *J Clin Epidemiol*. 1989;42(8):703–9.
27. Kondrup J. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. *Clinical Nutrition*. 2003;22(3):321–36.
28. Capes S E, Hunt D, Malmberg K, et al. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. *Stroke*. 2001;32(10):2426–32.
29. Xu J, Yalkun G, Wang M, et al. Impact of Infection on the Risk of Recurrent Stroke Among Patients With Acute Ischemic Stroke. *Stroke*. 2020;51(8):2395–403.
30. Kasner S E. Clinical interpretation and use of stroke scales. *Lancet Neurol*. 2006;5(7):603–12.
31. Rinkel L A, Nguyen T T M, Guglielmi V, et al. High Admission Glucose Is Associated With Poor Outcome After Endovascular Treatment for Ischemic Stroke. *Stroke*. 2020;51(11):3215–23.
32. Zonneveld T P, Nederkoorn P J, Westendorp W F, et al. Hyperglycemia predicts poststroke infections in acute ischemic stroke. *Neurology*. 2017;88(15):1415–21.
33. Matz K, Keresztes K, Tatschl C, et al. Disorders of glucose metabolism in acute stroke patients: an underrecognized problem. *Diabetes Care*. 2006;29(4):792–7.
34. McCowen K C, Malhotra A, Bistrain B R. Stress-induced hyperglycemia. *Critical Care Clinics*. 2001;17(1):107+.
35. Turina M, Fry D E, Polk H C, Jr. Acute hyperglycemia and the innate immune system: clinical, cellular, and molecular aspects. *Crit Care Med*. 2005;33(7):1624–33.

36. Perner A, Nielsen S E, Rask-Madsen J. High glucose impairs superoxide production from isolated blood neutrophils. *Intensive Care Med.* 2003;29(4):642–5.
37. Parsons M W, Barber P A, Desmond P M, et al. Acute hyperglycemia adversely affects stroke outcome: a magnetic resonance imaging and spectroscopy study. *Ann Neurol.* 2002;52(1):20–8.
38. Anderson R E, Tan W K, Martin H S, et al. Effects of glucose and PaO<sub>2</sub> modulation on cortical intracellular acidosis, NADH redox state, and infarction in the ischemic penumbra. *Stroke.* 1999;30(1):160–70.
39. Pulsinelli W A, Waldman S, Rawlinson D, et al. Moderate hyperglycemia augments ischemic brain damage: a neuropathologic study in the rat. *Neurology.* 1982;32(11):1239–46.
40. Johnston K C, Bruno A, Pauls Q, et al. Intensive vs Standard Treatment of Hyperglycemia and Functional Outcome in Patients With Acute Ischemic Stroke: The SHINE Randomized Clinical Trial. *Jama.* 2019;322(4):326–35.
41. Mi D, Wang P, Yang B, et al. Correlation of hyperglycemia with mortality after acute ischemic stroke. *Ther Adv Neurol Disord.* 2018;11:1756285617731686.

## Figures

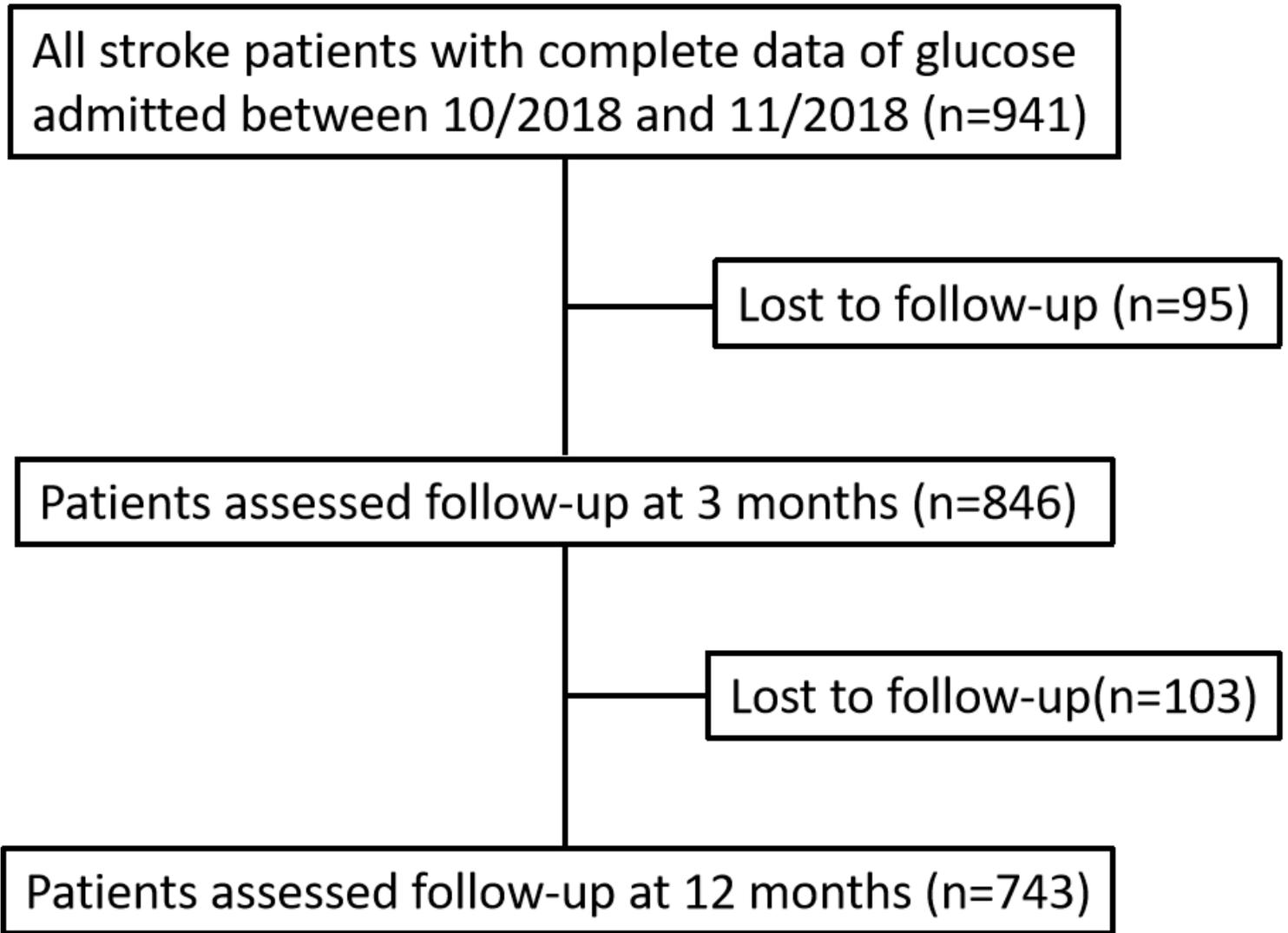
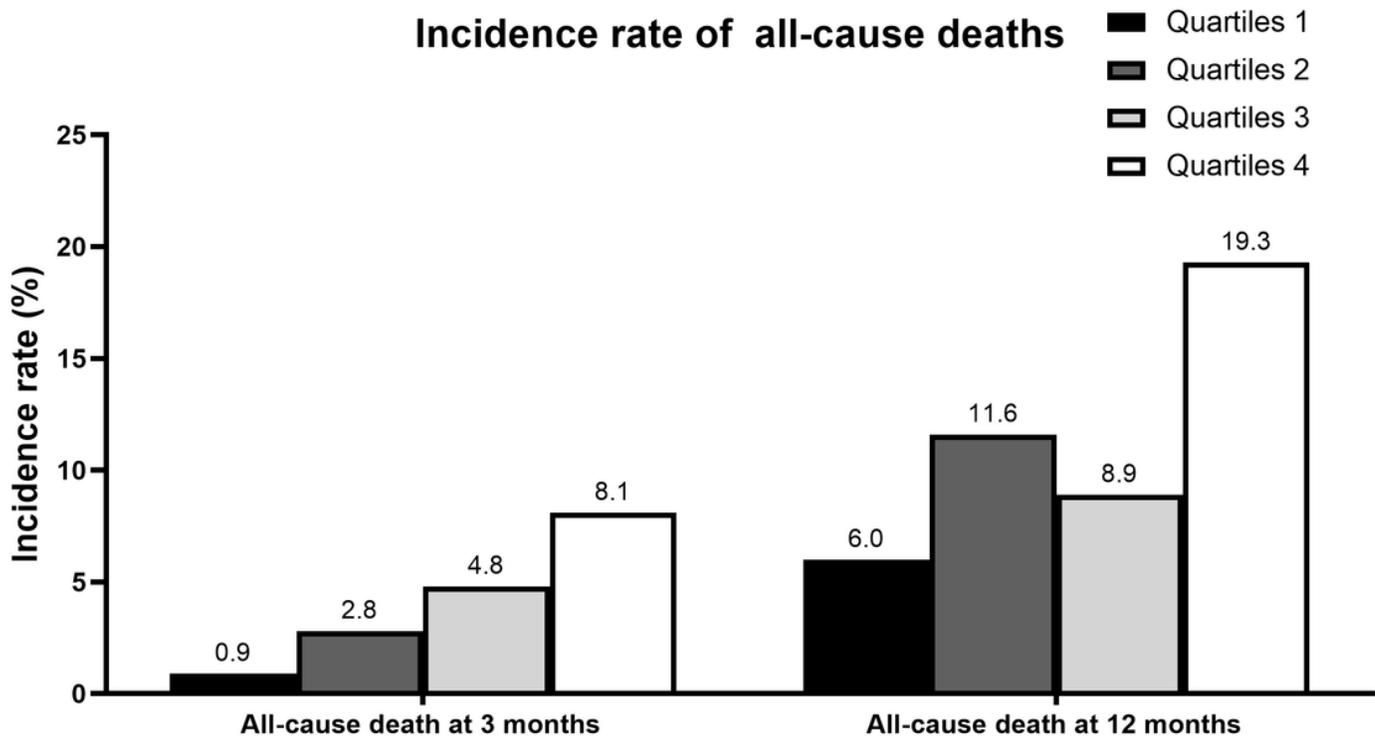


Figure 1

Flowchart of study participants



**Figure 2**

The incidence rate of 3- and 12-month all-cause mortality after stroke across quartiles of the FBG/HbA1c ratio

**Figure 3**

Logistic regression of 12-month all-cause death according to FBG/HbA1c quartiles in subgroup analysis

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [AdditionalFile1.pdf](#)