Increased glycemic variability associated with a poor 30-day functional outcome in acute intracerebral hemorrhage

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OBJECTIVE Intracerebral hemorrhage (ICH) is associated with a poor prognosis and high mortality, but no study has elucidated the association between glycemic variability (GV) and functional outcome in ICH. The authors of this study aimed to determine whether GV is a predictor of 30-day functional outcome in ICH patients.

METHODS The study recruited 366 patients with first-ever acute-onset ICH in the period during 2014 and 2015. Fasting blood glucose was assessed on admission and with 7-day continuous monitoring. Glycemic variability was calculated and expressed by the standard deviation (Glu_{SD}) and coefficient of variation (Glu_{CV}). Patients were divided into groups of those with diabetes mellitus (DM), stress hyperglycemia (SHG), and normal glucose (NG). Functional outcome was measured using the modified Rankin Scale.

RESULTS The numbers of patients with DM, SHG, and NG were 108 (29.5%), 127 (34.7%), and 131 (35.8%), respectively. As compared with the DM patients, those with SHG had higher mortality (29.9% vs 15.7%, $p < 0.05$) and a poorer prognosis (64.6% vs 52.8%, $p < 0.05$). Poor prognosis was associated with both high Glu_{SD} (OR 1.54, 95% CI 1.19–1.99) and high Glu_{CV} (1.05, 1.02–1.09), especially in the DM group. The area under the receiver operating characteristic curve was greater for the Glu_{SD} (OR 0.929, 95% CI 0.902–0.956) and the Glu_{CV} (0.932, 0.906–0.958) model than the original model (0.860, 0.823–0.898) in predicting a poor outcome.

CONCLUSIONS Stress hyperglycemia may be associated with increased mortality and a poor outcome in ICH, and increased GV may be independently associated with a poor outcome, particularly in ICH patients with DM.

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KEY WORDS glycemic variability; stress hyperglycemia; functional outcome; intracerebral hemorrhage; vascular disorders

STROKE is the second leading cause of death worldwide and the first in China, and the absolute number of people with a first stroke, who are stroke survivors, who have stroke-related deaths, and who have disability-adjusted life-years lost due to stroke has increased in the past 2 decades.^{11,40} Intracerebral hemorrhage (ICH) is a serious disease, accounting for 10%–15% of stroke cases, and has a high case fatality rate of about 35%–50% as well as a poor prognosis, with only 10%–20% surviving and

living independently at 30 days.^{20,30} Risk factors for early death and a poor functional outcome in ICH include a low Glasgow Coma Scale (GCS) score at admission, large hematoma volume, intraventricular hematoma (IVH), and hypertension.^{15,23,26} Early intervention and management of these factors may ameliorate the poor prognosis in ICH.

Hyperglycemia is a common phenomenon in ICH patients and can be caused by diabetes mellitus (DM) or stress hyperglycemia (SHG).²⁷ The latter disorder gener-

ABBREVIATIONS AUC = area under the receiver operating characteristic curve; CV = coefficient of variation; DBP = diastolic blood pressure; DM = diabetes mellitus; FBG = fasting blood glucose; GCS = Glasgow Coma Scale; Glu_{CV} = coefficient of variation of glucose; Glu_{SD} = standard deviation of glucose; GV = glycemic variability; HbA1c = glycosylated hemoglobin; HDL-C = high-density lipoprotein cholesterol; ICH = intracerebral hemorrhage; IVH = intraventricular hematoma; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; mRS = modified Rankin Scale; NG = normal glucose; SBP = systolic blood pressure; SD = standard deviation; SHG = stress hyperglycemia; TC = total cholesterol; TG = triglyceride; WBC = white blood cell.

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ally refers to transient hyperglycemia in patients without previous evidence of DM.⁸ The measurement of glycosylated hemoglobin (HbA1c) has unique application value, and an HbA1c $\geq 6.5\%$ is widely considered the gold standard for DM diagnosis.¹ Many studies have investigated the effect of hyperglycemia on the prognosis of ICH but have not measured the HbA1c level to distinguish whether the hyperglycemia resulted from DM or SHG.^{2,14,32,33} The level of glucose in SHG can revert to normal but continues to be high in DM, so it must be accounted for in continuous glucose monitoring. No studies have observed the relationship between glycemic fluctuation and functional outcome in acute-onset ICH.

Recently, glycemic variability (GV), an important index of glycemic fluctuations measured with continuous glucose monitoring, has been implicated in the disease-associated process of dysglycemia.²⁴ The standard deviation (SD) and coefficient of variation (CV) of the glucose value are considered strong independent indexes for determining GV, although the best method for characterizing GV in hospitalized patients has not been agreed on.^{29,31} Several studies have demonstrated high GV associated with significantly increased mortality in critically ill patients.^{9,19} However, no study has reported on the association between GV and clinical outcomes in hospitalized patients, particularly those with acute-onset ICH.

In the present study we emphasize the importance of distinguishing between DM and SHG in hyperglycemia and the fasting blood glucose (FBG) level monitored for 7 continuous days. We evaluated the association of hyperglycemia in DM or SHG and GV as measured by continuous monitoring of FBG for 7 days with functional outcome at 30 days in acute-onset ICH.

Methods

Study Participants

We recruited 366 patients with first-ever acute-onset ICH who were admitted to the Department of Neurology Medicine and Surgery Services in the First Affiliated Hospital of Shantou University Medical College between January 1, 2014, and December 31, 2015. All patients were 18 years of age or older and were admitted to the hospital within 24 hours of the first symptoms of disease, with the diagnosis of ICH confirmed by CT or MRI studies. On the basis of ICH guidelines from the American Heart Association, clinical management was established at the discretion of the treating physician.¹⁷ Patients with pituitary tumors, hyperthyroidism, acute pancreatitis, and endocrine tumors that may cause hyperglycemia were excluded. Patients with traumatic hemorrhage or recurrent episodes of hemorrhage (for example, subarachnoid hemorrhage, brain tumor or hemorrhagic transformation of ischemic stroke, and subdural or extradural hemorrhage) were also excluded. This study was conducted according to guidelines in the Declaration of Helsinki, and all procedures involving humans were approved by the Ethics Committee of the First Affiliated Hospital of Shantou University Medical College. Written informed consent was obtained from all participants. The required sample size was determined by assuming an OR 1.5 for group comparison

at the 5% significance level; therefore, a sample size of 53 per group was needed to attain 90% power, as calculated by NCSS-PASS 2005.

Neuroradiological Methods

From CT scans and MR images, we recorded hematoma location (basal ganglia, lobar, brainstem, cerebellum, or thalamus), presence of IVH, and hematoma volume (classified as < 20 , $20\text{--}40$, and ≥ 40 ml) measured using the ABC/2 method (A, greatest hemorrhage diameter; B, diameter perpendicular to A; C, number of slices multiplied by slice thickness).¹⁸ Initial neurological deficit was determined using the GCS, usually used to assess coma and impaired consciousness;³⁴ GCS scores were classified as 13–15 (mild disability), 9–12 (moderate disability), and ≤ 8 (severe disability). Functional outcome was measured using the modified Rankin Scale (mRS),⁴ scored by a designated neurologist to evaluate therapeutic effects and prognosis at 30 days after admission. The mRS scores were divided into good outcome (mRS score < 3) and poor outcome (mRS score ≥ 3), with an mRS Score of 6 considered as death.³⁹

Medical Records

Medical records were examined for previous diseases including myocardial infarction (MI), hypertension, and DM. Diagnosis of prior MI was based on the medical history of the patient. In accordance with the World Health Organization (WHO)/International Society of Hypertension statement,³⁸ hypertension was diagnosed as blood pressure $\geq 140/90$ mm Hg measured at least twice or if a patient was taking antihypertensive medication. Diabetes mellitus was defined according to the criteria of the American Diabetes Association—that is, FBG ≥ 7.0 mmol/L, random glucose ≥ 11.1 mmol/L measured at least twice, or HbA1c $\geq 6.5\%$ —or as a history of DM (medical record of DM and/or taking insulin or oral hypoglycemic agents).¹ Accordingly, all participants were divided into 3 groups: DM (history of DM or HbA1c $\geq 6.5\%$ and FBG ≥ 7.0 mmol/L), SHG (no history of DM, HbA1c $< 6.5\%$, and FBG ≥ 7.0 mmol/L), and normal glucose (NG; no history of DM, HbA1c $< 6.5\%$, and FBG < 7.0 mmol/L).

We collected venous blood from fasting patients at least 8 hours after ICH onset and at 5:00–6:00 each morning of the 7 consecutive days after admission. All examinations were performed in the clinical laboratory of the hospital. Fasting blood glucose was measured via the enzymatic method using an auto-analyzer (Beckman Coulter Inc.), and HbA1c was measured via the high-performance liquid chromatographic method using an automated glycohemoglobin analyzer (Tosoh Corp.).

Glycemic indices such as SD of 7-day FBG level (Glu_{SD}) and CV of 7-day FBG level (Glu_{CV}) were calculated; Glu_{CV} was calculated using the equation $\text{Glu}_{\text{CV}} = 100\% \times \text{Glu}_{\text{SD}} / (\text{mean glucose})$.²⁸ Patient age and sex, health habits (for example, smoking status, alcohol intake), systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (calculated as $\text{SBP} - \text{DBP}$), white blood cell (WBC) count ($10^9/\text{L}$), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein

cholesterol (HDL-C), and triglycerides (TG) at admission were also collected.

Statistical Analysis

Qualitative variables are expressed as frequencies (%) and continuous variables as the mean $\pm$ standard deviation. Continuous variables were analyzed for normality using the Kolmogorov-Smirnov test. Significant differences between groups were assessed with the Mann-Whitney U-test for skewed variables and Pearson's chi-square test with or without Bonferroni correction for categorical variables. Bivariate analysis was initially performed to identify a significant association between individual variables and 30-day functional outcome. Variables with a $p \leq 0.05$ on bivariate analysis were included in the multivariate model (that is, the original model). In the multivariate models, variables with a $p < 0.05$ were retained by forward logistic regression elimination. Odds ratios with 95% confidence intervals were calculated. We separately added Glu_{SD} and Glu_{CV} to the original model to create the Glu_{SD} model and Glu_{CV} models. We also analyzed the area under the receiver operating characteristic curve (AUC) to judge the discrimination ability of various statistical methods.¹⁶ Statistical analyses involved the use of SPSS for Windows 13.0 (SPSS Inc.) and R version 3.2.0 (R Foundation for Statistical Computing, <http://www.R-project.org>). Two-tailed tests of significance were reported, with $p < 0.05$ considered statistically significant.

Results

Study Population

A total of 366 ICH patients were divided into 3 glucose groups, with 108 (29.5%), 127 (34.7%), and 131 (35.8%) in the DM, SHG, and NG groups, respectively (Table 1). The rate of newly diagnosed DM on admission, according to an HbA1c level $\geq 6.5\%$, was 15.3% (56/366). The variables hypertension, SBP, DBP, initial GCS score, hematoma volume, IVH, WBC count, TC, TG, admission FBG and HbA1c levels, Glu_{SD}, and Glu_{CV} all significantly differed among the 3 glucose groups (all $p < 0.05$). Hyperglycemia was frequent in patients with a low initial GCS score (≤ 8), hematoma volume ≥ 40 ml, and IVH (all $p < 0.05$). Patients in the SHG group had the highest WBC count, and those in the DM group had the highest HbA1c level (both $p < 0.05$). As compared with the NG group, both the DM and SHG groups had higher SBP, admission FBG level, and Glu_{SD} and Glu_{CV} for 7-day FBG (all $p < 0.05$). The dynamic changes in 7-day FBG in the 3 glucose groups are represented in Fig. 1. The level of FBG was higher in both the DM and SHG groups than in the NG group, with a downward trend.

Study End Points

Clinical Characteristics

In total, 46.7% of the ICH patients (171/366) had a poor outcome (mRS score ≥ 3) at 30 days. The categories of age ≥ 65 years, hypertension or MI, smoking, drinking, initial GCS score, hematoma location, IVH, hematoma volume, SBP, LDL-C, HDL-C, TG, admission FBG and HbA1c levels, WBC count, Glu_{SD}, and Glu_{CV} differed be-

tween the good and poor outcome groups (all $p < 0.05$; Table 2).

The poor prognosis rates in the DM, SHG, and NG groups were 52.8%, 64.6%, and 24.4%, respectively (Fig. 2). The poor prognosis rate was highest in the SHG group as compared with the DM ($p = 0.045$) and NG groups ($p < 0.001$) and was significantly higher in the DM group than in the NG group ($p < 0.001$). Overall mortality at 30 days was 16.1% for the entire cohort. Mortality was highest for the SHG group compared to the DM group (29.9% vs 15.7%, $p = 0.011$) and the NG group (3.1%, $p < 0.001$), and mortality was significantly higher for the DM group than the NG group ($p < 0.001$).

An independent risk factor for a poor outcome in ICH patients was SHG (OR 2.62, 95% CI 1.07–6.44) but not DM (1.69, 0.64–4.43; Table 3). Poor prognosis was associated with an increased FBG level on admission (OR 1.13, 95% CI 1.05–1.22). Other predictors were an age ≥ 65 years, initial GCS score ≤ 8 , brainstem hematoma, and hematoma volume ≥ 20 ml (all $p < 0.05$).

Association Between GV and Outcome

On separately adding Glu_{SD} and Glu_{CV} to the Glu_{SD} and Glu_{CV} models, respectively, based on the significant variables on bivariate analysis, we found that an independent risk factor for a poor outcome was a high level of Glu_{SD} (OR 1.54, 95% CI 1.19–1.99) or Glu_{CV} (1.05, 1.02–1.09); the WBC count was newly included in the model, and admission FBG level was excluded (Table 4). An age ≥ 65 years, initial GCS score ≤ 8 , brainstem hematoma, and hematoma volume ≥ 40 ml were still predictors of a poor outcome (all $p < 0.05$).

On stratification by glucose group, all risk factors in the entire cohort (that is, age, initial GCS score, hematoma location, hematoma volume, IVH, WBC count, and Glu_{SD}) associated with 30-day functional outcome were included in the Glu_{SD} model. Risk factors for a poor outcome were a high Glu_{SD} (OR 1.94, 95% CI 1.13–3.34) in the DM subset and a high WBC count (1.22, 1.07–1.40) in the SHG subset. An age ≥ 65 years and large hematoma volume were still risk factors for a poor outcome in all subsets; brainstem hematoma and IVH were significant predictors in the DM and SHG subsets; and initial GCS score ≤ 8 was a predictor of a poor outcome in the DM and NG subsets (all $p < 0.05$).

A similar analysis was performed for the Glu_{CV} model. Here too risk factors for a poor outcome were a high Glu_{CV} (OR 1.14, 95% CI 1.04–1.26) in the DM subset and a high WBC count (1.22, 1.07–1.39) in the SHG subset. An age ≥ 65 years and hematoma volume ≥ 40 ml remained predictors of a poor outcome in all subsets (Table 4).

Assessing Prediction Models

The AUC was 0.860 (95% CI 0.823–0.898) for the original logistic model, 0.929 (0.902–0.956) for the Glu_{SD} model, and 0.932 (0.906–0.958) for the Glu_{CV} model (Fig. 3). The AUC for the Glu_{SD} or Glu_{CV} model was greater than that for the original model in predicting a poor outcome; thus, adding GV for 7-day FBG to the model improved prediction of the 30-day functional outcome for patients with acute ICH.

TABLE 1. Baseline clinical characteristics of 366 patients with ICH, according to glucose group

Variable	Total (n = 366)	DM (n = 108)	SHG (n = 127)	NG (n = 131)	p Value*
Age ≥65 yrs	156 (42.6)	53 (49.1)	49 (38.6)	54 (41.2)	0.248
Males	217 (59.3)	63 (58.3)	71 (55.9)	83 (63.4)	0.463
Previous disease					
Hypertension	271 (74.0)	96 (88.9)	91 (71.6)†	84 (64.1)†	<0.001
MI	102 (27.9)	31 (28.7)	36 (28.3)	35 (26.7)	0.933
Smoking	166 (45.4)	47 (43.5)	57 (44.9)	62 (47.3)	0.834
Drinking	114 (31.1)	39 (36.1)	41 (32.3)	34 (26.0)	0.227
SBP in mm Hg	164.6 ± 31.4	171.9 ± 28.7	168.1 ± 31.9	155.7 ± 31.2†‡	<0.001
DBP in mm Hg	97.2 ± 18.7	97.9 ± 16.5	100.5 ± 20.1	93.4 ± 18.5‡	0.010
PP in mm Hg	67.6 ± 20.8	74.0 ± 19.1	67.7 ± 22.4	62.2 ± 19.1	0.356
Initial GCS score					<0.001
13–15	145 (39.6)	34 (31.5)	37 (29.1)†	74 (56.5)†‡	
9–12	102 (27.9)	40 (37.0)	28 (22.0)†	34 (26.0)†‡	
≤8	119 (32.5)	34 (31.5)	62 (48.8)†	23 (17.6)†‡	
Hematoma location					0.966
Basal ganglia	151 (41.2)	44 (40.7)	54 (42.5)	53 (40.4)	
Lobar	94 (25.7)	26 (24.1)	32 (25.2)	36 (27.5)	
Brainstem	39 (10.6)	12 (11.1)	15 (11.8)	12 (9.2)	
Cerebellum	48 (13.1)	13 (12.0)	16 (12.6)	19 (14.5)	
Thalamus	34 (9.3)	13 (12.0)	10 (7.9)	11 (8.4)	
Hematoma vol in ml					<0.001
<20	179 (48.9)	47 (43.5)	48 (37.8)†	84 (64.1)†‡	
20–40	102 (27.9)	39 (36.1)	32 (25.2)	31 (23.7)†‡	
≥40	85 (23.2)	22 (20.4)	47 (37.0)	16 (12.2)†‡	
IVH	189 (51.6)	57 (52.8)	83 (65.4)	49 (37.4)†‡	<0.001
WBC count in 10 ⁹ /L	12.6 ± 7.0	11.9 ± 5.3	14.5 ± 10.2†	11.4 ± 4.6‡	0.002
TC in mmol/L	4.8 ± 1.3	5.2 ± 1.7	4.8 ± 1.2	4.6 ± 1.2†	0.023
LDL-C in mmol/L	3.0 ± 1.4	3.1 ± 1.4	2.8 ± 1.5	2.9 ± 1.2	0.427
HDL-C in mmol/L	1.1 ± 0.5	1.1 ± 0.4	1.1 ± 0.6	1.1 ± 0.4	0.645
TG in mmol/L	1.5 ± 1.4	1.7 ± 1.6	1.2 ± 1.1†	1.4 ± 1.3	0.011
Admission FBG level in mmol/L	8.7 ± 4.2	11.3 ± 4.5	10.2 ± 3.7	5.2 ± 0.9†‡	<0.001
Admission HbA1c level in %	6.5 ± 1.4	7.8 ± 1.9	6.0 ± 0.3†	5.7 ± 0.2†	<0.001
Glu _{SD} in mmol/L	1.9 ± 1.5	2.7 ± 1.6	2.4 ± 1.3	0.7 ± 0.3†‡	<0.001
Glu _{CV} in %	22.5 ± 11.6	27.5 ± 11.7	27.4 ± 11.1	13.74 ± 5.0†‡	<0.001

n = number of patients; PP = pulse pressure.

Data are expressed as the mean ± SD or as number (%). Boldface type indicates statistical significance.

* Comparison among the DM, SHG, and NG groups.

† p < 0.05, compared with the DM group.

‡ p < 0.05, compared with the SHG group.

Discussion

Hyperglycemia has been found to be associated with a poor prognosis in ICH, creating much attention among clinical scientists.^{2,3,14,32,33} However, there is not enough emphasis on distinguishing between SHG and DM among ICH patients in the clinic. Moreover, the study of the correlation of continuous glucose monitoring and GV with the prognosis of ICH has not been performed. The current study may be the first to focus on the functional outcome associated with continuous glucose monitoring in ICH. We monitored the FBG level on admission and for 7 continuous days after admission in patients with acute-onset

ICH. We investigated the associations among admission hyperglycemia, fluctuation in the continuous 7-day FBG level, and 30-day functional outcome.

Hyperglycemia and Outcome After ICH

We found that 64.2% of ICH patients had hyperglycemia at admission, which included 29.5% of patients in the SHG group and 34.7% in the DM group. We found that patients with a low initial GCS score, large hematoma volume, and IVH on admission frequently had hyperglycemia. Moreover, a high admission FBG level was an independent risk factor for an early (30-day) poor outcome in acute ICH,

FIG. 1. Dynamic changes in 7-day FBG level in 3 glucose groups of hospitalized patients with ICH. Figure is available in color online only.

and patients with SHG had a higher mortality and poorer prognosis rate than those with DM. A possible reason is that ICH patients with SHG had lower initial GCS scores, larger hematoma volumes, higher WBC counts, and IVH more often than the patients with DM or normal blood glucose. Related literature has shown that hyperglycemia substantially affects neurological functional recovery and prognosis in ICH, regardless of whether the hyperglycemia is caused by diabetes or not,¹³ although DM can be characterized by chronic sustained hyperglycemia and the influence of the stress reaction may not be severe.

A study in Finland reported that DM predicted a poor prognosis and an early death in ICH and that admission hyperglycemia was not a risk factor for a poor functional outcome, although the study did not distinguish hyperglycemia in undiagnosed DM from that in SHG by measuring HbA1c level.³⁵ With its unique application value, HbA1c is widely considered the gold standard for DM diagnosis, and hyperglycemia according to this value in undiagnosed DM can affect the analysis of functional outcome.^{8,37} We measured the HbA1c level and found that 15.3% of ICH patients had newly diagnosed DM, which corresponded well with the 12%–25% reported by Clement and colleagues.⁶ Moreover, we found that a high FBG level on admission was associated with a 30-day poor functional outcome for ICH patients, particularly those with SHG.

Generally, glucose management for SHG and DM is similar in the acute setting but different later. Glucose management in the enrolled patients with ICH included glucose control, anti-infection agents, nutrient support, treatment of primary disease, and prevention of complications, strategies mainly based on the guidelines of the American Heart Association¹⁷ and the standards of medical care in DM.¹ Glucose control for DM and SHG was similar when the glucose level was ≥ 10.0 mmol/L; that is, therapy with a dose of 1–2 U of insulin or more per hour via intravenous insulin pump was administered until the glucose level was decreased to 7.8–10.0 mmol/L for at least 2 days. However, when the glucose level was < 10.0 mmol/L in patients with DM, hypoglycemic treatment via subcutaneous insulin injection or oral hypoglycemic agents was continued to keep the glucose level in the nor-

TABLE 2. Baseline clinical characteristics associated with 30-day functional outcome in 366 ICH patients

Variable	Good Outcome	Poor Outcome	p Value
No. of patients	195 (53.3)	171 (46.7)	
Age ≥ 65 yrs	63 (32.3)	93 (54.4)	<0.001
Males	112 (57.4)	105 (61.4)	0.457
Previous disease			
Hypertension	128 (65.6)	143 (83.6)	<0.001
MI	44 (22.6)	58 (33.9)	0.016
Smoking	76 (39.0)	90 (52.6)	0.006
Drinking	44 (22.6)	70 (40.9)	<0.001
SBP (mm Hg)	158.2 $\pm$ 31.2	171.8 $\pm$ 30.3	<0.001
DBP (mm Hg)	94.5 $\pm$ 16.9	100.2 $\pm$ 20.1	0.063
PP (mm Hg)	64.1 $\pm$ 20.3	71.6 $\pm$ 20.7	0.051
Initial GCS score			<0.001
13–15	117 (60.0)	28 (16.4)	
9–12	61 (31.3)	41 (24.0)	
≤ 8	17 (8.7)	102 (59.6)	
Hematoma location			<0.001
Basal ganglia	74 (38.0)	77 (45.0)	
Lobar	63 (32.3)	31 (18.1)	
Brainstem	8 (4.1)	31 (18.1)	
Cerebellum	31 (15.9)	17 (9.9)	
Thalamus	19 (9.7)	15 (8.8)	
Hematoma vol in ml			<0.001
< 20	139 (71.3)	40 (23.4)	
20–40	39 (20.0)	63 (36.8)	
≥ 40	17 (8.7)	68 (39.8)	
IVH	58 (29.7)	131 (76.6)	<0.001
Admission FBG in mmol/L	7.5 $\pm$ 3.4	10.16 $\pm$ 4.71	<0.001
Admission HbA1c in %	6.2 $\pm$ 0.4	6.8 $\pm$ 1.8	0.002
WBC (10^9 /L)	11.0 $\pm$ 4.4	14.4 $\pm$ 9.3	<0.001
TC (mmol/L)	4.9 $\pm$ 1.5	4.6 $\pm$ 1.2	0.530
LDL-C in mmol/L	3.2 $\pm$ 1.3	2.7 $\pm$ 1.4	<0.001
HDL-C in mmol/L	1.2 $\pm$ 0.4	1.1 $\pm$ 0.5	0.015
TG in mmol/L	1.6 $\pm$ 1.5	1.3 $\pm$ 1.2	0.030
Glu _{SD} in mmol/L	1.4 $\pm$ 1.1	2.5 $\pm$ 1.6	<0.001
Glu _{CV} in %	19.5 $\pm$ 10.1	26.0 $\pm$ 12.3	<0.001
Glucose groups			<0.001
NG	99 (50.8)	32 (18.7)	
SHG	45 (23.1)	82 (48.0)	
DM	51 (26.2)	57 (33.3)	

Data are expressed as the mean $\pm$ standard deviation or as number (%). Boldface type indicates statistical significance.

mal range (4.4–6.1 mmol/L; diet and exercise can also be suggested); glucose levels only needed to be monitored in the patients with SHG.

Glycemic Mechanism of Outcome

We found a high proportion of ICH patients with acute hyperglycemia on admission, and SHG predicted a poor

FIG. 2. Poor prognosis and mortality rate at 30 days in 3 glucose groups of hospitalized ICH patients.

functional outcome. Hyperglycemia induces an inflammatory response and promotes hemoglobin, ferroheme, and iron release after red blood cell lysis,¹² and inflammation progresses in response to various stimuli to produce inflammatory signaling via activated microglia, subsequently releasing proinflammatory cytokines and chemokines that attract peripheral inflammatory infiltrates.⁴¹ Furthermore, the inflammatory process seems to enhance glucose toxicity in brain tissue, which also leads to metabolic dysregulation and secondary brain injury.³⁶

The pathophysiological mechanisms of hyperglycemia are different between SHG and DM. Stress hyperglycemia is usually defined as hyperglycemia resolving spontaneously after the dissipation of acute illness. It represents a transient hyperglycemia lasting for a few days or weeks in patients without previous evidence of DM, and it is probably related to the primary disease, underlying type of disease, severity of disease, and stage of illness. With timely and appropriate treatment of the primary disease, effects of the stress reaction such as the release of catecholamines, glucagon, and cortisol may be effectively reduced, thus possibly decreasing the SHG level.⁸ Stress hyperglycemia is the body's stress response when a stimulus is greater than the body can tolerate; SHG is thereby generated by the change in homeostasis and neuroendocrine derangements.⁸ During the response, high levels of inflammatory cytokines such as TNF- α and IL-6 are produced simultaneously, which results in injury to vessel endothelial cells, vessel structure, and the blood-brain barrier and leads to hemorrhagic infarct conversion.¹⁰ In contrast, the hyperglycemia in DM mainly results from a combination of insulin resistance and/or β -cell secretory defects¹ and may take years to develop. Glycemic control in DM is mainly through stimulating the release of insulin or increasing the sensitivity of insulin.⁵

A Protective Role for GV

Recently, the GV that refers to fluctuations in glucose values²⁵ has been proposed to be implicated in the disease-associated process of dysglycemia and a marker of glycemic control.²⁹ Several studies have demonstrated that

TABLE 3. Multivariate analysis of independent predictors of 30-day poor outcome after ICH (original model)

Variable	OR (95% CI)	p Value
Age ≥ 65 yrs	4.63 (2.35–9.09)	<0.001
Initial GCS score		<0.001
13–15	1.00	
9–12	1.17 (0.53–2.54)	0.700
≤ 8	7.09 (2.98–16.82)	<0.001
Hematoma location		<0.001
Basal ganglia	1.00	
Lobar	0.86 (0.36–2.02)	0.720
Brainstem	23.68 (6.51–86.16)	<0.001
Cerebellum	1.19 (0.43–3.25)	0.738
Thalamus	0.60 (0.20–1.81)	0.365
Hematoma vol in ml		<0.001
<20	1.00	
20–40	6.52 (2.93–14.47)	<0.001
≥ 40	7.14 (2.80–18.26)	<0.001
IVH	5.14 (2.54–10.42)	<0.001
Admission FBG level	1.13 (1.05–1.22)	0.002
Glucose group		0.012
NG	1.00	
SHG	2.62 (1.07–6.44)	0.036
DM	1.69 (0.64–4.43)	0.287

Boldface type indicates statistical significance.

increased GV is negatively associated with a poor prognosis and an early death in critically ill patients^{9,19} and in patients with congestive heart failure.⁷ We found GV to be an independent risk factor for a poor prognosis in acute-onset ICH, especially in patients with DM. Furthermore, after adjusting for other related variables, both our Glu_{SD} and Glu_{CV} models, as compared to our original model, specifically predicted a poor prognosis with no significant difference between the Glu_{SD} and Glu_{CV} models. This finding did not agree with the results of Mendez et al., who reported that the SD of glucose was a better metric than CV.²²

The ICH patients with DM and greater GV had wide fluctuations in glucose levels and poor glycemic control. Although we did not find DM to be an independent risk factor for a poor prognosis in ICH, the DM patients with greater GV tended to have a poor outcome, which means the stress reaction also existed in the patients. However, distinguishing between SHG and DM is difficult in the clinic; thus, GV may be a valuable marker to reflect the stress reaction from severe primary disease and excessive inflammation. Therefore, GV could be a valuable marker for effective glycemic control and outcome in ICH patients with DM. It is important to improve the prognosis in ICH patients with DM by strengthening the management of glucose. Glycemic variability is still not a readily available or well-used metric in ICH in the clinic,²¹ and more comprehensive research on this factor is needed.

Study Advantages

There are certain advantages in our work. First, by ob-

TABLE 4. Multivariate logistic regression analysis of the association between GV (Glu_{SD} or Glu_{CV}) and 30-day poor outcome after ICH

Variable	Glu _{SD} Model				Glu _{CV} Model			
	Entire Cohort	DM Subset	SHG Subset	NG Subset	Entire Cohort	DM Subset	SHG Subset	NG Subset
Age ≥65 yrs	6.21 (3.02–12.78)	9.79 (1.34–71.57)	9.32 (2.48–35.08)	10.52 (2.45–45.15)	6.39 (3.08–13.22)	8.92 (1.87–56.85)	8.76 (2.36–32.54)	10.39 (2.34–44.43)
Initial GCS score								
13–15	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
9–12	0.95 (0.42–2.13)	1.12 (0.32–30.21)	1.36 (0.27–6.87)	5.31 (0.89–31.81)	1.03 (0.46–2.30)	2.31 (0.34–32.36)	1.48 (0.29–7.47)	5.20 (0.88–30.91)
≤8	4.59 (1.86–11.36)	2.13 (0.11–0.89)	2.16 (0.44–10.65)	34.14 (4.36–67.17)	5.08 (2.08–12.43)	3.09 (0.11–0.98)	2.56 (0.56–11.77)	27.21 (4.38–66.96)
Hematoma location								
Basal ganglia	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Lobar	0.72 (0.30–1.73)	1.14 (0.11–12.42)	1.10 (0.22–5.61)	0.43 (0.07–2.81)	0.72 (0.30–1.72)	1.28 (0.11–15.55)	1.17 (0.23–5.89)	0.42 (0.06–2.72)
Brainstem	19.29 (5.16–72.16)	13.37 (3.85–27.34)	26.50 (3.74–66.85)	7.69 (0.51–15.01)	21.81 (5.81–81.89)	58.21 (7.11–93.82)	91.34 (4.68–83.47)	7.38 (0.50–14.69)
Cerebellum	0.76 (0.26–2.25)	0.19 (0.08–4.11)	1.66 (0.23–11.70)	1.83 (0.20–16.63)	0.78 (0.27–2.28)	0.14 (0.01–4.10)	2.07 (0.32–13.07)	1.77 (0.20–15.93)
Thalamus	0.55 (0.18–1.71)	0.38 (0.03–4.39)	0.90 (0.12–6.59)	0.59 (0.05–7.05)	0.52 (0.17–1.62)	0.29 (0.02–3.62)	0.81 (0.12–5.64)	0.59 (0.05–7.08)
Hematoma vol in ml								
<20	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
20–40	0.84 (0.44–2.80)	0.26 (0.20–3.49)	3.48 (0.67–18.01)	3.95 (0.44–35.78)	5.72 (2.51–13.06)	8.74 (1.21–62.99)	3.78 (0.74–19.38)	4.01 (0.44–36.64)
≥40	6.21 (3.46–12.72)	1.02 (0.03–0.54)	10.27 (1.53–69.03)	11.35 (2.16–59.53)	7.59 (2.83–20.34)	22.12 (3.44–80.51)	12.72 (2.02–80.15)	11.13 (2.13–58.17)
IVH	5.87 (2.80–12.30)	29.52 (9.84–69.63)	4.37 (1.07–17.87)	3.50 (0.76–16.16)	5.78 (2.77–12.05)	22.58 (10.04–96.55)	4.06 (0.94–17.56)	3.46 (0.75–16.01)
WBC	1.07 (1.04–1.16)	1.04 (0.87–1.25)	1.22 (1.07–1.40)	0.95 (0.79–1.16)	1.08 (1.03–1.15)	1.04 (0.86–1.27)	1.22 (1.07–1.39)	0.96 (0.79–1.16)
Glu _{SD}	1.54 (1.19–1.99)	1.94 (1.13–3.34)	1.24 (0.65–2.36)	1.90 (0.11–33.31)	Not included	Not included	Not included	Not included
Glu _{CV}	Not included	Not included	Not included	Not included	1.05 (1.02–1.09)	1.14 (1.04–1.26)	0.98 (0.93–1.05)	1.02 (0.88–1.19)

Data expressed as OR (95% CI). Boldface type indicates statistical significance.

FIG. 3. Receiver operating characteristic curves for the original, Glu_{SD} (SD), and Glu_{CV} (CV) models for predicting 30-day poor outcome in ICH. Figure is available in color online only.

serving ICH patients in regular hospital units rather than the intensive care unit, we provided a novel view of the implication of GV for these specific patients. Second, by relying on both medical history and an examination of the HbA1c level for nondiabetic patients, rather than basing our observations only on medical history, we could determine whether hyperglycemia was associated with DM or SHG. Third, we collected FBG data at admission and with 7-day continuous monitoring in order to observe dysglycemia immediately, thereby avoiding influential factors of food metabolism. Fourth, we analyzed admission FBG level and GV over 7 days of continuous monitoring as well as other factors as they related to functional outcome in ICH through multivariate analysis. We eliminated the influence of other risk factors to better understand the relationship between glycemic index and prognosis. In brief, the study provided an improved understanding of hyperglycemia and GV in ICH that could help to elucidate the pathophysiology of ICH and lead to more effective management.

Study Limitations

Several limitations are acknowledged. First, we did not collect data on factors such as nutritional status, fluids, and time of administration of insulin, which may affect the assessed GV. Second, we did not attempt to answer whether early insulin treatment for hyperglycemia could be beneficial because our patients were not observing strict glycemic control. Third, we did not evaluate other glycemic indexes of GV such as mean amplitude of glycemic excursion and mean absolute glucose rate of change, which may indicate that our results are unilateral. Further studies should consider other glycemic indexes of GV.

Conclusions

Stress hyperglycemia may be associated with increased mortality and a poor outcome in ICH, and increased GV may be independently associated with a poor outcome,

particularly in ICH patients with DM. Both Glu_{SD} and Glu_{CV} improved the prediction of 30-day functional outcome in acute ICH.

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Disclosures

The authors report no conflict of interest concerning the materials and methods used in this study or the finding specified in this paper.

Author Contributions

Conception and design: QY Zhang. Acquisition of data: Y Wu, Wang. Analysis and interpretation of data: Y Wu, Ding. Drafting the article: QY Zhang, Y Wu. Critically revising the article: QY Zhang, Y Wu. Reviewed submitted version of manuscript: QY Zhang, Y Wu. Approved the final version of the manuscript on behalf of all authors: QY Zhang. Statistical analysis: Ding, Wen, Dong. Administrative/technical/material support: QY Zhang, J Wu, SC Zhang. Study supervision: QY Zhang.

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