

Effects of Stress Hyperglycemia Ratio on 1-Year Clinical Outcome after Thrombolytic Therapy for Acute Ischemic Stroke

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Abstract

Background

Stress hyperglycemia manifests as transient hyperglycemia in the context of illness with or without known diabetes, which may cause poor clinical outcome in acute ischemic stroke (AIS) patients. The present study intended to evaluate the association between stress hyperglycemia ratio (SHR) and 1-year clinical outcome after treatment with recombinant tissue plasminogen activator (r-tPA) for AIS patients and compare the predictive effect of fasting glucose concentration, glycosylated hemoglobin (HbA1c) and SHR.

Methods

Data from 205 AIS patients following thrombolytic therapy with r-tPA in the Third Affiliated Hospital of Wenzhou Medical University from Apr. 2016 to Apr. 2019 were retrospectively reviewed. We grouped AIS patients according to SHR tertiles to contrast the 1-year clinical outcome. Multivariate regression analysis was carried to further analyze the association between SHR and AIS prognosis. Moreover, the receiver operating characteristics (ROC) curve analysis was used for the purpose of comparing the prognostic effects of fasting glucose concentration, HbA1c and SHR on AIS patients.

Results

SHR was an independent predictor for 1-year poor outcome (OR 1.447; 95% CI, 1.124-1.864, p = 0.004) but not the mortality of AIS patients. Restricted cubic spline regression showed a linear relationship between SHR and the odds of poor outcome. Furthermore, SHR is a fair predictor to predict 1-year poor outcome. The cut-off value of SHR levels was 0.79 with 71.0% sensitivity and 72.0% specificity.

Conclusions

The increased SHR was strongly associated with 1-year poor outcome following thrombolytic therapy with r-tPA. Meanwhile, SHR had higher predictive value for prognosis of AIS patients than fasting glucose concentration and HbA1c.

Trial registration

Retrospectively registered

Background

Acute ischemic stroke (AIS), a pervasive type of stroke, the major therapeutic method is intravenous or intra-arterial recombinant tissue plasminogen activator (r-tPA) or mechanical endovascular therapies. However, there are inherent risks in term of the process of thrombolysis using r-tPA, while benefiting eligible patients. That is why it is crucial to find biomarkers that can predict the prognosis of AIS patients. Previous studies have demonstrated that the poor clinical outcome following thrombolytic therapy with rtPA for AIS patients was associated with an elevated random glucose concentration at admission or an elevated fasting glucose concentration, both of which had limitations in distinguishing chronic poor management of background glucose levels and a physiologic stress response to AIS [1,2].

Stress hyperglycaemia might be a more reliable predictive biomarker of AIS patients than absolute glucose concentration, including the random and fasting glucose concentrations. The glycosylated hemoglobin (HbA1c) was a relatively stable index that could reflect the glucose control of patients with diabetes in the past 3 months. The glucose-to-HbA1c ratio (GAR) has been used for assessing stress hyperglycemia in previous study. Higher risk of symptomatic intracranial hemorrhage and recurrent stroke were observed in patients with high GAR level [3,4]. Recently, a novel index introduced by Roberts et al.[5] called Stress hyperglycemia ratio (SHR) was applied for assessing stress hyperglycemia. SHR was defined as the first fasting glucose concentration within 24 hours of admission divided by the estimated average glucose concentration derived from the HbA1c. SHR was more intuitive in responding to stress hyperglycemia intensity than GAR and it emphasized the essentiality of glucose changes. According to the reports, SHR was associated with the poor function outcome following mechanical thrombectomy in AIS [6]. Meanwhile, the latest article demonstrated that SHR was associated with poor functional outcome in AIS patients after 3-month intravenous thrombolysis, which was the first one concerning whether SHR could predict the clinical outcome following thrombolytic therapy with r-tPA for AIS patients [7]. On the basis of that article, the purpose of our study was to explore the relationship between the SHR and the 1-year clinical outcome after thrombolytic therapy with r-tPA for AIS patients and compare the predictive effect of fasting glucose concentration and SHR.

Methods

Study Population

A total of 359 patients, with a clinical diagnosis of AIS following thrombolytic therapy with r-tPA, were derived from the Third Affiliated Hospital of Wenzhou Medical University from Apr. 2016 to Apr. 2019. They were excluded for the following exclusion criteria: (1) reception of bridging therapy followed by; (2) with conditions affecting the HbA1c level, including renal failure (serum creatinine concentration greater than 180umol/L) and anemia (hemoglobin < 100g/L); (3) with the incomplete baseline data; (4) with the missing follow up data. Finally, 205 cases were included in this analysis (Figure 1).

The study was approved by the Ethics Committee of the Third Affiliated Hospital of Wenzhou Medical University and was performed in accordance with the Declaration of Helsinki. All subjects signed a written informed consent form.

Data Collection

The basic clinical data of AIS patients were collected through looking up the illness record, including basic demographic characteristics (sex and age), medical history (hypertension, diabetes mellitus,

Hyperlipidemia, history of stroke, atrial fibrillation and smoking) and blood biochemical indicators (Hemoglobin, Creatinine) on 24 hours admission. Stroke severity was evaluated by the National Institutes of Health Stroke Scale (NIHSS) at different points.1-year modified Rankin Scale (mRS) scores after onset of AIS, collected by two trained physicians on phone interview, was used to evaluate the functional outcome. In addition, death time were recorded if the patient were told to die.

Assessment of Stress Hyperglycemia Ratio

The fasting venous blood samples within the first 24 hours after admission were drawn during the morning hours after an overnight fast (at least 8h). The HbA1c level was tested by using high-performance liquid chromatographic analysis, which was uesd to calculate the estimated average glucose concentration using the following equation: (1.59 × HbA1c)-2.59 [8]. SHR was estimated as the following equation: [fasting serum glucose concentration (mmol/L)] / [(1.59 × HbA1c)-2.59]. According to the tertile of SHR, AIS patients were further categorized into three groups.

Definitions of Outcome

AIS patients with a 1-year mRS score of 0-2 were defined as the good prognosis group, while the remaining patients were in the poor prognosis group [9]. Moreover, 1-year mRS score of 6 can represent death status.

Statistical Analysis

Statistical analyses were performed through SPSS Statistics 24.0 software (SPSS Inc., Chicago, IL), R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) and MedCalc Statistical Software version 15.2.2 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2015). Continuous variables met normal distribution were presented with mean ± standard deviation (SD) while these not normally distributed were presented with median and interguartile range (IQR). Categorical variables are presented as frequency and percentage. Differences among SHR groups were compared through one-way analysis of variance (ANOVA), Kruskal–Wallis test or Chi-squared test when appropriately. We used a logistic regression model to estimate odds ratios (OR) with 95% confidence intervals (CIs) for 1-year poor outcome while a Cox regression model to estimate the hazard ratio (HR) with 95% CIs for death (log-log plots was performed to test the the proportional hazards assumption). Model 1 was univariable analysis. In model 2, we adjusted for age and gender. In model 3, we adjusted for age, gender and other significant covariates in the univariable analysis. Restricted cubic splines (model 3) with 3 knots (at the 10th, 50th, 90th percentiles) were further performed to find the association between SHR level and AIS outcome. The first tertile of the SHR was set as the reference for restricted cubic splines. Finally, the receiver operating characteristics (ROC) curve analysis was used for the purpose of exploring the predictive ability of fasting glucose concentration, HbA1c and SHR in AIS patients. p < 0.05 was considered to be statistically significant.

Results

Baseline Characteristics of Study Samples

205 AIS patients were included in our study, with a mean age of 69 years, and 127 (61.9%) of them were male and 78 (38.1%) were female. The median NIHSS score on admission was 7. According to the values of SHR levels, all patients were classified into three groups (T1: SHR < 0.70; T2: 0.70 \leq SHR \leq 0.83; T3: SHR > 0.83). For these three groups, there were no remarkable differences in terms of age, gender, onset to needle time, door to needle time, TOAST subtype, hemoglobin, creatinine, HbA1c, hypertension, Diabetes, hyperlipidemia, history of stroke and atrial fibrillation. Fasting glucose, NIHSS score on admission, NIHSS score on 24 hours and NIHSS score on 7 days of the patients in T3 group were dramatically increased compared to those in T1 group (p < 0.001, p < 0.001, p < 0.001, p < 0.001, respectively). Conversely, proportion of smoking was remarkably declined (p = 0.010) (Table 1).

The Correlation between SHR Levels and 1-year Outcome

After the 1-year follow-up, a total of 143 (69.7%) AIS patients was incorporated in the good prognosis group and the remaining 62 (30.3%) patients were in the poor prognosis group. In addition, 34 patients in poor prognosis group were dead and their death time were recorded. Moreover, distribution of 1-year mRS score in the tertiles of SHR levels revealed that high SHR levels were accompanied by high incidence of poor outcome and mortality (Figure 2).

We carried both univariate and multivariate logistic regression analysis for the purpose of obtaining a deeper appreciation of the association between SHR levels and the 1-year outcome. In model 1 without any adjustment, higher SHR level was associated with an increasing risk of 1-year poor outcome (T3 vs. T1: OR = 5.994, 95% CI [2.696-13.330] and per 0.1 point increase: OR = 1.475, 95% CI [1.225-1.777]) and mortality (T3 vs. T1: HR = 6.659, 95% CI [2.275-19.491] and per 0.1 point increase: HR = 1.285, 95% CI [1.128-1.463]).

The association between SHR and the risk of poor outcome and mortality were still significant after adjusting for age and gender in model 2. In model 3, we further adjusted for history of stroke, atrial fibrillation, smoking and admission NIHSS scores. SHR levels remained a striking predictor of poor outcome in AlS patients with OR of 5.587 (95% Cl, 1.909-16.349, p = 0.002) in T3 and OR of 1.447 (95% Cl, 1.124-1.862, p = 0.004) per 0.1-point increase. However, no associations were observed between SHR levels and 1-year mortality after being adjusted for potential confounders (Table 2). In order to further investigate the correlation between SHR levels and 1-year poor outcome, the restricted cubic spline regression of model 3 with 3 knots (at the 10th, 50th, 90th percentiles) were performed (Figure 3). Elevated SHR was associated with an increased risk of poor outcome (p = 0.014) and a linear association was observed.

Analysis of the Predictors for 1-year Poor Outcome in AIS Patients

ROC curves were performed to differentiate the efficiency of predicting 1-year poor outcome in AIS patients (Figure 4). HbA1c couldn't predict the poor outcome of AIS patients (p = 0.506).

Though fasting glucose could distinguish 1-year poor outcome and good outcome, it seems not a reliable predictor (AUC = 0.647; 95% Cl, 0.578-0.713; p < 0.001). SHR is a fair predictor to predict 1-year poor outcome. The cut-off value of SHR levels was 0.79 with 71.0% sensitivity and 72.0% specificity and AUC was 0.706 (95% Cl, 0.638-0.767).

Discussion

In this retrospective interventional cohort study, we explored the association between SHR and the prognostic value of thrombolytic therapy with r-tPA in AIS through 205 cases from the Third Affiliated Hospital of Wenzhou Medical University. Meanwhile, we compared the predictive effect of fasting glucose concentration, HbA1c and SHR. The main findings were as follows: (1) SHR was significantly associated with 1-year clinical outcome in AIS patients. (2) The AUC of SHR was larger than that of fasting glucose concentration and HbA1c. (3) After adjustments for age, gender, history of stroke, atrial fibrillation, smoking, history of stroke and admission NIHSS score, the predictive value of SHR for 1-year poor outcome was still significant, but it lost significance for 1-year mortality.

The previous work had indicated that SHR could be used as a strong predictor of poor clinical outcome after mechanical thrombectomy for AIS patients [6]. There have also been studies highlighting that SHR could predict the 3-month clinical outcome of patients following thrombolytic therapy with r-tPA [7]. In this study, in order to further explore the relationship between SHR and clinical outcome for AIS patients, we evaluated 1-year outcome and found that SHR was significantly correlated with the 1-year poor clinical outcome receiving thrombolytic therapy with r-tPA for AIS patients. However, the mechanisms of the association between an increased SHR and poor outcome following thrombolytic therapy with r-tPA for AIS patients were seemingly unknown. There were several possible explanations for this phenomenon. (1) Stress hyperglycemia, a stress response due to abnormal regulation of the neurohumoral endocrine system, can result in a cycle of excessive hepatic glucose production and insulin resistance, contributing to the increased blood glucose [10,11]. Not only does the increased blood glucose reduce the fibrinolytic activity of r-tPA, inhibiting the dissolution of venous thrombosis, but also changes the permeability of the blood barrier, leading to cerebral edema [12-14]. (2) Stress hyperglycemia may give rise to reperfusion injury by increased oxidative stress and inflammation [15,16]. (3) AIS patients are mostly associated with lipid metabolism disorders, increased low-density lipoprotein, and increased blood lipids, which could cause endothelial cell damage and aggravate inflammatory and stress responses. Under the high blood sugar state, the glycated low-density lipoprotein is swallowed by macrophages and transformed into foam cells, which adhere to the blood vessel wall, accelerating the formation of atherosclerosis and cerebrovascular disease complications, affecting prognosis. In previous studies, scholars mostly focused on the prognosis effect of blood glucose for AIS patients. However, the fasting glucose concentration has the disadvantage in distinguishing between stress hyperglycemia and chronic high background glucose concentration. On the contrary, SHR is a relative indicator that can be quantitatively evaluated for hyperglycemia. Therefore, SHR is expected to replace fasting glucose concentration as a novel generation of predictive indicator.

Definitions of stress hyperglycemia were different among previous studies. The time and method to draw the blood sample were also inconsistent. In addition, patients with a bridging therapy after intravenous thrombolysis were not excluded in some studies. Due to the similar research methods, the level of HbA1c and blood glucose in our study was similar to the study by Merlino G et al [3]. Besides, our study not only proved that SHR levels were related to the 1-year clinical outcome after thrombolysis with r-tPA, but also confirmed by ROC that the prognostic effect of SHR was better than fasting glucose and HbA1c. However, this study also inevitably had several limitations. There was no way to trace causality for the reason that our study was a retrospective interventional cohort study. Our research was designed to collect data only from one hospital, so the sample size was limited, which may result in the selection bias. What's more, plenty of possible mechanisms on the relationship of SHR and prognosis in AlS patients were not taken into account, thus experimental studies should be carried to support our point of view.

Conclusions

The present study found that increased SHR was strongly associated with 1-year poor outcome following thrombolytic therapy with r-tPA. Meanwhile, SHR had higher predictive value for prognosis of AIS patients than fasting glucose concentration and HbA1c.

Abbreviations

Acute ischemic stroke, AIS; Recombinant tissue plasminogen activator, r-tPA; Glycosylated hemoglobin, HbA1c; The glucose-to-HbA1c ratio, GAR; Stress hyperglycemia ratio, SHR; Modified Rankin Scale, mRS; National Institutes of Health Stroke Scale, NIHSS; Interquartile range, IQR; Odds ratios, OR; Confidence intervals, CIs; Receiver operating characteristics, ROC.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Third Affiliated Hospital of Wenzhou Medical University and was performed in accordance with the Declaration of Helsinki. All subjects signed a written informed consent form.

Consent for publication

All authors consent for publication.

Availability of data and material

The data that support the findings of this study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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None.

Author's contributions

Conceptualization and design, DY and GC; Methodology, DY, GC and JR; Software, JR and HH; Validation, JR and HH; Formal Analysis, JR, HH, NY and CY; Investigation, DY and GC; Resources, DY and GC; Data Curation, DY, JR, HH, NY, CY, BG, JH, WP, FS, XZ, and TZ; Writing-Original Draft Preparation, DY, JR, HH; Writing-Review & Editing, DY, GC, JR, HH, NY, CY, BG, JH, WP, FS, XZ, and TZ; Visualization, DY, JR, and HH; Supervision, DY and GC; Project Administration, DY and GC. All authors read and approval the final manuscript.

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Tables

Table 1 Characteristics of AIS patients according to SHR tertiles.

Variable	Total	SHR < 0.70	$0.70 \leq SHR \leq$	SHR > 0.83	<i>p</i>
	(n = 205)	(n = 75)	(n = 63)	(n = 67)	value
Demographic data			(11 00)		
Age (vears)	69.00 ±	66.89 ±	70.16 ± 11.14	70.27 ±	0.171
	12.17	11.66		13.48	
Gender (male, n.%)	127 (61.9)	49 (65.3)	40 (63.4)	38 (56.7)	0.547
Stroke risk factors (n.%)					
Hypertension (n.%)	124 (60.4)	41 (54.6)	38 (60.3)	45 (67.1)	0.314
Diabetes (n.%)	35 (17.0)	9 (12.0)	9 (14.2)	17 (25.3)	0.083
Hyperlipidemia (n.%)	24 (11.7)	6 (8.0)	6 (9.5)	12 (17.9)	0.151
History of stroke (n.%)	25 (12.1)	12 (16.0)	6 (9.5)	7 (10.4)	0.444
Atrial fibrillation (n.%)	45 (21.9)	12 (16.0)	13 (20.6)	20 (29.8)	0.132
Current smoking (n.%)	47 (22.9)	26 (34.6)	10 (15.8)	11 (16.4)	0.010
Laboratory data					
Hemoglobin (g/L)	132 (123- 144)	132 (123- 143)	132 (123-144)	135 (121- 146)	0.884
Creatinine (umol/L)	68 (61-75)	69 (62-76)	67 (60-74)	66 (59-75)	0.378
Fasting Glucose (mmol/L)	5.38 (4.67- 6.75)	4.65 (4.28- 5.09)	5.33 (4.93-5.95)	6.76 (5.95- 9.24)	< 0.001
HbA1c	6.06 (5.77- 6.03)	6.10 (5.83- 6.71)	6.03 (5.68-6.46)	6.17 (5.58- 6.99)	0.352
Stroke subtype					0.557
Cardioembolic	76 (37.1)	25 (33.3)	22 (34.9)	29 (43.2)	
Atherosclerotic	78 (38.1)	28 (37.3)	28 (44.4)	22 (32.8)	
Small vessel/lacunar	32 (15.6)	15 (20.0)	9 (14.2)	8 (11.9)	
Cryptogenic/others	19 (9.2)	7 (9.3)	4 (6.3)	8 (11.9)	
Clinical data					
Onset to needle time (min)	163 (126- 205)	170 (125- 210)	154 (120-202)	163 (131- 204)	0.623
Door to needle time (min)	55 (45-73)	53 (43-71)	57 (45-80)	58 (47-79)	0.353
Admission NIHSS	7 (5-11)	6 (4-9)	7 (5-11)	10 (6-16)	<

scores					0.001
24h NIHSS scores	5 (2-9)	4 (2-6)	4 (2-9)	9 (5-13)	< 0.001
7 days NIHSS scores	4 (1-8)	2 (1-4)	4 (1-8)	7 (3-12)	< 0.001

Abbreviations: AIS, acute ischemic stroke; SHR, stress hyperglycemia rate; NIHSS, national institute of health stroke scale;

mRS, modified Rankin Scale; HbA1c, Hemoglobin A1c.

Table 2 Adjusted Odds Ratio or Hazard Ratio for	1-year prognosis of AIS patients.
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	SHR	Poor outcome	р	Death	p
		OR (95% CI)		HR (95% CI)	
Model 1	T1	1	0.077	1	0.059
	Τ2	2.150 (0.921-5.020)	< 0.001 < 0.001	3.050 (0.956-9.725)	0.001
	T3	5.994 (2.696- 13.330)		6.659 (2.275- 19.491)	< 0.001
	increase	1.475 (1.225-1.777)		1.285 (1.128-1.463)	
Model 2	T1	1	0.205	1	0.166
	T2	1.795 (0.726-4.438)	< 0.001 <	2.279 (0.710-7.312)	0.007
	T3	5.733 (2.390- 13.750)		4.453 (1.490- 13.306)	< 0.001
	increase	1.538 (1.241-1.905)	0.001	1.279 (1.114-1.467)	
Model 3	T1	1	0.228	1	0.398
	T2	1.946 (0.659-5.746)	0.002	1.690 (0.500-5.713)	0.106
	Т3	5.587 (1.909-	0.004	2.641 (0.816-8.336)	0.227
	Per 0.1 point increase	1.447 (1.124-1.862)		1.106 (0.939-1.303)	

Model 1 is univariate analysis.

Model 2 is adjusted for age and gender.

Model 3 is additional adjusted for history of stroke, atrial fibrillation, smoking and admission NIHSS scores



Figure 1

Flow diagram showing the patient selection process.



Flow diagram showing the patient selection process.



Distribution of 1-year mRS in the tertiles of increasing SHR levels.



Figure 2

Distribution of 1-year mRS in the tertiles of increasing SHR levels.



Association between SHR and poor clinical outcome on 1 year using restricted cubic splines (model 3) with 3 knots (at the 10th, 50th, 90th, percentiles). The solid line indicates odds ratio while the shadow indicates 95%Cls. The dashed line is the reference line (odds ratio = 1). Reference of SHR was 0.70.



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Receiver operating characteristic curve (ROC) of SHR, fasting glucose and HbA1c on the prognosis of AIS patients between poor outcome and good outcome.



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