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ORIGINAL RESEARCH

Clinical Significance of Stress Hyperglycemic Ratio and Glycemic Gap in Ischemic Stroke Patients Treated with Intravenous Thrombolysis

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Objective: The clinical significance of different glycemic parameters has been rarely investigated in ischemic stroke patients treated with intravenous tissue plasminogen activator (IV tPA). This study was aimed to investigate the association between different glycemic parameters and favorable functional outcome in patients treated with IV tPA.

Methods: Patients with ischemic stroke who received IV tPA therapy at our stroke center were retrospectively enrolled. Four glycemic parameters were collected including admission glucose, HbA1c, stress hyperglycemia ratio (SHR) and glycemic gap (GG). Additional information was also recorded including demographics, medical history, stroke severity, imaging measures and mRS score at discharge. We used 5 machine learning models to investigate the predictive value of glycemic parameters.

Results: Our study included 294 patients treated with IV tPA. SHR and GG were independently associated with favorable functional outcome (adjusted OR for SHR 0.03, 95% CI 0.01–0.72, P = 0.03; adjusted OR for GG 1.024, 95% CI 1.00–1.05, P = 0.04).

Conclusion: SHR and GG were associated with functional outcomes in acute ischemic stroke patients with intravenous thrombolysis.

Keywords: stroke, thrombolysis, tissue plasminogen activator, glucose, hyperglycemia

Introduction

China has a great burden of stroke and the prevalence of stroke continued to increase in the past 7 years.[1] Intravenous thrombolysis is one of the most important treatment for ischemic stroke.[2] Among all clinical factors for functional outcomes in patients treated with intravenous tissue plasminogen activator (IV tPA),[3] only onset-to-needle time delay, blood pressure and glucose are modifiable. Higher admission glucose has been reported to be related to worse functional outcomes and higher mortality due to lactic acidosis accumulation, release of matrix metalloproteinase-9 and disruption of the blood–brain barrier.[4] Elevated glucose level may impair the fibrinolytic effect of alteplase and result in decreased rates of recanalization.[5] Considering patients with admission hyperglycemia (>22.15 mmol/L) were excluded from the European Cooperative Acute Stroke Study III trial,[6] these guidelines do not strongly recommend the use of tPA in patients with persistent elevated level of blood glucose.[7,8]

The Stroke Hyperglycemia Insulin Network Effort (SHINE) was a large-scale, randomized clinical trial that enrolled over 1000 ischemic stroke patients with admission hyperglycemia within 12 hours from stroke onset.[9] The patients were randomized to receive intensive hypoglycemia therapy versus standard hypoglycemia therapy for 3 days. However, the patients in the intensive hypoglycemia therapy group failed to achieve better functional outcome compared with the standard hypoglycemia therapy. The subgroup analyses revealed that none of the glycemic parameters, including baseline

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glucose, HbA1C, glycemic gap (GG), stress hyperglycemia ratio (SHR) and blood glucose variability, were associated with favorable outcome in patients with ischemic stroke.[10] The frustrating results of the SHINE trial raised concern on the clinical significance of glucose and glycemic parameters. Moreover, few study have investigated the significance of these glycemic parameters (GG and SHR) in patients treated with IV tPA.

In our study, we sought to investigate the correlation between different glycemic parameters and functional outcomes in patients treated with IV tPA.

Methods

Our study was an exploratory, retrospective, observational cohort study at a single stroke centre. Our study protocol was approved by the Ethics Committee of Beijing Tiantan Hospital (No.: KY2019-019- 05). The Ethics Committee of Beijing Tiantan Hospital also allowed waiver of informed consent and de-identification of patient information based on a retrospective study design.

In our study, patients treated with IV tPA at our stroke center were recruited. The patients were enrolled in the study population if they met the following inclusion criteria: 1) diagnosed with ischemic stroke; 2) treated with 0.9 mg/kg alteplase within 4.5 hours from stroke onset. Patients were excluded if 1) admission glucose or HbA1c data were incomplete; 2) no modified Rankin Scale (mRS) score was available at discharge.

We divided the included patients into 4 groups according to the quartiles of admission glucose. Other glycemic parameters included HbA1c, GG and SHR. GG was calculated as[11] admission glucose - (28.7 * HbA1c) + 46.7. The SHR was calculated as[12] admission glucose/HbA1c. Admission glucose was sampled immediately after admission and before the injection of tPA. HbA1c was sampled the morning after tPA injection. We collected demographic information, medical and medication history, alcohol/tobacco status, time metrics of IV tPA, and stroke severity (measured by NIHSS score[13]). Etiology of stroke was classified based on the Trial of Org 10,172 in Acute Stroke Treatment (TOAST) classification.[14] Considering that only non-contrast CT scans were performed before IV tPA in clinical practice, large vessel occlusion was assessed based on MR angiography after IV tPA. Symptomatic intracerebral hemorrhage (sICH) was evaluated based on the standards of the National Institute of Neurological Disorders and Stroke rt-PA Stroke (NINDS) Criteria[2] and Safe Implementation of Thrombolysis in Stroke (SITS)[15] Criteria. The study outcome was a favorable functional outcome, defined as mRS score 0–2 at discharge (a common scale to assess the independent status ranging from 0 to 6 with a higher score indicating poorer independent status).[16,17]

Statistical Analyses

Normally distributed data were displayed as mean ± SD and compared using the ANOVA analyses. Skewed data were displayed as median (interquartile range) and compared using the Kruskal–Wallis tests. Categorical data were displayed as number (percentage) and compared using the χ^2-tests. We used the Kruskal–Wallis test with multi-comparisons if skewed data and multi-comparisons with Bonferroni adjustment if categorical data. Multivariable logistic regression analyses were used to investigate the association between glycemic parameters and favorable outcome adjusting for confounders with a P value ≤ 0.05 in the baseline comparisons.

A total of 5 machine learning models were established to test whether the addition of admission glucose or glycemic parameters was beneficial to improve the predictive power of the machine learning models in predicting favorable functional outcome. We established a decision tree model (dtc), a k-Nearest Neighbor (kNN) model, a multilayer perceptron (mlp) model, a random forest (rfc) model, and an extreme gradient boosting (XGBoost) model by including the common factors related to clinical outcome of ischemic stroke: age, sex, onset-to-needle time, bridging mechanical thrombectomy (MT), admission NIHSS score, pre-mRS score, medical history (hypertension, atrial fibrillation, diabetes mellitus, hyperlipidemia and prior stroke), smoking, drinking, admission systolic blood pressure (SBP), antiplatelet therapy and TOAST classification. Before training the machine models, the study population was divided into a training cohort (70%, to train the models) and a test cohort (30%, to test the predictive power). We compared the predictive ability of machine learning models before and after adding admission glucose using operating characteristic (ROC) curves and area under curve (AUC). The machine learning models and subsequent ROC curves were performed using Python 3.6 (Python Software Foundation, Beaverton, OR, USA; https://www.python.org/).

Results

A total of 595 patients received IV tPA within 4.5 hours in our stroke center from October 1st, 2018 to November 5th, 2020. Among the patients treated with IV tPA in our stroke center, 77 patients had no discharge mRS score, 97 patients had no admission glucose data and 127 patients had no HbA1c data (Supplementary Material). In the final study, a total of 294 patients were enrolled. Compared with excluded patients, the included patients tended to have higher rates of MT and comorbidities (Supplementary Material). Among the final included patients, the mean age was 62.43 ± 12.02 years and 219 (74.49%) were male. The median door-to-needle (DNT) time was 45 (35.00–63.75) minutes, and onset-to-needle time was 167.5 (128.25–223.75) minutes. The median admission NIHSS score was 5 (3–9). Among the included patients, 32 (10.88%) patients underwent MT after IV tPA therapy. Compared with the Q1-Q3 of admission glucose groups, the Q4 group showed a higher proportion of hypertension ($P = 0.01$), atrial fibrillation ($P = 0.02$) and diabetes mellitus ($P < 0.001$). More patients were observed to have a history of smoking or currently smoking in the Q4 group ($P = 0.02$). The Q4 group also tended to have higher levels of HbA1c ($P < 0.001$), SHR ($P < 0.001$) and glycemic gap ($P < 0.001$) (Table 1). Pairwise comparisons of the four glucose parameters showed statistically significant difference.

Correlation Between Glycemic Parameters and Functional Outcome

Among the included patients, 175 (59.5%) patients achieved favorable functional outcome at discharge. Multivariable logistic regression models showed that, among the different glucose parameters, GG and SHR were independently associated with functional outcome in the adjusted models (adjusted OR for SHR 0.03, 95% CI 0.01–0.72, $P = 0.03$; adjusted OR for GG 1.024, 95% CI 1.00–1.05, $P = 0.04$). Restrict cubic spline showed the non-linear relationship between the OR value and these two glycemic parameters (Figure 1).

GG and SHR in Machine Learning Models

A total of 5 machine learning models were established to investigate whether adding GG and SHR was beneficial to improve the predictive power of the machine learning models in predicting favorable functional outcome. All of the 5 machine learning models showed a non-statistically significant improvement in predictive power (Supplementary Material).

Discussion

In the current study, we investigated the association between glycemic parameters and clinical outcome in patients treated with IV tPA. SHR and GG were significantly associated with clinical functional outcome at discharge.

A systematic review of 32 studies found that SHR was associated with poor clinical outcome in patients with ischemic stroke.[18] An observational study recruited patients treated with IV tPA and found that high SHR was associated with poor clinical outcomes.[19] In accordance with this observational study,[19] our study also found the inverse relationship between SHR and favorable clinical outcome. However, the role of GG in patients treated with IV tPA has not been well defined. Our study reported that GG was associated with poor clinical outcome. SHR and GG are glycemic parameters combined with acute (random glucose) and chronic (HbA1c) hyperglycemia. Hence, the correlation between these two combined glycemic parameters and clinical outcomes might be explained with the influence of both acute and chronic glycemia.

Considering that hypoglycemia might mimic the symptoms of ischemic stroke, a random glucose test was performed in all patients prior to injection of tPA.[7] A prospective, observational study showed that admission hyperglycemia was associated with poor clinical outcomes in patients treated with IV tPA.[4] Another large-scale, observational study based on the Get With The Guidelines Stroke (GWTG-Stroke) database found that both acute and chronic hyperglycemia were associated with poor clinical outcomes in patients treated with tPA.[20] Hence, this large-scale cohort study[20] proposed that controlled clinical trials were required to investigate whether early intervention on glucose was beneficial to improve the clinical outcomes in ischemic patients. However, the SHINE trial showed that intensive hypoglycemia therapy failed to improve clinical outcomes significantly in ischemic stroke patients.[9] The negative results from the SHINE trial raised new attention to the clinical significance of glucose in ischemic stroke patients.[21]

Table 1 Baseline Characteristics Between Different Levels of Admission Glucose in Patients Treated with IV tPA

	Overall (n=294)	Q1 3.96–5.90 mmol/L (n=74)	Q2 5.91–6.90 mmol/L (n=73)	Q3 6.91–8.75 mmol/L (n=75)	Q4 8.77–28.69 mmol/L (n=72)	P value
Age, years (mean (SD))	62.43 (12.02)	59.73 (12.79)	62.23 (12.79)	64.56 (11.78)	63.18 (10.23)	0.09
Male, n (%)	219 (74.49)	57 (77.03)	53 (72.60)	55 (73.33)	54 (75.00)	0.93
DNT time (median [IQR])	45.00 [35.00, 63.75]	50.00 [36.25, 75.00]	44.00 [33.00, 63.00]	43.00 [34.00, 60.50]	45.50 [37.50, 62.50]	0.24
Time from symptom onset to needle, min (median [IQR])	167.50 [128.25, 223.75]	165.00 [130.00, 218.75]	167.00 [127.00, 210.00]	171.00 [136.50, 234.00]	170.00 [128.00, 225.25]	0.66
Bridging mechanical thrombectomy, n (%)	32 (10.88)	8 (10.81)	9 (12.33)	11 (14.67)	4 (5.56)	0.34
Admission NIHSS score (median [IQR])	5.00 [3.00, 9.00]	5.00 [3.00, 8.00]	5.00 [3.00, 10.00]	6.00 [4.00, 9.00]	5.50 [3.00, 9.00]	0.37
Pre-mRS score, n (%)						0.11
0	233 (79.25)	60 (81.08)	61 (83.56)	61 (81.33)	51 (70.83)	
1	29 (9.86)	11 (14.86)	5 (6.85)	4 (5.33)	9 (12.50)	
2	17 (5.78)	1 (1.35)	5 (6.85)	4 (5.33)	7 (9.72)	
3	12 (4.08)	1 (1.35)	2 (2.74)	6 (8.00)	3 (4.17)	
4	3 (1.02)	1 (1.35)	0 (0.00)	0 (0.00)	2 (2.78)	
Hypertension, n (%)	180 (61.22)	41 (55.41)	36 (49.32)	50 (66.67)	53 (73.61)	0.01
Atrial fibrillation, n (%)	34 (11.56)	2 (2.70)	12 (16.44)	13 (17.33)	7 (9.72)	0.02
Diabetes mellitus, n (%)	74 (25.17)	6 (8.11)	6 (8.22)	19 (25.33)	43 (59.72)	<0.001
Hyperlipidemia, n (%)	36 (12.24)	9 (12.16)	8 (10.96)	12 (16.00)	7 (9.72)	0.68
Prior stroke, n (%)	62 (21.09)	15 (20.27)	12 (16.44)	15 (20.00)	20 (27.78)	0.40
Prior antiplatelet therapy, n (%)	48 (16.33)	12 (16.22)	10 (13.70)	13 (17.33)	13 (18.06)	0.9
Prior statin therapy, n (%)	41 (13.95)	15 (20.27)	5 (6.85)	8 (10.67)	13 (18.06)	0.07
Smoking, n (%)	184 (62.59)	57 (77.03)	44 (60.27)	44 (58.67)	39 (54.17)	0.02
Drinking, n (%)	145 (49.32)	45 (60.81)	32 (43.84)	39 (52.00)	29 (40.28)	0.06
Admission SBP level, mmHg (mean (SD))	152.71 (23.83)	152.50 (26.40)	151.93 (21.20)	149.25 (22.62)	158.52 (24.73)	0.25
Admission DBP level, mmHg (mean (SD))	88.69 (13.88)	88.23 (13.52)	87.93 (14.20)	87.87 (13.19)	91.30 (14.94)	0.56
TOAST, n (%)						0.19
LAA	222 (75.51)	56 (75.68)	52 (71.23)	57 (76.00)	57 (79.17)	
CE	49 (16.67)	9 (12.16)	13 (17.81)	15 (20.00)	12 (16.67)	
SAA	9 (3.06)	3 (4.05)	4 (5.48)	1 (1.33)	1 (1.39)	

(*Continued*)

Table 1 (Continued).

	Overall (n=294)	Q1 3.96–5.90 mmol/L (n=74)	Q2 5.91–6.90 mmol/L (n=73)	Q3 6.91–8.75 mmol/L (n=75)	Q4 8.77–28.69 mmol/L (n=72)	P value
OTHER	8 (2.72)	4 (5.41)	0 (0.00)	2 (2.67)	2 (2.78)	
UNKNOWN	6 (2.04)	2 (2.70)	4 (5.48)	0 (0.00)	0 (0.00)	
Admission blood glucose, mmol/L (median [IQR])	6.90 [5.90, 8.75]	5.52 [5.23, 5.71]	6.35 [6.15, 6.55]	7.81 [7.40, 8.30]	11.09 [9.70, 14.83]	<0.001*
HbA1c, % (median [IQR])	6.00 [5.70, 6.80]	5.70 [5.50, 6.00]	5.80 [5.60, 6.10]	6.10 [5.75, 6.60]	7.70 [6.77, 8.83]	<0.001*
SHR (median [IQR])	1.15 [1.01, 1.38]	0.95 [0.88, 1.01]	1.08 [1.03, 1.15]	1.27 [1.18, 1.37]	1.55 [1.39, 1.74]	<0.001*
Glycemic gap (median [IQR])	−1.76 [−16.43, 22.94]	−20.00 [−27.07, −12.54]	−6.07 [−15.58, 0.61]	11.14 [−0.19, 23.22]	40.58 [17.46, 63.57]	<0.001*
Triglyceride level, mmol/L (mean (SD))	1.85 (1.35)	1.72 (1.31)	1.89 (1.52)	1.72 (1.29)	2.03 (1.28)	0.66
Cholesterol level, mmol/L (median (SD))	4.61 (1.28)	4.89 (1.16)	4.37 (1.33)	4.56 (1.19)	4.65 (1.36)	0.33
Low density lipoprotein level, mmol/L (mean (SD))	2.59 (0.87)	2.66 (0.88)	2.63 (0.95)	2.50 (0.78)	2.58 (0.90)	0.72
Fazekas scale, n (%)						0.97
0	22 (9.36)	6 (9.68)	5 (8.33)	5 (8.47)	6 (11.11)	
1	142 (60.43)	35 (56.45)	35 (58.33)	37 (62.71)	35 (64.81)	
2	52 (22.13)	16 (25.81)	15 (25.00)	11 (18.64)	10 (18.52)	
3	19 (8.09)	5 (8.06)	5 (8.33)	6 (10.17)	3 (5.56)	
Large vessel occlusion, n (%)	74 (25.17)	14 (18.92)	24 (32.88)	20 (26.67)	16 (22.22)	0.24
sICH-NINDS, n (%)	16 (5.44)	3 (4.05)	4 (5.48)	1 (1.33)	8 (11.11)	0.07
sICH-SITS, n (%)	8 (2.72)	1 (1.35)	1 (1.37)	1 (1.33)	5 (6.94)	0.09
Discharge mRS 0–2, n(%)	175 (59.5)	48 (64.90)	48 (65.80)	43 (57.30)	36 (50.00)	0.04

Note: *Pairwise comparisons of the four glucose parameters showed statistically significant difference.

Abbreviations: DNT, door-to-needle; IV, intravenous thrombolysis; tPA, tissue plasminogen activator; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10,172 in Acute Stroke Treatment; LAA, large atherosclerosis artery; CE, cardiac embolism; SAA, small artery occlusion; SBP, systolic blood pressure; DBP, diastolic blood pressure; sICH, symptomatic intracerebral hemorrhage; NINDS, National Institute of Neurological Disorders and Stroke rt-PA Stroke; SITS, Safe Implementation of Thrombolysis in Stroke; SHR, Stress Hypoglycemia Ratio.

Chronic hyperglycemia was also reported as a predictor for poor functional outcome in patients with ischemic stroke.[22] Subgroup analyses from the Safe Implementation of Treatments in Stroke International Stroke Thrombolysis Register (SITS-ISTR) cohort found that the association between admission hyperglycemic and clinical outcome was more significant in patients without a known history of diabetes.[4] HbA1c had a more significant role compared to medical history from patients in assessing chronic hyperglycemia.[20] The subgroup analyses[20] from the GWTG confirmed that HbA1c >6.5% exerted a role in poor clinical outcomes. However, a large-scale observational study showed that HbA1c ≥6.5% was not significantly associated with poor functional outcome.[23] The conflicting results generated a controversial relationship between HbA1c and functional outcome. Compared with single admission hyperglycemia

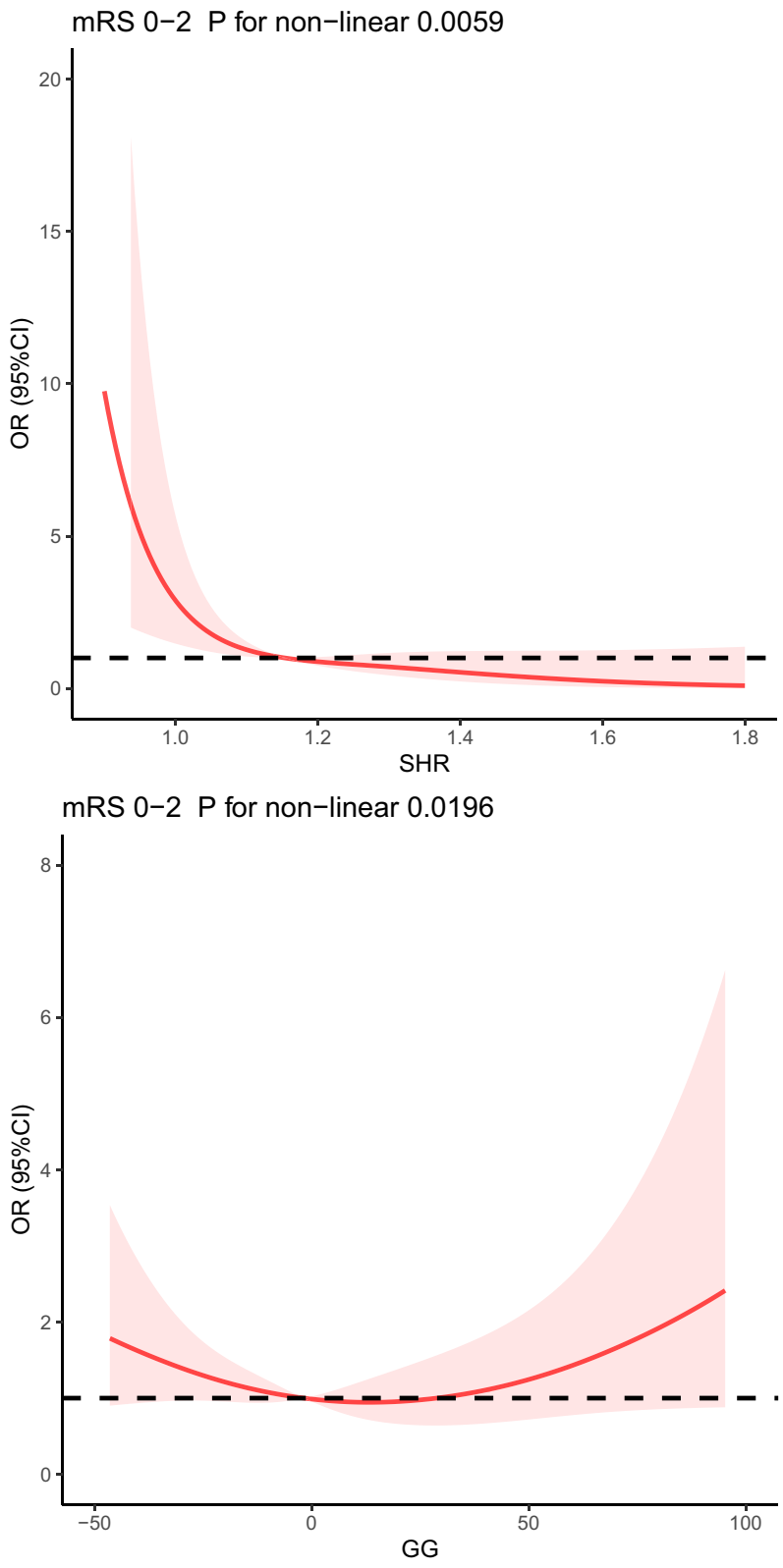

Figure 1 Restricted cubic splines to delineate the relationship between SHR or GG and adjusted OR for in-hospital clinical outcomes.

or HbA1c ≥6.5%, admission hyperglycemia combined with HbA1c ≥6.5% may be a more significant marker to predict unfavorable functional outcomes in ischemic stroke patients.[24] Hence, more investigations were warranted to determine the role between chronic hyperglycemia combined with acute hyperglycemia in the role of deteriorating the functional outcomes in ischemic patients.

Hyperglycemia was reported to be devastating for the integrity of BBB, and disruption of BBB might result in cerebral edema and hemorrhagic transformation.[25,26] Hypercoagulability and impaired fibrinolytic activity are also associated with hyperglycemia.[27] Besides, hyperglycemia might generate additional hemodynamic damage by inhibiting vasodilatation.[28,29] In patients treated with IV tPA, hyperglycemia might increase the secretion of plasminogen activator inhibitor-1 to attenuate the fibrinolytic activity of tPA and decrease the recanalization rate.[30,31] In addition, damaged BBB due to hyperglycemia might allow tPA penetrate into brain tissue and deteriorate the neurological impairment considering the neurotoxicity of tPA.[25] Moreover, hyperglycemia could generate reperfusion injury via oxidative stress and inflammatory process with increased expression of the endothelial adhesion molecules and monomeric C-reactive protein.[32–34]

Our study has some limitations. First, our study was based on a database from a single study center with retrospective study design. Compared with a multi-center registry or double-blinded trial, our study might have potential bias. Second, our study only collected glucose data on admission without glucose data at other time points during hospitalization. In the clinical practice, only patients diagnosed with diabetes had repeated measures on glucose. These diabetes patients tended to receive repeated glucose tests with fingertip blood during hospitalization, while all of the patients received admission glucose tests with intravenous blood. Hence, it was difficult to collect multiple blood glucose samples at different time points in all of our study patients. Third, 90-day follow-up was not conducted and we failed to compare the 90-day independent status based on mRS score in our study. Due to the COVID-19 outbreak, follow-up visit was difficult to perform. Discharge mRS score was used in our outcome assessments considering its robust association with 90-d mRS score.[35] Fourth, large vessel occlusion was measured with MRA/CTA within 24 hours after injection of tPA. Some patients might achieve recanalization when measuring vessel occlusion within 24 hours in our study. However, this bias might be limited considering the low admission NIHSS score in our study and the low recanalization rate of alteplase in larger vessel occlusion reported before.[36]

Conclusion

SHR and GG were associated with functional outcomes in acute ischemic stroke patients with intravenous thrombolysis.

Data Sharing Statement

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

Ethics Approval and Consent to Participate

The study was approved by the ethics committee of Beijing Tiantan Hospital (No.: KY2019-019- 05). The fully de-identified data on the patients enrolled in the current study and its retrospective study design enables this study conducted under a waiver of informed consent by the local institutional review board of Beijing Tiantan Hospital. All methods were carried out in accordance with relevant guidelines and regulations. Our study complies with the Declaration of Helsinki.

Consent for Publication

Not applicable. No information or images that could lead to identification of a study participant were mentioned in our study.

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Disclosure

The authors have no conflicts of interest to declare.

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