# Impact of Relative Blood Glucose Changes on Mortality Risk of Patient with Acute Ischemic Stroke and Treated with Mechanical Thrombectomy

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*Background and purpose:* The impacts of stress hyperglycemia and hypoglycemia on mortality of acute ischemic stroke patients treated with mechanical thrombectomy (MT) are largely unclear. This study aimed to use stress hyperglycemia ratio (SHR) to evaluate the influence of pretreatment relative blood glucose changes on mortality risk after MT. *Methods:* The study retrospectively enrolled 321 acute ischemic stroke patients treated with MT. SHR was calculated as random blood glucose at admission divided by average blood glucose which estimated by glycosylated hemoglobin (HbA1c). Patients with HbAlc greater than or equal to 6.5% were considered to have background hyperglycemia, patients were tertiled according to their SHR. Binary logistic regression was used to analyze 90 days mortality between SHR categories. *Results:* Compared with the middle tertiles group (Q2) which the blood glucose is closet to baseline glycaemia, patients in the lowest tertiles group (Q1) and highest tertiles group (Q3) have a higher mortality risk (odds ratio [OR], 3.80; 95% confidence interval [CI], 1.31-11.06) (OR, 3.18; 95% CI, 1.25-8.12), the differences is still significant after further adjusted for admission hyperglycemia (≥11.1 mmol/L). In patients without background hyperglycemia, the mortality risk is significantly higher in Q3 group (OR, 3.01; 95% CI, 1.06-8.53), no significant differences was found between three groups after adjusted for admission hyperglycemia (≥11.1 mmol/L). *Conclusions:* SHR identified acute ischemic stroke patients with relative hyperglycemia and hypoglycemia may have higher mortality risk after MT.

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## Introduction

Dysglycemia is a common phenomenon during acute phase of severe illness. Both hyperglycemia and hypoglycemia can predict poor prognosis after critical illness.[1-4] The causes of hyperglycemia during severe illness may be poor control of chronic hyperglycemia, physiological stress, or both. Compared with chronic hyperglycemia, stress-induced hyperglycemia may be a better poor prognostic marker of acute illness.[5-7] Stress hyperglycemia is a kind of relative hyperglycemia, the degree of relative hyperglycemia depends on the severity of physiological stress and related to the risk of adverse prognosis. High incidence of stress hyperglycemia have been reported in nondiabetic (range from 3% to 71%) and diabetic patients (range from 46% to 84%).[8] However, the effect of background hyperglycemia makes it difficult to identify stress hyperglycemia from diabetic patients and the chronic hyperglycemia status may affect the prognostic impact of stress hyperglycemia,[9] this can used to explain the impact of stress hyperglycemia is more significant in nondiabetic patients. Therefore, analyzing the prognostic effect of stress hyperglycemia requires adjusting background hyperglycemia.

Stress hyperglycemia ratio (SHR) was introduced to control background glycaemia, the value was calculated as admission random blood glucose divided by average glucose which estimated by glycosylated hemoglobin ($HbA_{1c}$).[10] Previous studies used this index to analyze the impact of relative hyperglycemia on prognosis of critical illness patients, the results confirmed that SHR is a useful predictive marker of poor outcomes.[11] The novel index of SHR not only reflects relative hyperglycemia but also can reflect relative hypoglycemia. However, few studies have focused on the impact of relative hypoglycemia on prognosis. Although, the adverse effects of hypoglycemia have been well demonstrated, but most of the previous studies used absolute hypoglycemia rather than relative hypoglycemia as prognostic marker, suggested that the adverse effect of hypoglycemia on prognosis depending on the diabetic status and diabetic control status.[1] Whether relative hypoglycemia has the same predictive value as absolute hypoglycemia is unclear. This study aimed to validate the prognostic effect of relative hyperglycemia in ischemic stroke patients treated with mechanical thrombectomy (MT). We further hypothesis that after adjusted for baseline glycaemia, the relative hypoglycemia can also affect clinical outcomes.

## Method

### *Patients*

Patients included in this analysis were those enrolled in Endovascular Treatment for Acute Anterior Circulation Ischemic Stroke Registry study, which was a multicenter registry program involving 21 stroke centers in 10 provinces of China. Details of Acute Anterior Circulation Ischemic Stroke Registry have been described elsewhere.[12]

Patients were recommended for MT if they: (1) were diagnosed with acute ischemic stroke, (2) had large artery occlusion in anterior circulation, (3) aged 18 years or older, (4) had a premorbidity modified Rankin scale score less than 2, (5) had a pretreatment National Institutes of Health Stroke Scale (NIHSS) score >5. Patients were detained with MT if they (1) diagnosed with concomitant aneurysm or arteriovenous malformation, (2) diagnosed with malignant tumors, autoimmune diseases, hemorrhage diseases, or major organ failure. In order to maintain the homogeneity of the enrolled patients, we excluded patients treated with intra-arterial thrombolysis only and patients with incompletely baseline data. Ethics approval was obtained from each central ethic committees.

### *Baseline Assessments*

Stroke severity was assessed with NIHSS, pretreatment infarction core was quantified with Alberta Stroke Program Early CT Score[13] based on noncontrast computed tomography on admission. Collateral status was assessed with the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology.[14] Successful revascularization was defined as a modified Thrombolysis in Cerebral Infarction score of 2b/3.[15] Time from puncture to recanalization, intravenous thrombolysis treatment were collected from medical record. Imaging data were reviewed in blind manner by 2 physician/interventionists (Y.H. and H.W.), with advice of the third experienced physicians (W.Z.) in case of disagreement.

### *Assessment of Relative Hyperglycemia and Hypoglycemia*

Blood glucose level was monitored before and after MT. Glycosylated hemoglobin (HbAlc %) was measured shortly after the MT. Relative blood glucose changes was calculated with SHR as: [glucose (mg/dl) / 18] / [(1.59 × HbAlc) − 2.59].[10] HbAlc was used to distinguish background hyperglycemia and normal glycaemia, HbAlc greater than or equal to6.5% was considered to have background hyperglycemia. SHR reflects the relative fluctuation of blood glucose compared with background glycaemia, the acute evaluation and decline in plasma concentrations quantified by SHR is defined as relative hyperglycemia and hypoglycemia. Patients were grouped according to tertiles of SHR for further comparison.

*Outcomes Measurements*

Intracranial hemorrhage was classified as parenchymal hematoma, subarachnoid hemorrhage, and intraventricular hemorrhage accompanied by the deterioration of clinical symptoms, diagnosed based on CT scan and further classified as symptomatic and asymptomatic ones according to Heidelberg Bleeding Classification.[16] The complication pneumonia was collected from medical record, the 90 days mortality was obtained via clinical visit or telephone interview.

*Statistical Analysis*

Before statistic analyze, the Kolmogorov-Smirnov test was performed to test variables normality. The continuous variables were described as mean (standard deviation) and median (quartile) according to the normality distribution. Categorical variables expressed as number (percent). Univariate analysis for continuous variables was performed using the Student *t* test or Kruskal-Wallis test according to their normality of distribution, and $\chi 2$ or Fisher exact test for binary variables according to their sample size. Multivariable logistical regression was used to analysis independent predictors for mortality after MT, entered variables included age (>60 years), gender, neutrophil lymphocyte ratio (>7.07), preoperative ASPCTS, baseline NIHSS, coronary heart disease, puncture to end of revascularization (>90 minutes) and to compute odds ratio (OR) 95% confidence interval (CI) as estimate for each endpoint, 2-tailed *P* values of <.05 were considered statistically significant Data analyses were performed using the statistical software package SPSS 22.0 for Windows (IBM, Armonk, NY).

## Results

A total of 321 patients with an acute anterior circulation ischemic stroke and treated with MT were included in this analysis. The median value of SHR in the 3 tertiles groups are Q1 .81 (interquartile range [IQR] .70-.87), Q2 1.05 (IQR .97-1.10), and Q3 1.40 (IQR 1.26-1.58). Blood glucose level of Q2 group is closest to baseline glycaemia, compared with Q2 group, the Q1 group can reflect relative hypoglycemia and Q3 group reflect a relative hyperglycemia. Baseline characteristics were present in Table 1. Patients with higher SHR are more likely to have coronary heart disease and atrial fibrillation, have a higher

**Table 1.** *Baseline characteristics of patients according to the SHR tertiles groups*

| Baseline characteristics | Stress hyperglycemia ratio (SHR) | | | |
|---|---|---|---|---|
| | Q1 (n = 107) | Q2 (n = 107) | Q3 (n = 107) | *P* Value |
| SHR, median (IQR) | .8 (.7-.9) | 1.0 (.9-1.1) | 1.4(1.3-1.6) | <.001 |
| Age, mean (SD), y | 63 (12) | 65 (12) | 66 (11) | .143 |
| Male, n (%) | 72 (67.3) | 64 (59.8) | 60 (56.1) | .231 |
| Hypertension, n (%) | 72 (67.3) | 61 (57.0) | 72 (67.3) | .195 |
| Diabetes mellitus, n (%) | 31 (29.0) | 26 (24.3) | 25 (23.4) | .602 |
| Atrial fibrillation, n (%) | 34 (31.8) | 46 (43.0) | 53 (49.5) | .029 |
| Coronary heart disease, n (%) | 19 (17.8) | 32 (29.9) | 35 (32.7) | .032 |
| History of smoking, n (%) | 39 (36.4) | 24 (22.4) | 35 (32.7) | .070 |
| *Baseline measurements* | | | | |
| Blood glucose, median (IQR) mmol/L | 5.6 (5.0-6.3) | 6.8 (6.4-7.8) | 9.1 (7.9-11.7) | <.001 |
| HbAlc, median (IQR) | 6.1 (5.7-6.8) | 5.8 (5.4-6.2) | 5.6 (5.4-6.4) | <.001 |
| NLR, no. (%) | | | | <.001 |
| ≤7.07 | 64 (64.6) | 47 (45.6) | 35 (33.7) | |
| >7.07 | 35 (35.4) | 56 (54.4) | 69 (66.3) | |
| NIHSS score, median (IQR) | 15 (12-19) | 16 (12-20) | 17 (13-21) | .063 |
| ASPECTS score, median (IQR) | 9 (8-10) | 9 (8-10) | 9 (7-10) | .045 |
| *Procedures process and outcome* | | | | |
| IVT, n (%) | 27 (25.2) | 38 (35.5) | 35 (32.7) | .244 |
| PTR, no. (%) | | | | .443 |
| ≤90min | 43 (40.6) | 35 (33.3) | 43 (40.2) | |
| >90min | 63 (59.4) | 71 (67) | 64 (59.8) | |
| mTICI 2b-3, n (%) | 90 (84.1) | 94 (87.9) | 88 (82.2) | .509 |
| SICH, n (%) | 8 (7.5) | 19 (17.8) | 21 (19.6) | .027 |
| Mortality, n (%) | 16 (15.0) | 17 (15.9) | 30 (28.0) | .027 |
| Complications pneumonia, n. (%) | 26 (24.3) | 27 (25.2) | 40 (37.4) | .063 |

Abbreviations: ASITN/SIR, American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; IQR, interquartile range; IVT, intravenous thrombolysis; mTICI, modified thrombolysis in cerebral infarction; NIHSS, National Institutes of Health Stroke Scale; NLR, Neutrophil lymphocyte ratio; PTR, puncture to recanalization time; SD, standard deviation; SHR, Stress hyperglycemia ratio; SICH, symptomatic intracranial hemorrhage.

**Table 2.** *Baseline characteristics of patients without background hyperglycemia according to the SHR tertiles groups*

| Baseline characteristics | Stress hyperglycemia ratio (SHR) | | | |
|---|---|---|---|---|
| | Q1 (n = 74) | Q2 (n = 87) | Q3 (n = 82) | *P* Value |
| SHR, median (IQR) | .8 (.7-.9) | 1.0 (.9-1.1) | 1.4 (1.3-1.6) | <.001 |
| Age, mean (SD), y | 63 (11) | 63 (13) | 66 (12) | .167 |
| Male, n (%) | 55 (74.3) | 49 (56.3) | 47 (57.3) | .035 |
| Hypertension, n (%) | 50 (67.6) | 46 (52.9) | 50 (61.0) | .162 |
| Atrial fibrillation, n (%) | 23 (31.1) | 40 (46.0) | 40 (48.8) | .058 |
| Coronary heart disease, n (%) | 9 (12.2) | 25 (28.7) | 24 (29.3) | .018 |
| *Baseline measurements* | | | | |
| Blood glucose, median (IQR) mmol/L | 5.2 (4.9-5.8) | 6.7 (6.1-7.2) | 8.5 (7.7-10.2) | <.001 |
| HbAlc, mean, (SD) | 5.8 (.3) | 5.7 (.4) | 5.5 (.5) | <.001 |
| NLR, no. (%) | | | | .005 |
| ≤7.07 | 41 (62.1) | 38 (45.2) | 28 (35.0) | |
| >7.07 | 25 (37.9) | 46 (54.8) | 52 (65.0) | |
| NIHSS score, mean, (SD) | 15 (6) | 16 (7) | 17 (6) | .093 |
| ASPECTS score, median (IQR) | 9 (8-10) | 9 (7-10) | 9 (7-10) | .015 |
| *Procedures process and outcome* | | | | |
| IVT, n (%) | 18 (24.3) | 32 (36.8) | 30 (36.6) | .168 |
| PTR, no. (%) | | | | .827 |
| ≤90 min | 28 (38.4) | 29 (33.7) | 30 (36.6) | |
| >90 min | 45 (61.6) | 57 (66.3) | 52 (63.4) | |
| mTICI 2b-3, n (%) | 65 (87.8) | 75 (86.2) | 70 (85.4) | .901 |
| SICH, n (%) | 3 (4.1) | 16 (18.4) | 15 (18.3) | .013 |
| Mortality, n (%) | 8 (10.8) | 15 (17.2) | 22 (26.8) | .034 |
| Complications pneumonia, n (%) | 13 (17.6) | 18 (20.7) | 28 (34.1) | .034 |

Abbreviations: ASITN/SIR, American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; IQR, interquartile range; IVT, intravenous thrombolysis; NIHSS, National Institutes of Health Stroke Scale; NLR, Neutrophil lymphocyte ratio; mTICI, modified thrombolysis in cerebral infarction; PTR, puncture to recanalization time; SD, standard deviation; SHR, Stress hyperglycemia ratio; SICH, symptomatic intracranial hemorrhage.

admission blood glucose level (median 5.60, 6.80, 9.12 mmol/L in the first, second, and third tertiles of SHR groups), and lower HbAlc (median 6.1%, 5.8%, and 5.6 % in the first, second, and third tertiles of SHR groups), have a higher neutrophil lymphocyte ratio. Patients in the higher tertiles have lower baseline ASPCTS score. In the total cohort there was a significant difference in incidence of sICH, 90 days mortality and stroke associated pneumonia among 3 groups (Q1 7.5%; Q2 17.8%; Q3 19.6%, $P = .027$) (Q1 15%; Q2 15.9%; Q3 28%, $P = .027$) (Q1 24.3%; Q2 25.2%; Q3 37.4%, $P = .063$).

Table 2 shows the mortality of patients without background hyperglycemia. A total of 243 patients included in this cohort. The incidence of 90 days mortality (Q1 10.8%; Q2 17.2%; Q3 26.8%, $P = .034$), sICH (Q1 4.1%; Q2 18.4%; Q3 18.3%, $P = .013$) is significantly higher in the higher tertiles group.

After adjusted for confounders, the risk of 90 days mortality in Q1 and Q3 groups was significantly higher than

**Table 3.** *Multivariate analyze of stress hyperglycemia ratio (SHR) on mortality risk*

| Mortality | Model 1 | | Model 2 | |
|---|---|---|---|---|
| | Adjusted OR (95% CI) | *P* | Adjusted OR (95% CI) | *P* |
| Q2 | Ref | | Ref | |
| Q1 | 3.80 (1.31-11.06) | .014 | 3.92 (1.34-11.50) | .013 |
| Q3 | 3.18 (1.25-8.12) | .016 | 2.81 (1.07-7.41) | .037 |
| *P** | | .025 | | .033 |

CI, confidence interval; OR, odd ratio; Ref, reference.

Model 1: adjusted for age (≥60), sex, coronary heart disease, neutrophil/lymphocyte ratio >7.07, National Institutes of Health Stroke Scale on admission, preoperative Albert Stroke Program Early CT score, puncture to end of revascularization (>90 min), symptomatic intracranial hemorrhage.

Model 2: adjusted for model 1+admission hyperglycemia (≥11.1 mmol/L).

**P* for trend.

**Table 4.** *Multivariate analyze of stress hyperglycemia ratio (SHR) on mortality risk of patients without background hyperglycemia*

| Mortality | Model 1 | | Model 2 | |
|---|---|---|---|---|
| | Adjusted OR (95% CI) | *P* | Adjusted OR (95% CI) | *P* |
| Q2 | Ref | | Ref | |
| Q1 | 3.36 (.91-12.39) | .069 | 3.37 (.91-12.47) | .069 |
| Q3 | 3.01 (1.06-8.53) | .038 | 2.63 (.88-7.87) | .083 |
| *P** | | .083 | | .124 |

CI, confidence interval; OR, odd ratio; Ref, reference.

Model 1: adjusted for age (≥60), sex, coronary heart disease, neutrophil/lymphocyte ratio >7.07, National Institutes of Health Stroke Scale on admission, preoperative Albert Stroke Program Early CT score, puncture to end of revascularization (> 90 min), symptomatic intracranial hemorrhage.

Model 2: adjusted for model 1+admission hyperglycemia (≥11.1 mmol/L).

**P* for trend.

Q2 group (OR, 3.80; 95% CI, 1.13-11.06) (OR, 3.18; 95% CI, 1.25-8.12), after further adjusted for admission hyperglycemia (≥11.1 mmol/L), the differences is still significant Q1 (OR, 3.92; 95% CI, 1.34-11.50) Q3 (OR, 2.81; 95% CI, 1.07-7.41) (Table 3). In patients without background hyperglycemia, the 90 days mortality is still significantly higher in Q3 groups (OR, 3.01; 95% CI, 1.06-8.53), after further adjusted for admission hyperglycemia (≥11.1 mmol/L), no significant difference was found between the 3 groups (Table 4).

## Discussion

The results of this study demonstrated that, the stress induce hyperglycemia expressed as SHR can be a useful predictor for in-hospital and 90 days mortality in acute ischemic stroke patients treated with MT. Consistent with previous study, the predictive value of SHR is equally applicable in patients without background hyperglycemia. Different from previous researches, this study further shows that relative hypoglycemia reflected by SHR can also independently predict high risk of 90 days mortality in acute ischemic stroke patients after treated with MT.

The mechanism of hyperglycemia effect on ischemic brain tissue has been widely recognized. It can cause intracellular acidosis, worsen mitochondrial function, and increase the generation of reactive oxygen species and the concentration of extracellular glutamate.[17-19] These factors can exaggerate neuronal damage, expand final infarct volume and enhance reperfusion injury, caused blood brain barrier disruption directly lead to poor functional outcomes.[20-22] Considering the different causes of hyperglycemia, several studies divided patients into stress hyperglycemia and chronic hyperglycemia based on blood glucose level and HbAlc, conclusions suggested that the adverse effects of hyperglycemia were more significant in nondiabetic and diabetic patients with good previous blood glucose control.[5,6] Those patients have a lower or better controlled background blood glucose suggested that hyperglycemia is result from stress response. However, the methodological difficulties limit practical application of stress hyperglycemia.

This study used SHR to evaluate relative hyperglycemia, which has been suggested can more accurately quantify stress-induced hyperglycemia.[10,11] Stress hyperglycemia is mediated by activating hypotha-lamic-pituituary-adrenal axis and sympatho-adrenal system, increase the production of epinephrine, norepinephrine and proinflammatory cytokines result in excessive glucose production.[23] Several clinical evidence indicated that stress hyperglycemia is more than epiphenomenon of disease severity, it is also an important prognostic marker. Compared with chronic hyperglycemia, patients with stress hyperglycemia have more sever neuroendocrine derangements and inflammation, the greater oxidative stress and endothelia dysfunction may directly lead to poor prognosis. The increased level of stress hormones and cytokines may result in acute fluctuation of blood glucose, which has been reported to be an independent predictor of high mortality during acute illness.[24] Several cytokines involved in critical illness may contribute to up regulate expression and member localization of glucose transporters GLUT-1 and GLUT-3, facilitate glucose uptake and utilized by insulin independent tissue including peripheral and central nervous system, result in cellular glucose overload and toxicity,[9] whether this pathway mediate the detrimental effect of stress hyperglycemia is unknown.

In this study we further found relative hypoglycemia also predict higher 90 days mortality. The etiology of hypoglycemia is medical-induced and spontaneous, the former is common in diabetic patients received intensive blood glucose control. Previous studies used absolute glycemic threshold to defined hypoglycemia which plasma concentration low enough to cause symptom and with neurological deficits,[25] demonstrated that even mild hypoglycemia can predict high mortality in critical illness, especially in poor controlled diabetes.[1,3] Whether the background blood glucose can affect the role of hypoglycemia is unclear. Different from previous researches, we assessed hypoglycemia as a relative decline in plasma

concentration compared to background blood glucose, indicated that not necessarily to achieve diagnostic criteria of hypoglycemia, a certain degree of decline in plasma concentration will adversely affected prognosis. Several mechanisms may mediate the detrimental effects of hypoglycemia on ischemic brain tissue. First, acute hypoglycemia has been reported to increase clotting factors concentration, promote the aggregation of platelets, these functions are more pronounced in diabetic patients.[26,27] Second, acute hypoglycemia may influence endothelial dysfunction by increasing endothelin-1, high sensitivity C reactive protein, interleukins, cytokines, and marker of endothelial dysfunction.[28,29] Third, glucose reperfusion after hypoglycemia can activate NADPH oxidase increase the formation of superoxide lead to neural death and oxidative stress.[30] In this study, the relative hypoglycemia was not associated with high mortality in patients without baseline hyperglycemia, this is consistent with some previous study,[31] the pathophysiology process may related to micro or macrovascular complications in diabetic patients.

This study has several limitations which should be addressed when interpreting the result. First, the study data came from a register study, all the data were retrospective and approximately half of patients were excluded because lacked HbAlc value. It will inevitably produce a system biases. Second, compared with previous studies, we have a relatively small number of patients, in this study cohort most patients have no background hyperglycemia, and we did not analyze the relationship between relative glucose changes and clinical outcomes in background hyperglycemia patients. Finally, this study used admission hyperglycemia to calculate SHR, the post admission blood glucose changes after that and control status was not considered.

In conclusion, relative hyperglycemia expressed by SHR can be a useful predict marker of high in-hospital and 90 days mortality in acute ischemic stroke patients treated with MT. In addition to relative hyperglycemia, the relative hypoglycemia also related to high mortality. This conclusion illustrated the importance of intervention and monitoring of blood glucose. It may provide a reference for identifying patients who at high risk of mortality after receiving MT, indicated that better combine patient's baseline glycemic to analyze the cause of hyperglycemia when doing glycemic intervention, the therapeutic utility of SHR has not been confirmed. Critical ill patients who without background hyperglycemia, tight glucose control have been reported to improve clinical outcomes, however in preexisting diabetic patients tight blood glucose control may lead to rapid changes of glucose concentration, and the glycemic variability has been reported to be an independent predict of poor outcomes of critical ill patients.[32] SHR can be a simple index reflect stress-induced blood glucose changes, indicated that maintaining stable glucose level at the state of stress is critical to prognosis of acute ischemic stroke patients. Whether the regulation of patient's blood glucose according to SHR can improve the clinical prognosis still need large randomized clinical trial to confirm.

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