Impact of Stress Hyperglycemia Ratio on Recurrence in Elderly Patients with Mild Acute Ischemic Stroke: A Nested Case-Control Study Postprint

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Abstract

Background Against the backdrop of population aging in China, the incidence and recurrence rates of acute ischemic stroke (AIS) are increasing year by year, with high associated mortality and disability rates. In recent years, the stress hyperglycemia ratio (SHR) has been increasingly applied in cardiovascular and cerebrovascular diseases; however, research on its role in mild AIS recurrence remains scarce.

Objective To investigate the association between SHR and 1-year recurrence in elderly patients with mild AIS, thereby providing additional theoretical basis for the prevention of AIS recurrence.

Methods Patients initially diagnosed with mild AIS at Shijiazhuang Fifth Hospital from May 2018 to January 2022 were selected as study subjects. Using mild AIS diagnosis as the starting point and 1 year post-diagnosis as the endpoint, a nested case-control study design was employed. Patients who experienced recurrence within 1 year of diagnosis were included in the recurrence group and matched with a non-recurrence group at a 1:3 ratio based on "time of diagnosis, age, sex, infarct location, and diabetes status." A total of 70 patients were included in the recurrence group, and 210 matched patients were included in the non-recurrence group. Through the Hospital Information System (HIS), data on patient sex, age, history of hypertension, history of atrial fibrillation, BMI, baseline National Institutes of Health Stroke Scale (NIHSS) score, low-density lipoprotein cholesterol (LDL-C), glycated hemoglobin (HbA1c), admission random blood glucose, etc., were collected, and SHR was calculated. Multivariate conditional logistic regression analysis was used to investigate the association between SHR and 1-year recurrence in elderly patients with mild AIS.

Results The 280 patients had a mean age of (71.9$±$6.4) years; 176 were male (62.9%) and 104 were female (37.1%). Eighty-eight patients (31.4%) had a history of diabetes. Based on the median values, stress blood glucose $ $10 mmol/L was defined as high and <10 mmol/L as low; SHR >1.04 was defined as high and $ $1.04 as low. Multivariate conditional logistic regression analysis showed that stress blood glucose (OR=2.98, 95%CI=1.49~5.98) and SHR (OR=3.06, 95%CI=1.58~5.91) were influencing factors for 1-year recurrence in elderly patients with mild AIS (P<0.05). Among the 88 mild AIS patients with a history of diabetes, 22 experienced recurrence within 1 year and 66 did not; among the 192 mild AIS patients without a history of diabetes, 48 experienced recurrence within 1 year and 144 did not. Stratified multivariate conditional logistic regression analysis showed that SHR remained an influencing factor for 1-year recurrence in elderly mild AIS patients both with (OR=3.76, 95%CI=1.02~13.85) and without (OR=3.13, 95%CI=1.16~8.43) a history of diabetes (P<0.05). To further explore the relationship between SHR and mild AIS recurrence in the overall elderly mild AIS population, patients were divided into 4 subgroups based on SHR intervals of 1.00, 1.40, and 1.80. The results showed that SHR of 1.41~1.80 and >1.80 both significantly affected 1-year recurrence in elderly mild AIS patients compared with SHR $ $1.0 (P<0.05), and there was no interaction between SHR and diabetes status (P-interaction>0.05, P-trend<0.05, OR=1.627).

Conclusion Regardless of diabetes status, SHR has a consistent effect on 1-year recurrence in elderly patients with mild AIS and serves as an independent influencing factor. Compared with stress blood glucose, SHR has broader applicability. Higher SHR (per 0.4 increase) is associated with greater 1-year recurrence risk in elderly mild AIS patients (increased by 0.627-fold).

Full Text

Preamble

Nested Case-Control Study on the Impact of Stress Hyperglycemia Ratio on Recurrence of Mild Acute Ischemic Stroke in the Elderly

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Abstract

Background: Against the backdrop of population aging in China, the incidence and recurrence rates of acute ischemic stroke (AIS) are rising annually,

accompanied by high mortality and disability rates. In recent years, the stress hyperglycemia ratio (SHR) has been increasingly applied in cardiovascular and cerebrovascular diseases, though research on its role in mild AIS recurrence remains limited.

Objective: To investigate the association between SHR and 1-year recurrence in elderly patients with mild AIS, providing additional theoretical evidence for preventing AIS recurrence.

Methods: Patients newly diagnosed with mild AIS at Shijiazhuang Fifth Hospital between May 2018 and January 2022 were selected as study subjects. Using a nested case-control design with diagnosis as the starting point and 1-year follow-up as the endpoint, patients experiencing recurrence within one year were assigned to the recurrence group. A non-recurrence group was matched at a 1:3 ratio based on diagnosis timing, age, sex, infarct location, and diabetes status. Seventy patients were included in the recurrence group, with 210 matched patients in the non-recurrence group. Through the Hospital Information System (HIS), we collected data on sex, age, hypertension history, atrial fibrillation history, BMI, baseline NIHSS score, LDL-C, HbA1c, admission random blood glucose, and calculated SHR. Multivariate conditional logistic regression was used to explore the association between SHR and 1-year recurrence in elderly mild AIS patients.

Results: The 280 patients had a mean age of (71.9$±$6.4) years; 176 were male (62.9%) and 104 were female (37.1%); 88 patients (31.4%) had diabetes history. Based on median values, stress hyperglycemia $ $10 mmol/L was classified as high and <10 mmol/L as low; SHR >1.04 was classified as high and $ $1.04 as low. Multivariate conditional logistic regression showed that both stress hyperglycemia (OR=2.98, 95%CI=1.49-5.98) and SHR (OR=3.06, 95%CI=1.58-5.91) were influencing factors for 1-year recurrence in elderly mild AIS patients (P<0.05). Among 88 mild AIS patients with diabetes history, 22 experienced recurrence within one year and 66 did not; among 192 without diabetes history, 48 recurred and 144 did not. Stratified analysis revealed SHR remained a significant factor for recurrence in both diabetic (OR=3.76, 95%CI=1.02-13.85) and non-diabetic (OR=3.13, 95%CI=1.16-8.43) elderly mild AIS patients (P<0.05). When dividing the total elderly mild AIS population into 4 subgroups using SHR cutoffs of 1.00, 1.40, and 1.80, SHR levels of 1.41-1.80 and >1.80 were both associated with higher recurrence risk compared to SHR $ $1.0 (P<0.05), with no interaction between SHR and diabetes history (P-interaction>0.05, P-trend<0.05, OR=1.627).

Conclusion: Regardless of diabetes status, SHR is an independent influencing factor for 1-year recurrence in elderly mild AIS patients, with consistent effects across diabetic and non-diabetic populations. Compared with stress hyperglycemia alone, SHR has broader applicability. Higher SHR values are associated with greater recurrence risk, with each 0.4 increase in SHR corresponding to a 0.627-fold increase in recurrence risk.

Keywords: Stroke; Recurrence; Stress hyperglycemia ratio; Aged; Prognosis; Conditional logistic regression analysis

Introduction

In the context of China' s aging population, acute ischemic stroke (AIS) represents one of the most significant causes of disability. While stroke mortality has declined in recent years, both incidence and recurrence rates continue to rise, with a 1-year recurrence rate of 5.59% for cerebral infarction. Recurrent strokes account for 23–33% of all stroke cases, underscoring the critical importance of secondary prevention. Clinically, patients with mild AIS often achieve favorable outcomes after initial diagnosis, yet prognosis deteriorates substantially following recurrence, with dramatically increased disability risk. Consequently, mild AIS patients constitute a high-risk population for poor early neurological outcomes and disability. Identifying specific recurrence markers in this population is therefore essential for improving prognosis.

Previous studies have identified stress hyperglycemia as a factor influencing stroke recurrence, though findings remain inconsistent. The stress hyperglycemia ratio (SHR) adjusts for baseline glucose levels, addressing limitations in using stress hyperglycemia alone to evaluate AIS prognosis across different baseline glycemic states. Given these considerations, this nested case-control study aimed to investigate the association between SHR and stress hyperglycemia with recurrence in mild AIS patients.

Methods

Study Participants

Patients newly diagnosed with mild AIS at Shijiazhuang Fifth Hospital between May 2018 and January 2022 were selected as study subjects. Using a nested case-control design with diagnosis as the starting point and 1-year follow-up as the endpoint, patients experiencing recurrence within one year were assigned to the recurrence group. The non-recurrence group was matched at a 1:3 ratio based on diagnosis timing, age ($±$5 years), sex, infarct location, and diabetes status. Seventy patients were included in the recurrence group, with 210 matched patients in the non-recurrence group. The study was approved by the Medical Ethics Committee of Shijiazhuang Fifth Hospital (2022-022-1).

Inclusion Criteria

1. First-time AIS diagnosis meeting the 2018 Chinese Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke: (a) acute onset; (b) focal neurological deficits; (c) responsible lesions identified on CT or MRI with intracerebral hemorrhage excluded; (d) non-vascular causes excluded.
2. Age $ $60 years.
3. Baseline NIHSS score $ $3.

4. Treatment regimen essentially consistent with standard protocols.
5. Good patient compliance.
6. Signed informed consent.

Exclusion Criteria

1. Missing critical medical records that could not be obtained.
2. Severe hematologic, cardiovascular, respiratory, or immune system disease; hepatic or renal dysfunction; or life expectancy <1 year.
3. Severe limb deficits or mobility impairment.
4. Severe malnutrition.
5. Loss to follow-up.

Non-Recurrence Group Matching Through the HIS system, when each eligible recurrence case was identified, potential control patients from the same cohort who had not experienced recurrence and met inclusion criteria were selected. Matching criteria included admission interval <4 weeks, similar age ($±$5 years), same sex, same infarct location/territory, and identical diabetes status. Cases not meeting these criteria were excluded, and the next eligible case was selected. This process continued until a 1:3 matching ratio was achieved. Two matching attempts failed, resulting in a final sample of 280 patients.

Data Collection

Using a retrospective nested case-control design, general patient information was collected through the HIS system. Data included sex, age, hypertension history, atrial fibrillation history, BMI, baseline NIHSS score, diabetes history, exercise status, income, and education level. Laboratory results extracted from HIS included complete blood count, blood biochemistry, LDL-C, HbA1c, and admission random blood glucose (defined as stress glucose). Exercise status was defined as active exercise >3 times weekly for >30 minutes each session. Obesity was defined as BMI $ 28.0kg/m^{2}$ according to the 2021 Chinese Guidelines for Prevention and Control of Overweight and Obesity in Adults.

Follow-up data on recurrence, medical visits, and medication use at 1 year post-onset were obtained through telephone and WeChat surveys.

Quality Control

All investigators received standardized training to ensure consistency. A team of two senior physicians and two nurses conducted the study. Diagnosis of mild AIS, inclusion/exclusion determination, and non-recurrence group selection were performed by two senior physicians, with disagreements resolved by a third physician.

SHR Definition

SHR was calculated as admission random glucose divided by HbA1c-estimated average glucose:
SHR = Random Glucose / [(1.59 × HbA1c) - 2.59]
where (1.59 × HbA1c) - 2.59 represents the estimated average glucose over the previous 3 months.

Statistical Analysis

Data were analyzed using Stata 16.0 and GraphPad Prism 8.0. Categorical variables were expressed as frequencies, and normally distributed continuous variables as ($\bar{x}\pm s$). Univariate analysis was performed using conditional logistic regression. Variables with P$ $0.2 in univariate analysis, clinically significant variables, and basic factors (sex) were included in multivariate analysis. Multivariate conditional logistic regression was used to investigate the association between SHR and mild AIS recurrence. Stratified analysis was conducted based on diabetes history. Statistical significance was defined as $P<0.05$.

Results

Patient Baseline Characteristics

All 280 patients completed assessments. Age ranged 60–85 years, with mean age (71.9$±$6.4) years; 176 were male (62.9%) and 104 female (37.1%); 88 patients (31.4%) had diabetes history; 142 (50.7%) were from low-income families; 85 (30.4%) had hypertension history; 139 (49.6%) exercised regularly; 122 (43.6%) were obese; 29 (10.4%) had atrial fibrillation history. Based on median values, stress hyperglycemia $ $10 mmol/L was classified as high and <10 mmol/L as low; SHR >1.04 was classified as high and $ $1.04 as low .

Univariate Analysis

Using different baseline characteristics as independent variables and 1-year recurrence as the dependent variable (coding shown in), univariate conditional logistic regression revealed that age, hypertension history, stress hyperglycemia, and SHR were influencing factors for 1-year recurrence in elderly mild AIS patients ($P<0.05$) .

Multivariate Analysis

Total Mild AIS Population Analysis Considering the strong association between stress glucose and SHR, variables with P$ $0.2 in univariate analysis, clinically meaningful variables (including NIHSS score and exercise status), and basic factors (sex) were included as independent variables in multivariate logistic regression analysis (coding shown in). In Model 5, after adjusting for age, sex, NIHSS score, exercise status, education level, hypertension history, obesity,

and LDL-C, both stress hyperglycemia and SHR remained significant factors affecting 1-year recurrence in elderly mild AIS patients (P<0.05) .

Stratified Analysis by Diabetes History Since SHR differs from stress glucose by adjusting for baseline glucose, stratified analysis was performed based on diabetes history. Among 88 mild AIS patients with diabetes history, 22 experienced recurrence within 1 year and 66 did not; 54 had stress glucose $ $10 mmol/L and 34 had <10 mmol/L; 41 had SHR >1.04 and 47 had $ $1.04. Among 192 patients without diabetes history, 48 recurred and 144 did not; 52 had stress glucose $ $10 mmol/L and 140 had <10 mmol/L; 54 had SHR >1.04 and 138 had $ $1.04.

Using the same independent variables as in the total population analysis, stratified multivariate logistic regression showed SHR remained a significant factor for 1-year recurrence in both diabetic (OR=3.76, 95%CI=1.02-13.85) and non-diabetic (OR=3.13, 95%CI=1.16-8.43) elderly mild AIS patients (P<0.05) .

SHR Subgroup Analysis in Mild AIS Population To further explore the relationship between SHR and mild AIS recurrence, the total elderly mild AIS population was divided into 4 subgroups using SHR cutoffs of 1.00, 1.40, and 1.80. Results showed that SHR levels of 1.41-1.80 and >1.80 were both associated with higher recurrence risk compared to SHR $ $1.0 (P<0.05), with no interaction between SHR and diabetes history (P-interaction>0.05, P-trend<0.05) .

Discussion

AIS predominantly affects elderly individuals and is characterized by high recurrence rates, with recurrent patients experiencing higher mortality and disability than those with first-ever strokes, creating substantial burdens for families and society. Stress hyperglycemia refers to the phenomenon where blood glucose increases above baseline levels during acute illness such as stroke or injury, occurring in approximately half of AIS patients. However, current definitions of stress hyperglycemia remain inconsistent, with most studies using admission random glucose or fasting glucose.

Multiple studies have confirmed that stress hyperglycemia, compared to simple hyperglycemia, reflects AIS prognosis and predicts poor outcomes. Potential mechanisms include increased secretion of cortisol, inflammatory factors, and catecholamines during stress responses, leading to insulin resistance and enhanced gluconeogenesis. These substances also increase platelet aggregation, impair mitochondrial function, and cause vascular endothelial dysfunction. Additionally, both hyperglycemia and glucose fluctuations can exacerbate oxidative stress and inflammatory responses, worsening ischemia-reperfusion injury and affecting AIS prognosis. Hyperglycemia can also exert direct toxic effects on cells.

Our findings indicate that SHR, hypertension, and advanced age are not only risk factors for AIS but also associated with recurrence in elderly mild AIS patients. Elderly AIS patients often have vascular calcification, stenosis, and compromised immunity, with higher likelihood of multiple comorbidities—all established stroke risk factors. Age is a particularly important factor for AIS recurrence. Chronic hypertension and blood pressure instability damage vascular endothelium and elasticity, leading to poor vascular quality that affects stroke recurrence and requires active prevention.

Post-stroke stress hyperglycemia and glucose fluctuations can increase cerebral oxidative stress, vascular endothelial dysfunction, and impaired fibrinolysis, thereby increasing ischemic injury and recurrence risk. However, some studies have found no direct relationship between stress hyperglycemia and AIS prognosis, leading to the development of SHR by Roberts et al. Our results also demonstrate an association between SHR and 1-year recurrence in mild AIS. SHR is a robust indicator of stress hyperglycemia intensity, and the two show strong correlation.

After stratifying by diabetes history, stress hyperglycemia was only associated with recurrence in the non-diabetic population, suggesting SHR' s prognostic impact differs between diabetic and non-diabetic mild AIS patients. This phenomenon has been observed in other AIS studies, likely because baseline glucose acts as a confounding factor that stress glucose cannot distinguish, leading to unstable model results.

Compared to stress hyperglycemia alone, SHR has broader applicability, evaluating both diabetic and non-diabetic populations. Studies show SHR is superior for assessing stroke prognosis because HbA1c adjustment eliminates baseline glucose interference, making SHR, strictly speaking, the true measure of stress hyperglycemia. This adjustment enables better disease outcome prediction. Similar patterns exist in other vascular diseases: SHR predicts in-hospital major cardiovascular and cerebrovascular events in acute myocardial infarction patients better than stress glucose. Research has also identified high SHR as an independent risk factor for myocardial infarction prognosis, with greater predictive value than stress glucose.

Consistent with Roberts et al., our collected SHR values showed a linear distribution. Studies demonstrate SHR is associated with recurrence risk in mild AIS and transient ischemic attack (TIA), with higher SHR reflecting greater recurrence rates. Zhu et al. found that AIS recurrence risk increases with SHR elevation. Our SHR values ranged from 0.60 to 2.26. Using an interval of 0.4 from the minimum to standard value, we divided SHR into subgroups to further explore its linear relationship with mild AIS prognosis. Results showed high SHR was associated with recurrence, without interaction with diabetes status, indicating that unlike stress glucose, SHR' s impact on mild AIS recurrence is consistent regardless of diabetes status. This finding corroborates SHR' s linear characteristics.

Given these results, we further examined the trend relationship between SHR and mild AIS recurrence for better clinical interpretation and application. The trend was significant (P-trend<0.05, OR=1.627), indicating that each 0.4 increase in SHR corresponds to a 0.627-fold increase in recurrence risk. Research has also shown SHR is independently associated with critical illness, with each 0.1 increase associated with 20% higher critical illness risk. These results support SHR' s value for early screening in mild AIS patients to reduce recurrence risk.

Limitations

This study has several limitations. First, the sample size was limited, and as a retrospective study including only elderly patients, these factors restrict generalizability and require confirmation through multicenter, large-sample prospective trials. Second, this study does not provide specific guidance on whether SHR requires dynamic monitoring.

Conclusion

SHR, as a baseline glucose-adjusted measure of stress hyperglycemia, can predict recurrence risk in mild AIS patients regardless of diabetes status. SHR is associated with 1-year recurrence in elderly mild AIS patients, with each 0.4 increase in SHR corresponding to a 0.627-fold increase in recurrence risk. As an objective, economical, and readily available indicator, SHR may serve as a new tool for monitoring recurrence in elderly mild AIS patients and warrants further investigation.

Author Contributions

Kaiqian Gao proposed the main research objectives, designed the study, implemented the research, and wrote the manuscript. Kaiqian Gao and Yu Yang collected and organized data, performed statistical analysis, and created figures and tables. Fafa Dong revised the manuscript. Yanfang Hu was responsible for quality control and review, providing overall supervision.

This article has no conflicts of interest.

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Note: Figure translations are in progress. See original paper for figures.