Diabetology & Metabolic Syndrome

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Stress hyperglycemia is associated with early neurologic deterioration in patients with acute ischemic stroke after intravenous thrombolysis without hemorrhagic transformation

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Abstract

Background This aimed to elucidate the impact of stress hyperglycemia on early neurological deterioration (END) in patients with acute non-cardiogenic cerebral infarction who did not experience hemorrhagic transformation following intravenous thrombolysis to identify risk factors associated with END.

Methods This retrospective case-control study analyzed data from consecutive patients who received intravenous thrombolysis for acute ischemic stroke (AIS) without hemorrhagic transformation at the Stroke Center of The Fifth Affiliated Hospital of Sun Yat-sen University from January 2018 to February 2023. END was defined as an increase of more than 2 points on the National Institutes of Health Stroke Scale (NIHSS) within 7 days of admission.

Results A total of 250 patients (56 males, 22.4%) were included, with a mean age of 63.34 ± 12.90 years. Of them, 41 were classified into the END group and 209 into the non-END group. Stress hyperglycemia ratio (SHR) demonstrated a significant correlation with END (r=-0.003, P = 0.003). HbA1c (OR = 0.68, 95% CI: 0.481–0.921) and SHR (OR = 0.00, 95% CI: 0.0-0.051) were independently associated with END. Receiver-operating characteristic (ROC) curve analysis indicated that SHR had a sensitivity of 79.9%, specificity of 88.8%, and an area under the curve (AUC) of 0.857 for predicting END.

Conclusions SHR was significantly associated with END in patients with acute non-cardioembolic cerebral infarction who did not undergo hemorrhagic transformation after intravenous thrombolysis.

Keywords SHR, Acute ischemic stroke, Hemorrhagic transformation, Early neurologic deterioration

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Introduction

Acute ischemic stroke (AIS) is a leading cause of death and long-term disability worldwide [1], and its current primary treatments are intravenous thrombolysis and endovascular procedures, which are typically administered during the early phases of stroke management [2]. However, the effectiveness of these reperfusion therapies is limited by a strict time window, resulting in fewer than 10% of patients receiving these interventions [3]. A significant complication of stroke is early neurological deterioration (END), which is characterized by an increase of more than 2 points on the National Institutes of Health Stroke Scale (NIHSS) within 72 h of the initial assessment. Although the definitions of END can vary, its occurrence notably increases the risk of both morbidity and mortality [4, 5]. While extensive research has focused on END following hemorrhagic transformations after thrombolysis, there is limited investigation into END in patients with non-cardiogenic cerebral infarction who do not experience hemorrhagic transformation [6]. Herein, we designed this study to address this gap by examining the impact of stress hyperglycemia on END in patients with acute non-cardiogenic cerebral infarction, excluding those with hemorrhagic transformation following intravenous thrombolysis and to identify risk factors associated with END in this specific patient population.

Materials and methods

Study participants

Patients and the general public were not involved in the design or execution of this study.

Study design and criteria

This retrospective case-control study involved the retrieval and assessment of data from consecutive patients who underwent intravenous thrombolysis for AIS without hemorrhagic transformation at the Stroke Center of The Fifth Affiliated Hospital of Sun Yat-sen University between January 2018 and February 2023. All cases were diagnosed and managed according to a standardized protocol and care pathway, in adherence to established guidelines [7].

Inclusion criteria: Adults aged 18 years and older who presented with symptoms of AIS within 72 h of admission were included. AIS was confirmed by computed tomography (CT) scan or magnetic resonance imaging (MRI). Patients received intravenous thrombolytic therapy and did not experience hemorrhagic transformation during hospitalization.

Exclusion criteria: Patients were excluded if they had a history of psychiatric disorders, conditions that impeded NIHSS assessment, traumatic brain injury, or if they died before assessment.

Patients who experienced END during hospitalization were classified into the END group, while those who did not experience END were placed in the non-END group. END was defined as an increase in NIHSS score of more than 2 points within 7 days after admission [5].

Data collection and definitions

Demographic, clinical and laboratory data were extracted from patient records. The information collected included age, sex, smoking status, alcohol use, and medical history (including hypertension, diabetes, hyperlipidemia, previous transient ischemic attack, ischemic stroke, ischemic heart disease, atrial fibrillation, and heart failure). Laboratory measures included blood glucose, glycated hemoglobin (HbA1c), lipids, and homocysteine levels. Stroke classification was based on the Trial of Org 10,172 in Acute Stroke Treatment (TOAST) criteria [8]. Additional data included the affected cerebral areas and the NIHSS score upon admission. The impact of stroke on cerebral circulation was categorized as anterior, posterior, or both. Stroke types were grouped into large-artery atherosclerosis, cardioembolism, small-artery occlusion, stroke of another determined etiology, or stroke of undetermined etiology. Dyslipidemia was identified either through lipid profile measurements (cholesterol or triglyceride levels) or the use of medications such as statins. Smoking was defined as consistent smoking for more than six months [9].

Neuroimaging analysis

Neuroimaging data were comprehensively evaluated by both a radiologist and a neurologist, with the results being validated through mutual consensus. The neuroimaging assessment included detailed information on the affected cerebral circulation, the location of the infarction, and the subtype of the stroke. The impact of the stroke on cerebral circulation was categorized into three groups: anterior, posterior, or both. Stroke types were classified according to the Trial of Org 10,172 in Acute Stroke Treatment (TOAST) criteria, which include large-artery atherosclerosis, cardioembolism, small-artery occlusion, stroke of determined etiology, or stroke of undetermined etiology [8]. Carotid unstable plaques were evaluated using ultrasound based on the following criteria: a plaque is defined as a focal structure protruding into the arterial lumen by at least 0.5 mm or 50% of the surrounding intima-media thickness (IMT) or as having a thickness of 1.5 mm when measured from the media-adventitia interface to the intima-lumen interface [10].

Statistical analysis

Statistical analyses were conducted using SPSS (IBM Corp, Armonk, NY, USA) and the R programming language (version 4.0.2; R Foundation for Statistical

Computing, Vienna, Austria). Continuous data were presented as mean ± SD or median (interquartile range), while categorical data were expressed as frequencies (%), depending on their distribution. Group comparisons were performed using t-tests, Mann-Whitney U-tests, chi-square tests, or Fisher's exact tests, as appropriate. Factors associated with END were identified through Spearman correlation analysis and multivariable logistic regression, including variables that were significant in univariate analysis. The logistic regression model provided adjusted odds ratios (OR) with 95% confidence intervals. The area under the curve (AUC) was calculated to assess the accuracy of the test. A p-value of <0.05 was considered statistically significant.

Results

Patients' characteristics

This study included 250 patients, of whom 56 were male (22.4%), and the mean age was 63.34 ± 12.90 years. Among these, 41 were classified into the END group, while 209 were in the non-END group. The mean age for the END group was 63.54 ± 12.53 years, compared to 63.31 ± 12.97 years for the non-END group (Table 1). Smoking was more prevalent in the END group (58.54%) compared to the non-END group (44.02%), though this difference was not statistically significant ($P=0.088$). Similarly, alcohol use was higher in the END group (29.27%) compared to the non-END group (18.66%), but this difference was also not statistically significant ($P=0.123$). Hypertension was common in both groups (67.94% in the non-END group vs. 65.85% in the END group, $P=0.794$). Diabetes mellitus was present in 27.27% of the non-END group and 41.46% of the END group, approaching statistical significance ($P=0.069$). Hyperlipidemia and a history of stroke or transient ischemic attack (TIA) were similar between the groups. Admission systolic blood pressure (SBP) was 159.00 mmHg in the non-END group and 167.00 mmHg in the END group ($P=0.238$). Diastolic blood pressure (DBP) was 89.00 mmHg in the non-END group and 84.00 mmHg in the END group ($P=0.136$). NIHSS scores at admission were comparable between the groups, with a median score of 3.00 in both groups ($P=0.601$). Notably, homocysteine levels were significantly higher in the END group (15.45 μmol/L) compared to the non-END group (12.98 μmol/L, $P=0.005$). The stress hyperglycemia ratio (SHR) was lower in the END group (0.87) compared to

Table 1 Comparison of baseline clinical characteristics between the END and Non-END groups

Clinical characteristics	No. of cases ($n=250$)	Non-END ($n=209$)	END ($n=41$)	*P* value
Age, mean(± SD)	63.34 ± 12.90	63.31 ± 12.97	63.54 ± 12.53	0.917
Male, n (%)	56(22.40)	48(22.98)	8(19.51)	0.628
Alcohol use, n(%)	51(20.40)	39(18.66)	12(29.27)	0.123
Smoker, n(%)	116(46.40)	92(44.02)	24(58.54)	0.088
Alcohol use, n(%)	51(20.40)	39(18.66)	12(29.27)	0.123
Diabetes mellitus, n (%)	74(29.60)	57(27.27)	17(41.46)	0.069
Hypertension, n(%)	169(67.60)	142(67.94)	27(65.85)	0.794
Hyperlipidemia, n (%)	89(35.60)	73(34.93)	16(39.02)	0.616
History of stroke or TIA, n(%)	81(32.40)	68(32.54)	13(31.71)	0.917
SBP at admission (mmHg), median[IQR]	162.00[145.00,176.00]	159.00[145.00,175.00]	167.00[142.00,179.00]	0.238
DBP at admission (mmHg), median[IQR]	88.00[80.00,98.00]	89.00[80.00,98.00]	84.00[78.00,98.00]	0.136
NIHSS at admission, median[IQR]	3.00[1.00,7.00]	3.00[1.00,6.00]	3.00[1.00,7.00]	0.601
DNT(min), median[IQR]	38.00[29.00,52.00]	37.00[29.00,52.00]	39.00[26.00,53.00]	0.893
T-CH (mmol/L), median[IQR]	4.40[3.56,5.23]	4.39[3.64,5.25]	4.51[2.64,5.06]	0.205
TG (mmol/L), median[IQR]	1.37[0.98,1.97]	1.30[0.98,1.92]	1.67[1.18,2.09]	0.137
LDL-C (mmol/L), median[IQR]	2.76[2.07,3.40]	2.76[2.06,3.38]	2.93[2.10,3.41]	0.984
Homocysteine (μmol/L), median[IQR]	13.38[10.90,16.82]	12.98[10.82,16.56]	15.45[13.64,18.73]	0.005*
HbA1c(%), median[IQR]	5.90[5.50,6.60]	5.90[5.50,6.50]	6.00[5.40,7.20]	0.974
SHR, median[IQR]	0.91[0.86,0.97]	0.92[0.88,0.98]	0.87[0.82,0.95]	0.003*
TOAST subtype, n(%)				0.279
LAA	108(43.200)	85(40.670)	23(56.098)	
SOE	32(12.800)	27(12.919)	5(12.195)	
SAA	105(42.00)	93(44.500)	12(29.268)	
SUE	5(2.00)	4(1.91)	1(2.44)	
Carotid unstable plaque, n(%)	162(64.80)	136(65.07)	26(63.42)	0.839
Cerebral circulation affected by stroke, n(%)				0.693
Anterior circulation	162(64.80)	135(64.59)	27(65.85)	
Posterior circulation	53(21.20)	46(22.01)	7(17.07)	
Both	35(14.00)	28(13.40)	7(17.07)	

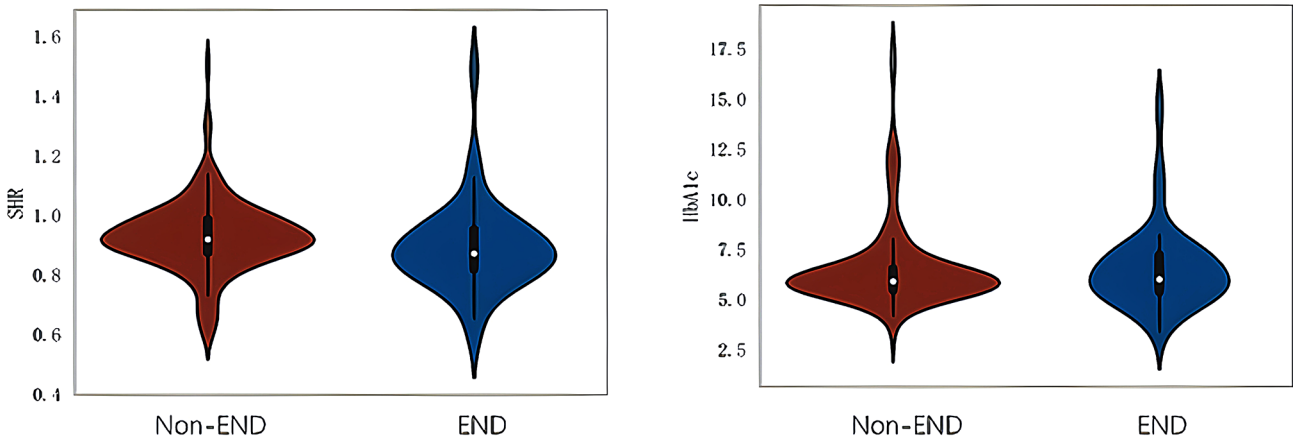

Fig. 1 Comparison of SHR, HbA1c between the END group and the non-END group

Table 2 Spearman correlation analysis for END

Variables	END	Age	Male	NIHSS at admission	DNT (min)	LDL-C (mmol/L)	HbA1c	SHR
END	0.000*	0.815	0.629	0.601	0.892	0.983	0.977	0.003*
Age	0.815	0.000*	0.663	0.000	0.851	0.000*	0.027*	0.096
Male	0.629	0.663	0.000*	0.392	0.822	0.338	0.839	0.656
NIHSS at admission	0.601	0.000*	0.392	0.000*	0.305	0.719	0.255	0.162
DNT (min)	0.892	0.851	0.822	0.305	0.000*	0.430	0.409	0.493
LDL-C (mmol/L)	0.983	0.000*	0.338	0.719	0.430	0.000*	0.737	0.475
HbA1c	0.977	0.027	0.839	0.255	0.409	0.737	0.000*	0.000*
SHR	0.003*	0.096	0.656	0.162	0.493	0.475	0.000*	0.000*

*$P<0.05$. END: early neurological deterioration; NIHSS: National Institutes of Health Stroke Scale; HbA1c: glycated hemoglobin; LDL-C: low-density lipoprotein cholesterol; SHR: stress hyperglycemia ratio; IQR: interquartile range; SD: standard deviation;

the non-END group (0.92, $P=0.003$) (Fig. 1). Other laboratory parameters, including triglycerides, total cholesterol, LDL-C, and HbA1c, showed no significant differences between the groups. The TOAST classification revealed a higher prevalence of large artery atherosclerosis in the END group (56.10%) compared to the non-END group (40.67%), although this difference was not statistically significant ($P=0.279$). Small artery occlusion was more common in the non-END group (44.50%) than in the END group (29.27%). Carotid unstable plaque presence and affected cerebral circulation did not differ significantly between the groups. These findings suggest a potential role of metabolic and biochemical factors, particularly blood glucose levels and the SHR, in END following intravenous thrombolysis in stroke patients without hemorrhagic transformation.

* $P<0.05$. END: early neurological deterioration; SD: standard deviation; TIA: transient ischemic attack; SBP: systolic blood pressure; DBP: diastolic blood pressure; IQR: interquartile range; NIHSS: National Institutes of Health Stroke Scale; DNT: door-to-needle time; ONT: onset-to-needle time; HbA1c: glycosylated hemoglobin; SHR: stress hyperglycemia ratio.

Correlation analysis of risk factors for END

Spearman correlation analysis was conducted to examine the relationships between various clinical variables and END (Table 2; Fig. 2), and the results revealed a significant correlation between END and the SHR (r = -0.003, $P=0.003$), indicating that a lower SHR is associated with a higher likelihood of END. Conversely, age did not exhibit a significant correlation with END ($r=0.000$, $P=0.815$). Similarly, gender (male) was not significantly correlated with END ($r=0.629$, $P=0.629$). The NIHSS score at admission also did not show a significant correlation with END ($r=0.601$, $P=0.601$). Door-to-needle time (DNT) was not significantly correlated with END ($r=0.892$, $P=0.892$). Low-density lipoprotein cholesterol (LDL-C) levels and glycated hemoglobin (HbA1c) levels did not exhibit significant correlations with END ($r=0.983$, $P=0.983$ and $r=0.977$, $P=0.977$, respectively). These findings underscore the significant association between SHR and END, suggesting that stress hyperglycemia may play a role in END in stroke patients. Other variables, including age, gender, NIHSS score, DNT, LDL-C, and HbA1c, did not show significant correlations with END in this cohort.

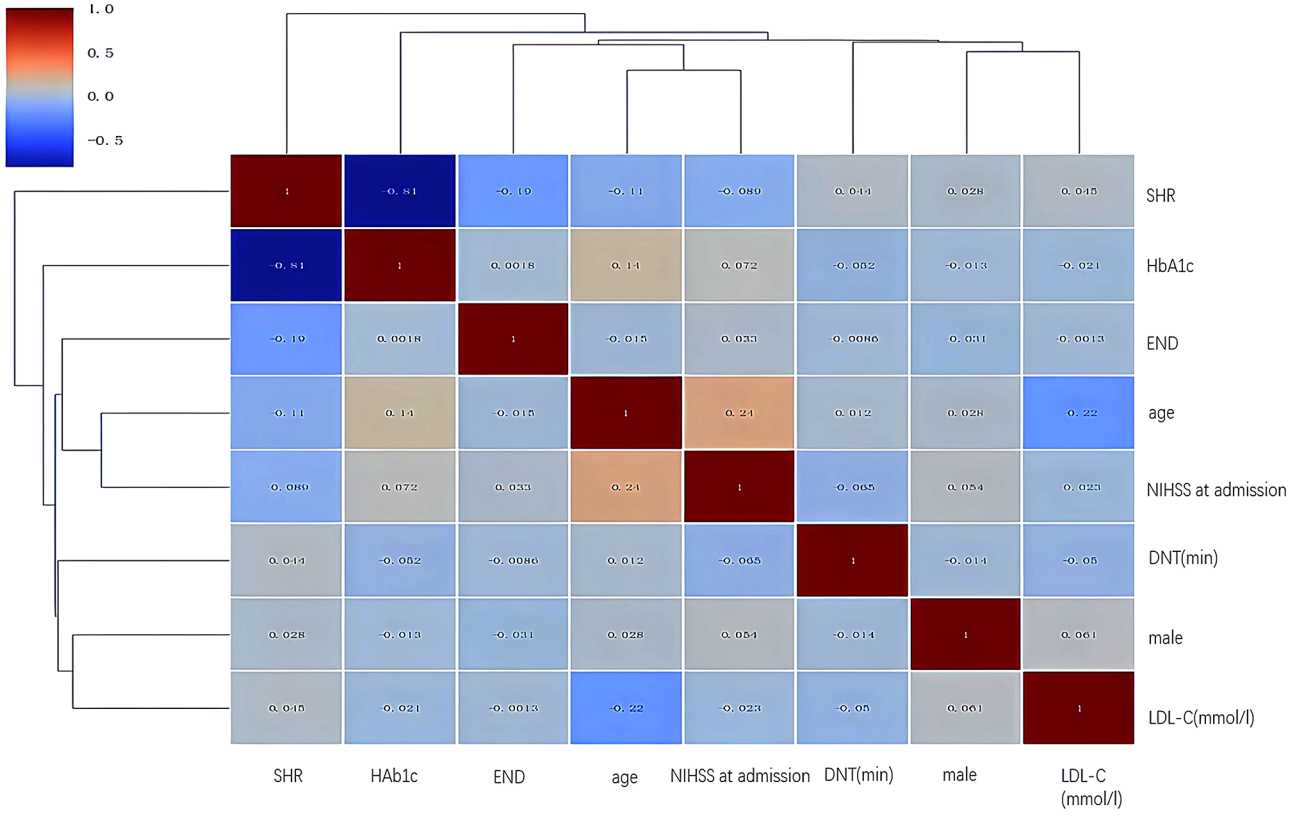

Fig. 2 Correlation heatmap related to END

Table 3 Logistic regression analysis of factors associated with END

Predictor	Estimate	SE	Z	*P*	Odds Ratio	Lower	Upper
(Intercept)	8.952						
Age	-0.006	0.014	-0.384	0.701	0.995	0.967	1.023
Male	-0.118	0.441	-0.268	0.789	0.889	0.353	2.031
NIHSS at admission	0.02	0.033	0.607	0.544	1.02	0.952	1.085
DNT	0.001	0.006	0.085	0.932	1.001	0.988	1.012
LDL-C(mmol/L)	-0.095	0.175	-0.545	0.586	0.909	0.64	1.273
HbA1c	-0.376	0.164	-2.293	0.022*	0.687	0.481	0.921
SHR	-8.398	2.942	-2.855	0.004*	0.0	0.0	0.051

*$P<0.05$

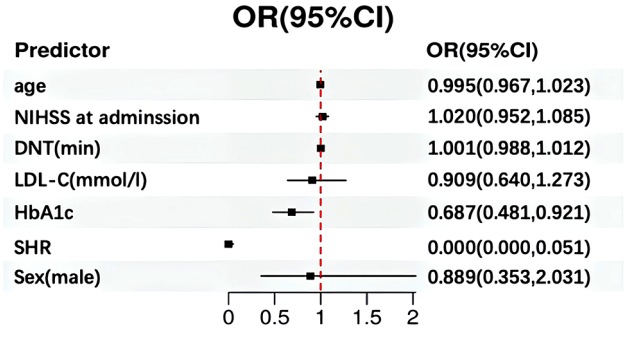

Fig. 3 Forest plot related to END

Regression analysis of END and clinical factors

To identify independent predictors of END, logistic regression analysis was performed, adjusting for potential confounders. The results are summarized in Table 3 and illustrated in Fig. 3. The logistic regression analysis included several predictors: age, gender, NIHSS score at admission, DNT, LDL-C levels, HbA1c, and the SHR. The intercept of the model was estimated at 8.952. Age was not a significant predictor of END (Estimate = -0.006, SE=0.014, Z = -0.384, P=0.701), with an OR of 0.995 (95% CI: 0.967–1.023). Gender (male) also did not significantly predict END (Estimate = -0.118, SE=0.441, Z = -0.268, P=0.789), with an OR of 0.889 (95% CI: 0.353–2.031). The NIHSS score at admission did not show a significant association with END

Table 4 Receiver operating characteristic curve of factors in distinguishing END

Variable	AUC	Sensitivity	Specificity	Youden index	Cutoff
HbA1c	0.501(0.411–0.607)	0.415(0.271–0.607)	0.789(0.634–0.858)	0.204(0.081–0.325)	6.700(6.300-7.052)
SHR	0.645(0.546–0.737)	0.799(0.583–0.858)	0.888(0.377–0.778)	0.287(0.178–0.478)	0.857(0.849–0.913)

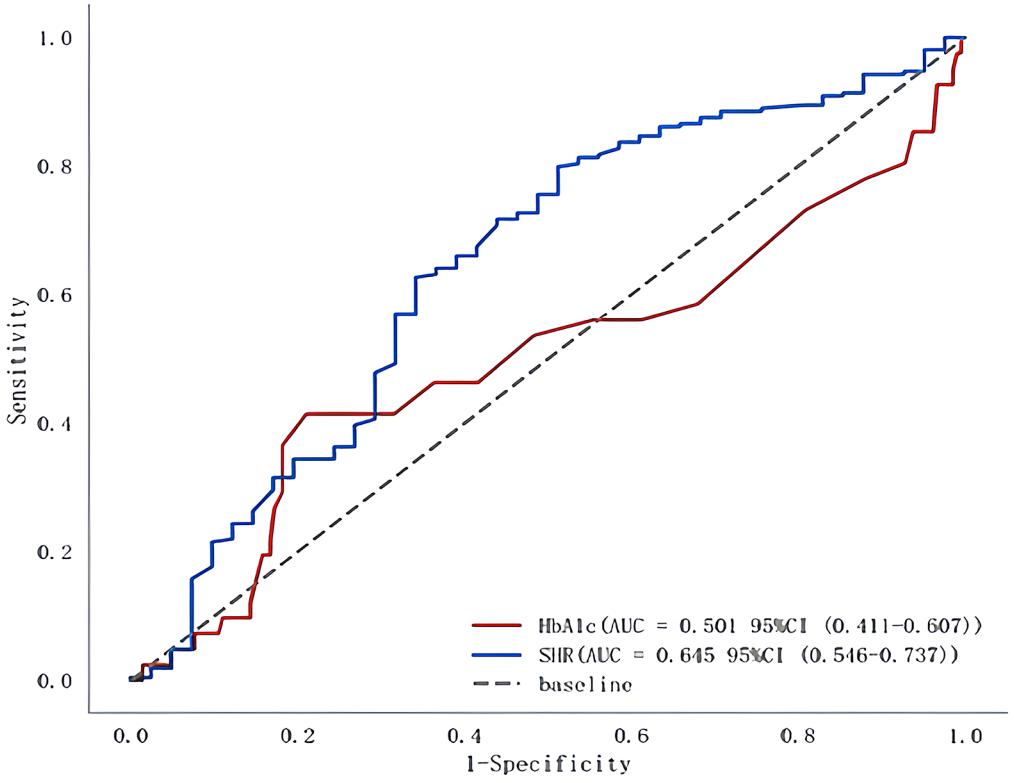

Fig. 4 ROC curve for END

(Estimate=0.020, SE=0.033, Z=0.607, *P*=0.544), with an OR of 1.020 (95% CI: 0.952–1.085). Similarly, DNT was not a significant predictor (Estimate=0.001, SE=0.006, Z=0.085, *P*=0.932), with an OR of 1.001 (95% CI: 0.988–1.012). LDL-C levels did not significantly predict END (Estimate = -0.095, SE=0.175, Z = -0.545, *P*=0.586), with an OR of 0.909 (95% CI: 0.640–1.273). In contrast, HbA1c emerged as a significant predictor of END (Estimate = -0.376, SE=0.164, Z = -2.293, *P*=0.022), with an OR of 0.687 (95% CI: 0.481–0.921), indicating that higher HbA1c levels were associated with a reduced risk of END. The SHR was also a significant predictor (Estimate = -8.398, SE=2.942, Z = -2.855, *P*=0.004), with an OR of 0.0 (95% CI: 0.0-0.051), suggesting a strong association between a lower SHR and increased likelihood of END. These findings highlight the significant role of metabolic factors, particularly HbA1c and SHR, in the risk of END in stroke patients. Other variables, including age, gender, NIHSS score, DNT, and LDL-C, did not show significant associations with END in this analysis.

Receiver operating characteristic curve of factors for distinguishing END

The ROC curve analysis was conducted to evaluate the ability of different factors to distinguish END. The results are detailed in Table 4 and illustrated in Fig. 4. The AUC for HbA1c was 0.501 (95% CI: 0.411–0.607), indicating poor discriminatory power. The sensitivity and specificity for HbA1c were 0.415 (95% CI: 0.271–0.607) and 0.789 (95% CI: 0.634–0.858), respectively. The Youden Index was 0.204 (95% CI: 0.081–0.325), and the optimal cutoff value was 6.700 (95% CI: 6.300-7.052). In contrast, the SHR demonstrated better discriminatory ability with an AUC of 0.645 (95% CI: 0.546–0.737). The sensitivity for SHR was 0.799 (95% CI: 0.583–0.858), and the specificity was 0.888 (95% CI: 0.377–0.778). The Youden Index for SHR was 0.287 (95% CI: 0.178–0.478), with a cutoff value of 0.857 (95% CI: 0.849–0.913). These results indicate that SHR has superior discriminatory power in identifying patients at risk of END compared to HbA1c, evidenced by its higher AUC, sensitivity, and specificity. The cutoff values for both HbA1c and SHR can be utilized as reference points in clinical practice to identify

patients at higher risk for END. The ROC analysis underscores the potential utility of SHR as a more reliable marker for predicting END in stroke patients, highlighting the importance of managing stress hyperglycemia in this population.

Discussion

This study aimed to elucidate the impact of the SHR on END in patients with cerebral infarction who underwent intravenous thrombolysis without hemorrhagic transformation. Additionally, the study sought to identify risk factors associated with END in this patient population. Our findings indicate that both HbA1c and SHR are significant predictors of END, with SHR demonstrating a particularly strong association. Notably, SHR exhibited a higher AUC compared to HbA1c, suggesting that SHR is a more reliable marker for distinguishing END. These results highlight the importance of monitoring both HbA1c and SHR in patients with acute non-cardiogenic cerebral infarction who have not experienced hemorrhagic transformation after intravenous thrombolysis. Such monitoring may aid in predicting and potentially mitigating the risk of END. Our study underscores the need for further research to explore the mechanisms underlying these associations and to develop targeted interventions for patients at risk of END.

Stroke remains a major global health issue, ranking as the second leading cause of death and significantly contributing to disability worldwide [11]. It accounts for approximately 11% of all fatalities, with substantial variations in prevalence across different regions and demographic groups [12]. Notably, stroke incidence is higher in low- and middle-income countries compared to high-income nations, with age-standardized incidence rates in less affluent areas being nearly twice as high as those in more affluent regions [13, 14]. This discrepancy underscores the influence of socioeconomic factors on stroke vulnerability.

Ischemic stroke, characterized by disrupted blood supply to the brain, requires prompt medical intervention to minimize cerebral injury and improve patient outcomes [15]. The primary treatments for AIS include reperfusion therapy, which consists of intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA) and mechanical thrombectomy [16]. These therapies aim to restore blood flow to affected brain regions. Despite the potential benefits of acute interventions, their effectiveness is limited by a narrow therapeutic window, the risk of hemorrhagic transformation, and the varied etiologies of stroke. Recent studies have shown that tirofiban can reduce the risk of END, although the incidence of intracranial hemorrhage was slightly higher with tirofiban [17, 18].

Complications following a stroke significantly contribute to elevated morbidity and mortality rates, with approximately 5.5 million stroke-related deaths reported globally each year [5]. END, characterized by the worsening of neurological status within the first few hours or days post-stroke, affects approximately 10–20% of patients [19]. END is linked to poorer functional outcomes, increased disability, and higher mortality rates [18, 20]. Preventive strategies for END emphasize maintaining hemodynamic stability, rigorous blood glucose control, and close monitoring for any signs of deterioration [21]. The variability in the incidence of END underscores the necessity for personalized care and highlights the need for continued research to identify high-risk individuals and develop targeted interventions [13].

The pathophysiology of END in ischemic stroke is multifaceted and not fully understood. END can arise from various mechanisms, including the expansion of the initial infarct due to ongoing ischemia, unstable atherosclerotic plaques, cerebral edema leading to increased intracranial pressure, hemorrhagic transformation within the infarcted area, and secondary embolic events [22]. Additionally, post-ischemic inflammatory responses can exacerbate tissue damage, significantly contributing to the onset of END [23]. Despite extensive research, substantial knowledge gaps remain regarding the specific triggers and underlying mechanisms of END. The heterogeneity of stroke pathology, along with the influence of comorbidities and pre-existing conditions, complicates the identification of consistent predictors or therapeutic targets for END [22]. Moreover, the variability in the timing of neurological decline among patients presents challenges in determining optimal intervention windows.

Current research faces several challenges, including the rapid and accurate identification of patients at high risk for END, the development of effective therapeutic strategies to prevent or mitigate END, and the establishment of standardized criteria for defining and evaluating neurological decline. Therefore, managing END in ischemic stroke continues to be a significant challenge in stroke care [24, 25], underscoring the urgent need for ongoing research to elucidate the underlying mechanisms and develop effective prevention and treatment strategies. While many studies have focused on END related to hemorrhagic transformation following thrombolysis in acute cerebral infarction, there is a notable lack of research on END associated with non-hemorrhagic transformation after thrombolysis in patients with acute cerebral infarction caused by non-cardiogenic embolisms [26].

It has been widely reported that stress hyperglycemia contributes to poor prognosis in patients experiencing acute ischemic stroke (AIS). However, its predictive value for early neurological deterioration (END) after

intravenous administration of recombinant tissue-type plasminogen activator (IV-rtPA) in AIS patients is still unclear [27]. The SHR is a metric used to assess the degree of hyperglycemia in acutely ill patients relative to their estimated baseline glucose levels. SHR aims to differentiate between true diabetic hyperglycemia and stress-induced glucose elevations, which have distinct implications for patient outcomes and management approaches [28]. Recently, SHR has gained recognition as an important prognostic indicator. Several studies have demonstrated that a higher SHR is associated with poorer outcomes in patients with acute coronary syndromes (ACS) [29]. Elevated SHR may indicate a higher risk of mortality, increased incidence of heart failure, and a greater likelihood of adverse cardiovascular events [30].

The mechanisms linking an elevated SHR to adverse cardiovascular outcomes are complex and multifaceted [31]. Stress-induced hyperglycemia can exacerbate oxidative stress and inflammation, leading to endothelial dysfunction and plaque instability [32]. Additionally, acute hyperglycemia may negatively impact myocardial function by altering myocardial metabolism and increasing the susceptibility of cardiomyocytes to ischemic injury [33]. Elevated stress-related hyperglycemia is often associated with increased levels of stress hormones such as cortisol and catecholamines, which can further exacerbate cardiovascular instability and contribute to poor outcomes [28].

The SHR has been extensively examined in the context of AIS and transient ischemic attacks (TIA). However, the influence of SHR on stroke prognosis remains debatable [4]. Previous research has often focused on absolute hyperglycemia as a determinant of stroke outcomes, overlooking variations in patients' baseline blood glucose levels. This oversight could confound the analysis of hyperglycemia's impact on prognosis [34]. To address this, SHR incorporates baseline glycemia into analyses, emphasizing the relative increase in blood glucose levels. Several studies have underscored the importance of SHR in predicting both short-term and long-term outcomes for AIS patients [35]. Elevated SHR has been linked to more severe initial neurological deficits, a higher incidence of END, and poorer functional outcomes at discharge and follow-up [6]. Despite its prognostic value, the use of SHR in ischemic cerebrovascular disease is still debated. A major point of contention is the variability in threshold values used to define elevated SHR, which differs widely across studies and populations. Furthermore, there is ongoing debate about whether adverse outcomes in AIS patients are primarily driven by hyperglycemia itself or by the underlying stress response. Some experts advocate targeting hyperglycemia to improve patient outcomes, while others suggest that focusing on the overall stress response might be more beneficial [36].

In this study, we found that the SHR was independently associated with adverse clinical outcomes, even after adjusting for other clinical risk factors. Both hyperglycemia at presentation and the increase in glucose levels, as indicated by SHR, were linked to poor functional outcomes. A high SHR may contribute to dysregulated inflammatory responses, which can lead to cerebral vasoconstriction and reduced cerebral blood flow, thereby impairing functional recovery [37]. This response is triggered by a surge in catecholamines, cortisol, and other inflammatory mediators, which promotes rapid glycogenolysis and the release of glucose from hepatic glycogen stores into the bloodstream. Consequently, it appears that acute fluctuations in glucose concentration, rather than persistently high blood glucose levels, are responsible for the observed adverse clinical outcomes.

The exact mechanisms by which the SHR influences outcomes in ischemic cerebrovascular disease remain under investigation, but several pathways are believed to be involved. Firstly, stress-induced hyperglycemia is associated with heightened inflammatory and neurohormonal responses, increased endothelial cell apoptosis, and elevated oxidative stress [38]. This oxidative stress activates matrix metalloproteinase gelatinase B (MMP-9), compromising the integrity of the blood-brain barrier (BBB) and leading to increased BBB permeability, which heightens the risk of brain edema and hemorrhage following reperfusion [39]. It has been shown that stress hyperglycemia predicts hemorrhagic transformation in AIS patients [40]. Secondly, stress hormones stimulate hepatic gluconeogenesis while inhibiting glucose uptake in peripheral tissues [41]. Pro-inflammatory cytokines can enhance the expression and membrane localization of glucose transporters GLUT-1 and GLUT-3, which promotes glucose uptake by insulin-independent tissues, including the central nervous system [42]. Excessive cellular glucose leads to increased brain lactate production, which may transform asymptomatic tissue into symptomatic tissue [43]. Thirdly, both acute and chronic hyperglycemia contribute to a prothrombotic state and may promote thrombus extension, which is closely linked to END [4]. This involves hyperglycemia and hyperinsulinemia elevating the expression of plasminogen activator inhibitor-1 (PAI-1), thereby reducing rt-PA activity [44]. Additionally, hyperglycemia can disrupt the endothelial glycocalyx layer, release coagulation factors, and increase platelet-endothelial adhesion [45]. The mechanisms underlying hyperglycemia-induced hypercoagulability are complex and warrant further investigation. Furthermore, stress hyperglycemia may reflect transient glycemic variability, which specifically induces oxidative stress [46]. Previous research has demonstrated that greater glycemic variability in AIS patients is associated with lower rates of neurological improvement during

hospitalization, potentially due to increased oxidative stress [47]. Finally, the extent of stress hyperglycemia may serve as an indicator of disease severity; in AIS patients, it can reflect the degree of ischemic injury, with severe neurological impairment closely related to endothelial dysfunction.

Our study also found that Hemoglobin A1c (HbA1c) can serve as a predictor of neurological deterioration following thrombolysis in patients with AIS. HbA1c is a form of hemoglobin covalently bonded to glucose, reflecting average blood glucose levels over the preceding two to three months, which corresponds to the lifespan of red blood cells [48]. This biomarker is commonly used in clinical settings to monitor long-term glycemic control in diabetic patients [49, 50]. Elevated HbA1c levels have been associated with the occurrence, progression, and prognosis of ischemic stroke. Specifically, high HbA1c levels correlate with an increased risk of both developing ischemic stroke and experiencing poorer outcomes after a stroke event [51]. The mechanisms by which HbA1c could predict END in AIS patients are complex. Elevated HbA1c levels indicate chronic hyperglycemia, which may exacerbate ischemic injury through several pathways [52]. Chronic hyperglycemia can lead to endothelial dysfunction, increased oxidative stress, and elevated levels of inflammatory markers. These factors collectively contribute to increased vulnerability of cerebral vasculature and neural tissue during an ischemic event. Furthermore, high HbA1c levels can promote a prothrombotic state, raising the risk of thrombus formation and extension, which may result in more extensive brain damage and poorer recovery outcomes [53]. Elevated HbA1c may also reflect poor pre-stroke glycemic control, indicating underlying vascular pathology that predisposes patients to ischemic damage and its complications. Additionally, pre-existing hyperglycemia might impair the efficacy of thrombolytic therapy by increasing blood-brain barrier permeability, thereby raising the risk of hemorrhagic transformation.

However, HbA1c measurement is not without limitations. Its reliability as a marker can be compromised under various conditions, including significant anemia, hemoglobinopathies, recent blood transfusions, and chronic kidney disease. These conditions can affect the lifespan of red blood cells or alter hemoglobin structure, potentially leading to misleading HbA1c levels [54]. Therefore, while HbA1c is a convenient and widely accessible marker, clinicians must be aware of these potential confounders when interpreting results [55].

This study had several limitations. It is a retrospective observational study with a modest sample size and was conducted at a single center. Additionally, patients who received endovascular therapy after intravenous thrombolysis (IV-rtPA) were excluded, which may have introduced selection bias. The study relied on admission blood glucose levels to calculate the SHR without considering glycemic changes and control at other time points. Furthermore, diabetes diagnosis was based on past medical history and HbA1c levels, without a detailed assessment of the patients' prior glycemic status. Despite these limitations, the study's strengths include a rigorous selection process and the inclusion of patients from a well-defined center.

In conclusion, this study suggests that SHR can be a valuable predictor of END in patients with AIS following intravenous thrombolysis. Large-scale, multicenter studies are still needed to further elucidate the role of SHR in predicting END in these patients.

Acknowledgements
We thank all departments in our hospital for their helpful services.

Author contributions
Study concept and design: Junjie Lei, Lei Zhang. Acquisition of data: Qian Fan. Analysis or interpretation of data: all authors. Junjie Lei wrote the first draft of the manuscript. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: Junjie Lei.

Funding sources
This study was supported by the National Natural Science Funds of China (grant number 81971098) to Lei Zhang and the Science and technology project for social development of Zhuhai (2420004000297) to Junjie Lei. The funding bodies had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript. All authors declare that they have no competing interests.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of the Fifth Affiliated Hospital of Sun Yat-sen University(K557). The requirement for individual consent was waived by the committee owing to the retrospective nature of the study. All procedures performed in this study involving human participants were in accordance with the ethical standards of The Fifth Affiliated Hospital of Sun Yat-Sen University committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Competing of interests
All authors declare that they have no competing interests.

Received: 21 August 2024 / Accepted: 21 November 2024
Published online: 26 November 2024

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