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ORIGINAL RESEARCH

Association of Admission Hyperglycemia with Clinical Outcomes in Patients with Symptomatic Intracranial Hemorrhage After Endovascular Treatment for Large Vessel Occlusive Stroke

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Background: Symptomatic intracranial hemorrhage (sICH) is a fatal complication after endovascular treatment (EVT) for acute large vessel occlusive (LVO) stroke. The aim of this study was to investigate the association between hyperglycemia and outcomes in patients with postprocedural sICH.

Methods: Of the 2567 patients with AIS who underwent EVT from two large multicenter randomized trials and two prospective multicenter registry studies, 324 patients occurred sICH with documented admission glucose were included in this study. The primary outcome was functional independence (defined as a modified Rankin Scale score of 0 to 2) at 90 days. Secondary outcomes included mRS score of 0 to 3, 0 to 1, and mRS score at 90 days. Safety outcome was the mortality within 90 days. Admission hyperglycemia was defined as a plasma blood glucose ≥7.8 mmol/L (140 mg/dL) in our analysis.

Results: Of 324 eligible participants included in this study, hyperglycemia was observed in 130 (40.1%) patients. The median age was 67 (IQR, 58–75) years, and median blood glucose level was 7.1 (IQR, 6.0–9.3) mmol/L. After adjusting for confounding variables, admission hyperglycemia was associated with decreased odds of functional independence (adjusted odds ratio[OR] 0.34; 95% CI 0.17–0.68; P= 0.003), decreased odds of favorable outcome (adjusted OR 0.31; 95% CI 0.16–0.58; P < 0.001) and increased odds of mortality (adjusted OR 2.56; 95% CI 1.47–4.45; P = 0.001) at 90 days. After 1:1 propensity score matching analysis, the results were consistent with multivariable logistic regression analysis.

Conclusion: In patients who suffered sICH after EVT for acute large vessel occlusive stroke, hyperglycemia is a strong predictor of poor clinical outcome and mortality at 90 days.

Keywords: stroke, large vessel occlusion, endovascular treatment, symptomatic intracranial hemorrhage, hyperglycemia

Introduction

With the exploration of medical treatment in recent years, endovascular treatment (EVT) has become widely accepted as the standard of treatment for large vessel occlusive (LVO) stroke.[1–6] While restoring vascular reperfusion, this treatment also increases the risk of intracranial hemorrhage, which is a common and fatal complication after EVT and has been shown to deteriorate neurological functional outcomes.[7]

During the acute phase of ischemic stroke, a significant proportion of patients develop hyperglycemia, regardless of their prior glycemic status. Previous studies have indicated that admission hyperglycemia was associated with poor neurological prognosis and increased mortality in patients with LVO.[8,9] The underlying mechanisms by which

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hyperglycemia exacerbates the clinical functional prognosis in stroke patients potentially encompass disrupting the permeability of the blood–brain barrier, accelerating endothelial cell apoptosis, promoting the release of neuroinflammatory factors, accelerating oxidative stress and increasing the production of superoxide.[10]

Simultaneously, despite the rapid advancements in technology, there are still specific factors that contribute to the elevated risk of symptomatic intracranial hemorrhage (sICH) following EVT, including mechanical damage to endothelial cells caused by surgical instruments, perforation, or the triggering of an endovascular inflammatory reaction.[11] When such conditions occur, they can have a significantly detrimental impact on neurological recovery following stroke and increase the risk of mortality.[12] Available studies have mainly focused on evaluating the association between admission glucose levels and outcomes in patients underwent EVT.[8,13,14] Nevertheless, whether hyperglycemia further exacerbates the poor neurological function of patients who develop sICH after EVT has not been fully explored.

Thus, using a combined nationwide multicenter stroke database merged from four studies, we aim to investigate the association between admission hyperglycemia and clinical outcomes in patients who experience sICH following EVT for LVO.

Materials and Methods

Study Design and Patients Selection

Data from a combined nationwide database, which collected from four multicenter studies of patients with AIS due to LVO underwent EVT, have included in this analysis: the BASILAR study, which prospectively enrolled patients with acute basilar artery occlusion from 47 stroke centers in China; the RESCUE BT randomized trial, which enrolled patients with acute large vessel occlusion stroke within 24 hours of onset from 55 stroke centers in China; the DEVT randomized trial, which is a multicenter, randomized controlled, open-label clinical trial included patients with AIS due to anterior LVO from 33 stroke centers in China and the SUSTAIN study, which is an observational, nationwide registry of consecutive patients with acute LVO who received EVT in 28 comprehensive stroke centers in China.

The inclusion criteria of this study were as follows: 1) age at least 18 years, 2) LVO of the posterior circulation or anterior circulation confirmed by head digital subtraction angiography, magnetic resonance angiography (MRA), or computer tomography angiography (CTA), and receiving EVTs within 24h of the estimated time of LVO. 3) patients who occurred sICH after EVT, which is defined in the *intracranial hemorrhage* section. A total of 2567 patients with LVO were included in the combined database, 360 patients developed sICH after receiving EVT and 36 patients with missing admission glucose values were excluded. Ultimately, the remaining 324 patients were enrolled in our analysis.

The study protocols were approved by the ethics committee of the Second Affiliated Hospital of the Army Medical University and all participating centers. Written informed consent was obtained from the patient or patient's representative in accordance with the Declaration of Helsinki.

Data Collection and Assessment of Admission Hyperglycemia

Demographic information and baseline clinical characteristics of all patients were obtained from the combined database, which included age, sex, glucose, systolic blood pressure, National Institutes of Health Stroke Scale (NIHSS), the Alberta Stroke Program Early Computed Tomography (ASPECT) score, history of smoking, intravenous thrombolysis, atrial fibrillation, diabetes, hypertension, hyperlipidemia, occlusion site and transient ischemic attack (TIA). Successful recanalization was defined as modified Thrombolysis In Cerebral Infarction (mTICI) score of 2b-3. Collateral vessel status was evaluated based on the American Society of Interventional and Therapeutic Neuroradiology/Society/Society of Interventional Radiology (ASITN/SIR) collateral vessel grading system. The classification of stroke etiologies was conducted following the Trial of Org 10172 in Acute Stroke Treatment (TOAST). Meanwhile, time indicators including the time from stroke onset to puncture and stroke onset to recanalization were recorded.

In parallel to previous studies, we defined the admission hyperglycemia as a plasma blood glucose ≥7.8 mmol/L (140 mg/dL) and severe hyperglycemia was defined as blood glucose ≥11.1 mmol/L (200 mg/dL).[15,16]

Intracranial Hemorrhage

All patients underwent brain computed tomography (CT) or magnetic resonance imaging (MRI) scan within 24 hours of the onset of large vessel occlusive stroke. The adjudication of intracranial hemorrhage was determined by two experienced, double-blinded neurologists based on follow-up CT or MRI within 48 h after EVT. Intracranial hemorrhage was defined following the guidelines of the Heidelberg Bleeding Classification.[17] The specific classification schemes included hemorrhagic infarction type-1 (HI-1, scattered small petechiae without mass effect); hemorrhagic infarction type-2 (HI-2, confluent petechiae without mass effect); parenchymatous hematoma type-1 (PH-1, hematoma within infarcted tissue, occupying less than 30% and without substantive mass effect); parenchymatous hematoma type-2 (PH-2, hematoma occupying 30% or more of the infarcted tissue, and accompanied by a substantial space-occupying effect); intracerebral hemorrhage outside the infarcted brain tissue or intracranial-extracerebral hemorrhage (This class included parenchymal hematoma remote from infarcted brain tissue, intraventricular hemorrhage, subarachnoid hemorrhage and subdural hemorrhage). A diagnosis of sICH was established if there was evidence of new-onset intracranial hemorrhage accompanied by any of the following conditions: (1) National Institutes of Health Stroke Scale (NIHSS) score increased ≥4 points; (2) NIHSS score increased ≥2 points in any subcategory; (3) a deterioration in the patient's condition necessitating intubation, hemicraniectomy, external ventricular drain placement, or any other major intervention; (4) a deterioration in neurologic function that could not be attributed to causes other than the observed intracranial hemorrhage.[7] A representative image of sICH is shown in Figure S2.

Clinical Outcomes

The degree of the patient's neurological recovery or disability in daily activities was assessed based on the modified Rankin Scale (mRS) score, which is a 7-level scale (range 0 [no symptoms] to 6 [death]) used to assess a patient's neurological deficits.[18] The primary efficacy outcome was the proportion of patients with functional independence, defined as an mRS score of 0 to 2 at 90 days. Secondary efficacy outcomes include favorable outcome (defined as mRS score of 0 to 3), excellent outcome (defined as mRS score of 0 to 1) and the mRS score (range, 0 to 6 points) at 90 days. Safety endpoint referred to the mortality within 90 days. All scores were evaluated by two experienced neurological specialists unaware of the patient's condition.

Statistical Analysis

Baseline characteristics of patients were compared separately by the presence or absence of admission hyperglycemia (Table 1), whether they achieved a functional independence (Table S1) and whether they survived at 90 days (Table S2). We described non-normally distributed continuous variables by medians and interquartile ranges (IQRs), while categorical variables were presented using absolute numbers and percentages. Categorical variables were compared using Fisher's exact test or χ^2 test. Non-normally distributed continuous variables were compared using Kruskal–Wallis test or Mann–Whitney *U*-test.

Clinical outcomes include mRS score of 0 to 2, mRS score of 0 to 3, mRS score of 0 to 1, mRS scores (range, 0 to 6 points) at 90 days and mortality within 90 days. Binary clinical outcomes were analyzed using univariate and multivariate logistic regression (Tables 2 and 3). In model 1, we adjusted for the following variables: age, sex, baseline NIHSS score, baseline systolic blood pressure, history of diabetes, successful recanalization, and intravenous thrombolysis. Further adjustments were made for smoking and baseline ASPECTS in model 2. The improvement in mRS scores (range, 0 to 6 points) at 90 days was assessed as a common odds ratio using ordinal logistic regression shift analysis (Tables 2 and 3 and Figure 1).

Additionally, we also did sensitivity analyses using propensity score matching and subgroup analysis. We used the nearest-neighbor matching algorithm and set a caliper width of 0.2 to perform 1:1 propensity score matching analysis. Subgroup analyses were conducted to determine the association between outcomes and glucose in patients with different baseline characteristics (Figure 2 and Figures S4-S6). Furthermore, we plotted the marginal effect diagram to visualize the predicted probability of functional independence and mortality with glucose in continuous changes (Figure S3). The data were presented as adjusted odds ratios (aOR) with corresponding 95% CIs to show statistical precision.

Table 1 Baseline Characteristics of the Included Patients Stratified by Hyperglycemia

Variables	All Patients				Propensity Score Matching			
	Overall (n=324)	Non-Hyperglycemia (n=194)	Hyperglycemia (n=130)	P value	Overall (n=208)	Non-hyperglycemia (n=104)	Hyperglycemia (n=104)	P value
Age (median [IQR])	67 (58–75)	66 (56–74)	69 (62–76)	0.02	69 (61–77)	69 (60–77)	69 (62–76)	>0.99
Sex, male, n (%)	189 (58.3)	123 (63.4)	66 (50.8)	0.02	105 (50.5)	51 (49.0)	54 (51.9)	0.68
NIHSS score (median [IQR])	18 (14–23)	18 (13–22)	19 (15–24)	0.02	19 (14–23)	20 (14–23)	19 (14–23)	0.53
Baseline ASPECTS, median (IQR)[a]	8 (7–10)	8 (7–10)	8 (7–9)	0.36	8 (7–9)	8 (7–10)	8 (7–9)	0.66
SBP, (median [IQR])	147 (130–163)	142 (127–159)	150 (132–170)	0.006	148 (130–165)	150 (130–160)	148 (130–169)	0.82
Glucose (median [IQR])	7.1 (6.0–9.3)	6.3 (5.5–6.9)	9.9 (8.7–12.0)	NA	7.8 (6.3–9.7)	6.3 (5.6–6.9)	9.7 (8.7–11.5)	NA
Smoking, n (%)	81 (25.0)	49 (25.3)	32 (24.6)	0.90	41 (19.7)	17 (16.3)	24 (23.1)	0.22
ASTIN/SIR grade[b]				0.49				0.34
0	57 (17.6)	38 (19.7)	19 (14.6)		38 (18.3)	23 (22.1)	15 (14.4)	
1	108 (33.4)	59 (30.6)	49 (37.7)		73 (35.1)	33 (31.7)	40 (38.5)	
2	118 (36.5)	71 (36.8)	47 (36.2)		71 (34.1)	33 (31.7)	38 (36.5)	
3	40 (12.4)	25 (13.0)	15 (11.5)		26 (12.5)	15 (14.4)	11 (10.6)	
Medical history, n/total n (%)								
Atrial fibrillation	145 (44.8)	86 (44.3)	59 (45.4)	0.85	88 (42.3)	39 (37.5)	49 (47.1)	0.16
Diabetes	61 (18.8)	16 (8.2)	45 (34.6)	<0.001	38 (18.3)	16 (15.4)	22 (21.2)	0.28
Hypertension	199 (61.4)	112 (57.7)	87 (66.9)	0.096	138 (66.3)	72 (69.2)	66 (63.5)	0.38
Hyperlipidemia	43 (13.3)	22 (11.3)	21 (16.2)	0.21	29 (13.9)	17 (16.3)	12 (11.5)	0.32
TIA	6 (1.9)	4 (2.1)	2 (1.5)	0.73	4 (1.9)	2 (1.9)	2 (1.9)	>0.99
Stroke Etiology (%)				0.08				0.76
LAA	133 (41.0)	70 (36.1)	63 (48.5)		93 (44.7)	48 (46.2)	45 (43.3)	
CE	160 (49.4)	103 (53.1)	57 (43.8)		93 (44.7)	44 (42.3)	49 (47.1)	
Other causes	31 (9.6)	21 (10.8)	10 (7.7)		22 (10.6)	12 (11.5)	10 (9.6)	
Occlusion site[c]				0.13				0.68
Anterior circulation	285 (88.0)	175 (90.2)	110 (84.6)		182 (87.5)	90 (86.5)	92 (88.5)	
Posterior circulation	39 (12.0)	19 (9.8)	20 (15.4)		26 (12.5)	14 (13.5)	12 (11.5)	
IVT	87 (26.9)	48 (24.7)	39 (30.0)	0.30	55 (26.4)	22 (21.2)	33 (31.7)	0.08
OTP, median (IQR), min[d]	296 (210–392)	300 (216–393)	286 (205–394)	0.57	297 (215–383)	300 (215–394)	294 (212–379)	0.85
OTR, median (IQR), min[e]	405 (319–521)	411 (317–520)	399 (319–527)	0.79	404 (325–520)	416 (327–520)	396 (325–505)	0.68

Notes: [a]Data were missing for 3 patients in the non-hyperglycemia group and 1 patients in the hyperglycemia group. [b]Data were missing for 1 patient in the non-hyperglycemia group. [c]Anterior circulation refers to the large vessel occlusion of the anterior circulation, including intracranial internal carotid artery, middle cerebral artery segment M1 and M2, posterior circulation refers to the large vessel occlusion of the posterior circulation, including distal basilar artery, middle basilar artery, proximal basilar artery and vertebral artery V4 segment. [d]Data were missing for 1 patient in the non-hyperglycemia group. [e]Data were missing for 1 patient in the non-hyperglycemia group.

Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; ASTIN/SIR, American Society of Intervention and Therapeutic Neuroradiology/Society of Interventional Radiology; CE, cardio-embolism; IQR, interquartile range; IVT, intravenous thrombolysis; LAA, large artery atherosclerosis; NIHSS, National Institutes of Health Stroke Scale; OTP, onset to puncture; OTR, onset to recanalization; SBP, systolic blood pressure; TIA, transient ischemic attack.

Table 2 Association Between Admission Hyperglycemia and Clinical Outcomes

	All Patients								Prosperity Score Matching			
	Non-hyperglycemia (n=194)	Hyperglycemia (n=130)	Crude analysis	P value	Model 1 [a]	P value	Model 2 [b]	P value	Non-hyperglycemia (n=104)	Hyperglycemia (n=104)	Unadjusted value (95% CI)	P value
			Unadjusted outcome variable value (95% CI)		Adjusted value (95% CI)		Adjusted value (95% CI)					
Primary outcome												
mRS score of 0–2, No. (%)[c]	66 (34.0)	21 (16.2)	0.37 (0.22–0.65)	<0.001	0.35 (0.18–0.68)	0.002	0.34 (0.17–0.69)	0.003	34 (32.7)	16 (15.4)	0.37 (0.19–0.73)	0.004
Secondary outcomes												
mRS score of 0–3[c]	94 (48.5)	28 (21.5)	0.29 (0.18–0.48)	<0.001	0.30 (0.16–0.55)	<0.001	0.31 (0.16–0.59)	<0.001	47 (45.2)	23 (22.1)	0.34 (0.19–0.63)	0.001
mRS score of 0–1, No. (%)[c]	32 (16.5)	12 (9.2)	0.52 (0.25–1.04)	0.07	0.44 (0.19–1.02)	0.06	0.42 (0.17–1.02)	0.06	18 (17.3)	9 (8.7)	0.45 (0.19–1.06)	0.07
mRS score at 90 days, median (IQR)[d]	4 (2–6)	6 (4–6)	0.35 (0.23–0.53)	<0.001	0.39 (0.24–0.62)	<0.001	0.39 (0.24–0.64)	<0.001	4 (2–6)	6 (4–6)	0.41 (0.25–0.68)	<0.001
Mortality, No. (%)[c]	54 (27.8)	67 (51.5)	2.76 (1.73–4.39)	<0.001	2.70 (1.56–4.68)	<0.001	2.60 (1.48–4.55)	0.001	32 (30.8)	52 (50.0)	2.25 (1.28–3.97)	0.005

Notes: [a]Model 1 adjusted for age, sex, baseline NIHSS, baseline SBP, history of diabetes, successful recanalization, and intravenous thrombolysis. [b]Model 2 adjusted for Model 1 and smoking, baseline ASPECTS and occlusion sites. [c]The outcome variable outcome was measured using odds ratio. The odds ratios were estimated from a binary logistic regression model. [d]The outcome variable outcome was measured using common odds ratio. The common odds ratio was estimated from an ordinal logistic regression model and indicates the odds of improvement of 1 point on the mRS.

Abbreviations: CI, confidence interval; IQR, interquartile range; mRS, modified Rankin Scale; OR, odds ratio.

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Table 3 Association of Glucose and Different Severity of Admission Hyperglycemia with Clinical Outcomes

	Number of Patients	Crude Analysis		Model 1[a]		Model 2 [b]	
		Unadjusted Outcome Variable value (95% CI)	P value	Adjusted value (95% CI)	P value	Adjusted value (95% CI)	P value
mRS score of 0–2, No. (%)[c]							
Glucose (continuous)	NA	0.86 (0.78–0.95)	0.003	0.86 (0.76–0.97)	0.01	0.83 (0.73–0.95)	0.005
Severity of hyperglycemia							
<7.8 mmol/L	66 (34.0)	Reference		Reference		Reference	
7.8–11.1 mmol/L	14 (16.7)	0.39 (0.20–0.74)	0.004	0.34 (0.16–0.74)	0.006	0.38 (0.17–0.84)	0.02
>11.1 mmol/L	7 (15.2)	0.35 (0.15–0.82)	0.02	0.35 (0.12–1.02)	0.054	0.27 (0.09–0.81)	0.02
mRS score of 0–3, No. (%)[c]							
Glucose (continuous)	NA	0.85 (0.77–0.93)	<0.001	0.87 (0.79–0.97)	0.01	0.86 (0.77–0.97)	0.01
Severity of hyperglycemia							
<7.8 mmol/L	94 (48.5)	Reference		Reference		Reference	
7.8–11.1 mmol/L	19 (22.6)	0.31 (0.17–0.56)	<0.001	0.30 (0.15–0.61)	0.001	0.34 (0.17–0.69)	0.003
>11.1 mmol/L	9 (19.6)	0.26 (0.12–0.57)	0.001	0.29 (0.11–0.77)	0.01	0.25 (0.09–0.70)	0.009
mRS score of 0–1, No. (%)[c]							
Glucose (continuous)	NA	0.90 (0.79–1.01)	0.083	0.86 (0.74–1.01)	0.06	0.82 (0.69–0.97)	0.02
Severity of hyperglycemia							
<7.8 mmol/L	32 (16.5)	Reference		Reference		Reference	
7.8–11.1 mmol/L	7 (8.3)	0.46 (0.19–1.09)	0.08	0.37 (0.14–1.00)	0.05	0.41 (0.15–1.13)	0.09
>11.1 mmol/L	5 (10.9)	0.62 (0.23–1.68)	0.35	0.62 (0.18–2.13)	0.45	0.45 (0.12–1.70)	0.24
mRS score at 90 days, median (IQR)[d]							
Glucose (continuous)	NA	0.88 (0.82–0.94)	<0.001	0.89 (0.82–0.96)	0.003	0.88 (0.81–0.95)	0.002
Severity of hyperglycemia							
<7.8 mmol/L	4 (2–6)	Reference		Reference		Reference	
7.8–11.1 mmol/L	6 (4–6)	0.36 (0.22–0.58)	<0.001	0.41 (0.19–0.87)	0.02	0.41 (0.24–0.69)	0.001
>11.1 mmol/L	6 (4–6)	0.33 (0.18–0.61)	<0.001	0.38 (0.23–0.63)	<0.001	0.35 (0.16–0.76)	0.008
Mortality[c]							
Glucose (continuous)	NA	1.13 (1.05–1.21)	0.001	1.11 (1.02–1.21)	0.02	1.12 (1.03–1.22)	0.01
Severity of hyperglycemia							
<7.8 mmol/L	140 (72.2)	Reference		Reference		Reference	
7.8–11.1 mmol/L	41 (48.8)	2.72 (1.60–4.62)	<0.001	2.82 (1.55–5.15)	0.001	2.57 (1.39–4.75)	0.003
>11.1 mmol/L	22 (47.8)	2.83 (1.46–5.46)	0.002	2.40 (1.04–5.53)	0.04	2.67 (1.13–6.31)	0.03

Notes: [a]Model 1 adjusted for age, sex, baseline NIHSS, baseline SBP, history of diabetes, successful recanalization, and intravenous thrombolysis. [b]Model 2 adjusted for Model 1 and smoking, baseline ASPECTS and occlusion sites. [c]The outcome variable outcome was measured using odds ratio. The odds ratios were estimated from a binary logistic regression model. [d]The outcome variable outcome was measured using common odds ratio. The common odds ratio was estimated from an ordinal logistic regression model and indicates the odds of improvement of 1 point on the mRS.

Abbreviations: CI, confidence interval; IQR, interquartile range; mRS, modified Rankin Scale; NA, not applicable; OR, odds ratio.

We used the SPSS version 26 (IBM Corp.) and R.version 4.0.5 (http://www.r-project.org) to perform statistical analyses in this study. Statistical significance was considered as P <0.05 and all hypothesis tests were two-sided. We excluded patients with missing essential data from our analysis, so we did not impute for missing data.

Results

Patient Characteristics

There were 360 acute LVO stroke patients who suffered sICH after EVT. 36 patients without baseline blood glucose concentration were excluded from this analysis and the remaining were included in this study (Figure S1). Of all 324 patients included in the analysis, 130 patients (40.1%) were hyperglycemic (≥7.8 mmol/L), and 194 (59.9%) were non-hyperglycemic (<7.8 mmol/L). The median age was 67 (IQR, 58–75), 189 patients (58.3%) were male, median baseline NIHSS score was 18 (IQR, 14–23), median baseline ASPECTS was 8 (IQR, 7–10) and the median glucose on admission was 7.1 mmol/L (IQR, 6.0–9.3 mmol/L). Baseline characteristics of these patients are summarized in Table 1.

Compared to the patients without admission hyperglycemia, hyperglycemia patients were older (median [IQR] 69 [62–76] vs 66 [56–74] years; P = 0.02); less often male (66 of 130 [50.8%] vs 123 of 194 [63.4%] patients; P= 0.02); higher NIHSS score (median [IQR] 19 [15–24] vs 18 [13–22]; P = 0.02); higher systolic blood pressure (median [IQR] 150 [132–170] vs 142 [127–159] mmHg; P = 0.006); higher history of diabetes (45 of 130 [34.6%] vs 16 of 194 [8.2%] patients; P < 0.001) and lower rates of successful recanalization (96 of 130 [73.8%] vs 165 of 194 [85.1%] patients; P = 0.01). Other variables did not differ significantly between the two groups (P > 0.05).

Association Between Admission Hyperglycemic and Outcomes

The baseline characteristics of patients categorized according to functional independence and mortality at 90 days are presented in Tables S1 and S2, respectively. At 90 days after onset of stroke, 87 (26.9%) of the patients achieved functional independence defined as mRS score 0 to 2 and the remaining 237 (73.1%) patients achieved poor outcome with an mRS score >2. Of all 324 enrolled participants, 203 (62.7%) patients survived at 90 days after the onset of stroke.

All in all, those with admission hyperglycemia had a worse clinical prognosis than those without admission hyperglycemia (Figure 1). The hyperglycemic group had a higher frequency of mRS score over 2 (83.8% versus 66.0%; P < 0.001) and death within 90 days (51.5% versus 27.8%; P < 0.001) than the non-hyperglycemic group (Table 2). After adjusting the confounding variables in model 1, hyperglycemic patients had a decreased likelihood of achieving functional independence (adjusted odds ratio[aOR], 0.35; 95% confidence interval [CI], 0.18–0.68; P = 0.002), coupled with an increased mortality rate within 90 days (adjusted OR, 2.70; 95% CI, 1.56–4.68; P < 0.001) compared with patients with normal blood glucose condition. After further incorporating smoking and baseline ASPECTS into adjusted model 2, the results remained significant (adjusted OR, 0.34; 95% CI, 0.17–0.68; P = 0.003; adjusted OR, 2.56; 95% CI, 1.47–4.45; P = 0.001). Secondary clinical outcomes including mRS score of 0 to 3 and mRS score at 90 days

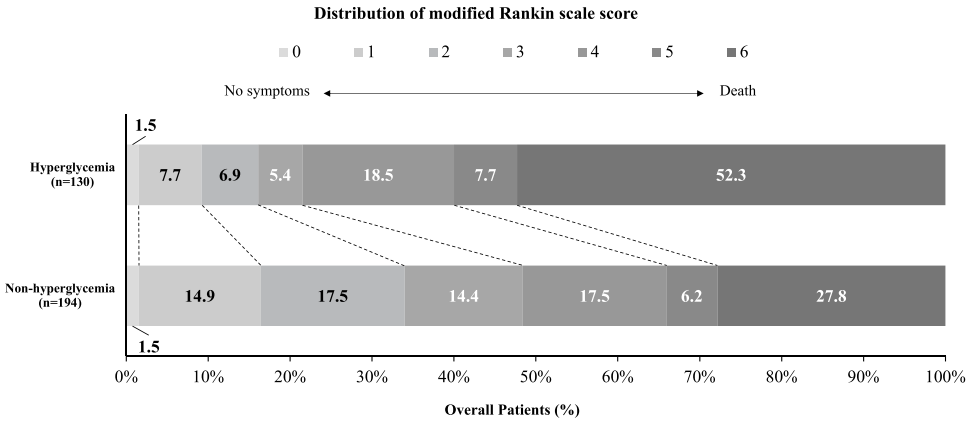

Figure 1 Modified Rankin scale (mRS) scores at 90 days. The distribution of the mRS score at 90 days after the onset of stroke in patients with and without hyperglycemia are presented in figure.

remained consistent with the primary endpoint. Hyperglycemic patients were less likely to achieve favorable outcome (adjusted OR, 0.29; 95% CI, 0.18–0.48; P < 0.001) and have a higher mRS score (6 [4–6] versus 4 [2–6]) at 90 days. However, when the mRS score of 0 to 1 were considered as a secondary efficacy outcome, the difference between the two groups was not statistically significant (Table 2).

We also categorized the severity of hyperglycemia in line with previous studies (Table 3).[15,16] The results showed that severe hyperglycemia, which defined as glucose more than 11.1mmol/L (200 mg/dL), was a critical indicator predicting poor clinical outcomes. Patients with severe hyperglycemia had approximate 0.27-fold probability of achieving mRS of 0 to 2 (adjusted OR, 0.27; 95% CI, 0.09–0.83; P = 0.02) compared to those who had normal glucose condition.

Admission Glucose as a Continuous Value Indicator

With blood glucose was considered as a continuous variable, similar results were observed: higher glucose values were associated with a decreased odds of functional independence and favorable outcome (adjusted OR, 0.83; 95% CI, 0.73–0.95; P = 0.005; adjusted OR, 0.87; 95% CI, 0.77–0.97; P = 0.01) and an increased risk of mortality (adjusted OR, 1.11; 95% CI, 1.02–1.21; P = 0.02) at 90 days (Table 3). Additionally, Figure S3 illustrates a decreased predicted probability of achieving functional independence and an increasing odds of mortality with increasing admission glucose value.

Propensity Score Matching Analysis

Baseline characteristics between patients with and without hyperglycemia groups achieved good balance after 1:1 propensity score matching analysis (Table 1). Proportions for mRS score of 0 to 2 and 0 to 3 in the hyperglycemia group were significantly lower than those who with normal glucose value (respectively, 15.4% vs 32.7%, P = 0.004; 22.1% vs 45.2%, P = 0.001). Meanwhile, hyperglycemia group had a higher mortality within 90 days (50.0% vs 30.8%, P = 0.005; Table 2).

Subgroup Analysis

Subgroup analyses for the primary endpoint are presented in Figure 2, there was a consistent effect on the association between admission hyperglycemia and 90-day functional independence across subgroups including age, sex, baseline NIHSS, baseline ASPECTS, successful reperfusion, history of diabetes and hypertension. Besides, the interaction analysis showed there is no heterogeneity among patients with different baseline characteristics (P for interaction > 0.05, Figure 2). Additionally, subgroup analyses for other clinical outcomes are presented in Figures S4–6.

Discussion

Using a pooled analysis from four national multicenter stroke databases, we explored the association between admission hyperglycemia and clinical outcomes in LVO patients who developed sICH after EVT. Our results showed that hyperglycemic patients had a decreased probability of achieving functional independence and an increased probability of death at 90 days after onset of stroke, suggesting that admission hyperglycemia is a strong predictor of poor neurological functional prognosis.

EVT has now evolved into the standard treatment for improving the neurological prognosis of patients with large vessel occlusive stroke.[1–5] Nevertheless, serious post-procedural complication such as sICH may reduce or offset the benefit–risk ratio of endovascular treatment and even worsen neurological recovery in stroke patients.[7] Concurrently, it has been observed that in critical illnesses such as acute ischemic stroke, more than one-third patients develop hyperglycemia in the acute phase, irrespective of their prior history of diabetes mellitus.[19] When this condition occurred, it would accelerate stroke progression, worsen neurological prognosis, and increase mortality of patients.[20,21] The underlying pathophysiologic mechanisms by which hyperglycemia exacerbates brain tissue damage and worsens stroke progression include increased oxidative stress, metabolic changes, neuroinflammation, vascular dysfunction and excitotoxity.[10]

Admission hyperglycemia can be classified into chronic hyperglycemia and acute post-stroke hyperglycemia mainly due to stress response. Chronic hyperglycemia is mostly caused by a relative deficiency of insulin due to diabetes

Subgroup	Patients,No.	Adjusted OR(95% CI)	P value for interaction
Overall	324	0.31 (0.16−0.60)	
Age,y			0.93
≤67	170	0.30 (0.12−0.75)	
>67	154	0.30 (0.11−0.88)	
Sex			0.21
Women	135	0.52 (0.21−1.26)	
Men	189	0.19 (0.06−0.62)	
Baseline NIHSS			0.63
≤18	167	0.33 (0.12−0.86)	
>18	157	0.26 (0.09−0.70)	
Baseline ASPECTS			0.31
≤8	175	0.44 (0.16−1.27)	
>8	145	0.18 (0.07−0.49)	
mTICI			0.67
0−2a	63	0.64 (0.05−8.04)	
2b−3	261	0.28 (0.14−0.57)	
Diabetes			0.72
No	263	0.30 (0.14−0.66)	
Yes	61	0.20 (0.02−2.02)	
Hypertension			0.75
No	125	0.43 (0.15−1.22)	
Yes	199	0.25 (0.10−0.65)	

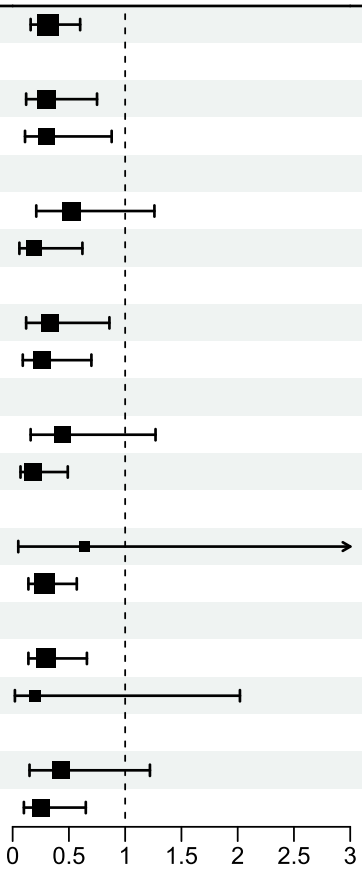

Figure 2 Subgroup analyses of primary outcome. The forest plot shows the differences in odds ratios (ORs) for functional Independence at 90 days in different subgroups. Adjusted variables include age, sex, NIHSS, ASPECTS, mTICI, diabetes mellitus, smoking, hypertension, occlusion site, systolic blood pressure and intravenous thrombolysis.
Abbreviations: NIHSS, National Institute of Health stroke scale; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; mTICI, modified Thrombolysis in Cerebral Infarction.

mellitus. Stroke patients with chronic hyperglycemia are often associated with multiple risk factors including accelerated atherosclerosis, cardiomyocyte dysfunction, atrial fibrillation, and ischemic heart disease.[22] Long-term abnormal blood glucose conditions could greatly interfere with neovascularization, causing damage to blood vessels and disrupting metabolism.[23] On the other hand, post-stroke hyperglycemia also presented in patients without a prior history of diabetes mellitus and could be referred to as dysglycemia or undiagnosed diabetes.[24] This acute hyperglycemia leads to elevated glucose concentration, disproportionately high lactate/pyruvate ratio and oxidative stress in brain extracellular compartments. Although the glycemic status of these patients may have gone undiagnosed prior to the stroke, there is no denying that abnormal glucose control will do damage to the cerebral vessels and increase the risk of cardiovascular events. Consequently, at the onset of acute ischemic stroke, they will suffer more brain tissue damage due to a wider range of underlying cerebrovascular lesions compared to those with normal glycemic status.[25]

A study published in 2019 found that admission hyperglycemia was an independent predictor of larger ischemia, reduced functional and cognitive outcomes and increased risk of mortality after stroke.[20] Besides, a sub-study analysis of highly effective reperfusion using multiple endovascular devices (HERMES) collaboration indicated that glucose concentration modified the treatment effect of EVT and found that patients whose admission glucose range between 90 and 100 mg/dL (5.0–5.5 mmol/L) had the highest treatment benefit of EVT.[21] Another post hoc analysis of the Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism (RESCUE) Japan Registry 2 showed that postprocedural sICH within 72 h were found to occur more frequently in the hyperglycemia group. Additionally, including sICH as a confounding variable in the multivariate regression model did not modify the association between

hyperglycemia and clinical outcomes, which suggested sICH is not an intermediate factor between the relationship of hyperglycemia and unfavorable outcomes.[26] These studies mainly concentrated on the association between admission hyperglycemia and outcomes after EVT. However, it is unclear whether the sICH occurrence after EVT in hyperglycemic patients leads to a further deterioration in stroke prognosis and the existing clinical evidence is scarce. Nonetheless, this relationship between the two should be emphasized and further explored as a means of identifying and intervening early in the acute stage of stroke and improving stroke outcomes.

Notably, regarding stroke with LVO, most of studies mainly included patients with anterior circulation stroke. Nevertheless, LVO in the posterior circulation should also be considered due to its high mortality and disability rates. In our analysis, patients with posterior and anterior circulation large vessel occlusion were both included and baseline characteristics show that more than one-third of patients presented with admission hyperglycemia, which is consistent with previous studies.[21] A wider range of population would make the conclusions more generalizable.

Although hyperglycemia has been shown to be an independent risk factor associated with poor prognosis, the efficacy of intensive glucose control remains controversial. Previous studies have demonstrated that in patients with critical illness or in surgical intensive care units (ICUs), intensive insulin therapy has definite benefits.[27,28] On the contrary, the Stroke Hyperglycemia Insulin Network Effort (SHINE) randomized clinical trial did not report this intervention, could improve favorable outcome at 90 days.[29] Even more, some studies have indicated that tight glucose control may be associated with large infarct sizes.[30] Intensive glucose control does reduce the harm caused by the elevation of plasma glucose but also increases the risk of hypoglycemia. Further studies are needed in the future to confirm the exact effects of intensive glucose control.

Our study has some limitations. First, it was a post hoc analysis and not prespecified, so it has the usual drawbacks of an observational study design, and inevitable biases may exist.[31] Second, patients with missing admission glucose value were excluded from our analysis. Additionally, we did not record repeated measurements of patients' glucose values during hospitalization, and this may help to confirm further effects of changes in glucose on stroke outcomes in our study. Third, the effect of intense glucose control in patients with hyperglycemia was not investigated in our study. Future studies should explore the robust evidence for glucose management based on previous study.

Conclusions

In conclusion, our study demonstrated that admission hyperglycemia might independently predict poor neurological functional prognosis and increased mortality in LVO stroke patients with sICH occurrence after EVT. Therefore, early identification of hyperglycemic patients during the urgent stage of stroke may contribute to improving the clinical prognosis of acute LVO stroke.

Abbreviations

ASPECTS, Alberta Stroke Program Early Computed Tomography Score; ASTIN/SIR, American Society of Intervention and Therapeutic Neuroradiology/Society of Interventional Radiology; CT, computer tomography; CTA, computer tomography angiography; EVT, endovascular treatment; ICU, intensive care unit; IQR, interquartile range; LVO, large vessel occlusion; mRS, modified Rankin scale; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; mTICI, modified Thrombolysis In Cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SHINE trial, the Stroke Hyperglycemia Insulin Network Effort trial; sICH, symptom intracranial hemorrhage; TIA, transient ischemic attack; TOAST, the Trial of Org 10172 in Acute Stroke Treatment.

Data Sharing Statement

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

Ethics Approval and Informed Consent

The study protocols were approved by the ethics committee of the Second Affiliated Hospital of the Army Medical University and all participating centers. Written informed consent was obtained from the patient or patient's representative, as required by national and local guidelines.

Consent for Publication

All authors approved the publication of this article.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas. All authors took part in drafting, revising or critically reviewing the article and gave final approval of the version to be published. All authors have agreed on the journal to which the article has been submitted and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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