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ORIGINAL RESEARCH

Association Between Admission Hyperglycemia and Outcomes After Endovascular Treatment in Acute Basilar Artery Occlusion

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ABSTRACT

Introduction: Admission hyperglycemia and high admission blood glucose levels have been associated with poor outcomes in acute ischemic stroke. However, the relationship between admission hyperglycemia and outcomes after endovascular treatment (EVT) in acute basilar artery occlusion (ABAO) still remain unclear. This study aimed to investigate the association between admission hyperglycemia and clinical outcomes in ABAO following EVT.

Methods: Patients from the BASILAR registry with admission blood glucose levels treated with EVT were included. We defined admission hyperglycemia as blood glucose levels ≥ 7.8 mmol/L. The primary outcome was favorable outcome [defined as a modified Rankin Scale score (mRS) of 0–3] at 90 days, Secondary outcomes included other functional outcomes (mRS 0–2, mRS 0–1) at 90 days, symptomatic intracerebral hemorrhage (sICH) within 48 h, and mortality at 90 days.

Results: Of 545 eligible patients included, the median age was 65 (IQR, 56–73) years, and median blood glucose level was 7.36 (IQR, 6.10–9.66) mmol/L. Multivariable logistic regression analysis showed that admission hyperglycemia was associated with decreased favorable outcome (mRS 0–3) (adjusted odds ratio = 0.52; 95% CI 0.35–0.79; $P = 0.001$), and increased mortality (adjusted odds ratio = 2.67; 95% CI 1.82–3.91; $P < 0.001$). Restricted cubic spline regression analysis showed that the blood glucose level had a non-linearity association with favorable outcome and mortality, and that

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there was no association between admission hyperglycemia and sICH.
Conclusions: Our study suggest that admission hyperglycemia is associated with an increased risk of poor functional outcomes and mortality in patients with ABAO treated with EVT.
Trial Registration: Chinese Clinical Trial Registry (http://www.chictr.org.cn), ChiCTR180001475.

Keywords: Admission hyperglycemia; Stroke; Acute basilar artery occlusion; Endovascular treatment; Blood glucose

Key Summary Points

Why carry out this study?

High admission blood glucose levels have been associated with poor outcomes in anterior circulation acute ischemic stroke. However, the relationship between admission hyperglycemia and outcomes after endovascular treatment (EVT) in acute basilar artery occlusion (ABAO) still remain unclear. This study aimed to explore the association between admission hyperglycemia and clinical outcomes in ABAO following EVT.

What was learned from the study?

Statistical analysis showed that admission hyperglycemia was associated with reduced favorable outcome and increased mortality in ABAO patients.

Our study provides evidence that admission hyperglycemia is associated with an increased risk of poor functional outcomes and mortality in patients with ABAO treated with EVT. The addition of admission hyperglycemia to decision-support tools for endovascular treatment should be evaluated in future studies.

INTRODUCTION

Glucose is essential for normal cerebral function but may also aggravate ischemic brain injury [1]. Hyperglycemia is commonly found in patients with or without preexisting diabetes mellitus in the acute phase of ischemic stroke, with a proportion of approximately 40% [2]. Several studies have shown that admission hyperglycemia is associated with worse functional outcome and lower recanalization rates after acute ischemic stroke (AIS), whether or not patients were treated with intravenous thrombolysis (IVT) [3–5]. There are several mechanisms by which high blood glucose level might exert detrimental effects on the brain: hyperglycemia may promote intracellular acidosis within the ischemic penumbra, induce free radical formation, damage the blood–brain barrier causing brain edema, and exacerbate the thrombo-inflammatory cascade [6].

With the advent of endovascular treatment (EVT) as the new standard of therapeutic strategy for patients in AIS with large-vessel occlusion, patients treated with EVT have the highest rate of recanalization of the occluded vessel [7]. The association between admission hyperglycemia and clinical outcomes in acute ischemic stroke after EVT have also been evaluated in previous studies [8–11]. In addition, the above studies were either performed in selected patient populations from randomized trials or in cohort studies on anterior circulation or just included a small sample of basilar artery populations.

To date, due to the lack of a large sample size of patients with acute basilar artery occlusion, the relationship between admission hyperglycemia and outcomes after EVT in acute basilar artery occlusion (ABAO) still remain unclear. Therefore, this study aimed to explore the association between admission hyperglycemia and clinical outcomes in ABAO following EVT.

METHODS

Study Design and Patient Selection

We used data from the BASILAR registry [12]. BASILAR was a prospective cohort study from January 2014 to May 2019, including 47 stroke centers. For the current study, we used data of all patients treated with EVT. All participating subcenters were obligated to recruit consecutive patients, and all patients or their legal representatives supplied informed consent. Inclusion criteria were as follows: (1) age greater than or equal to 18 years; (2) the estimated time of ABAO was presented within 24 h; (3) ABAO proven by using imaging examinations such as computed tomography angiography, magnetic resonance angiography, or digital subtraction angiography; (4) patients with admission blood glucose levels treated with EVT; and (5) ability to provide informed consent. Exclusion criteria were as follows: (1) clinically significant disability with a modified Rankin score (mRS) > 2; (2) neuroimaging confirmed the presence of cerebral hemorrhage; (3) missing 90-day follow-up information; (4) currently pregnant or lactating; (5) severe, advanced, or terminal illness; and (6) incomplete baseline image and time measurement data. This study involves human participants and was approved by Xinqiao Hospital Affiliated to Army Medical University. ID: 201308701. Participants gave informed consent to participate in the study before taking part. The study was conducted in accordance with the 1964 Declaration of Helsinki.

Data Collection

Baseline characteristics, including demographics, stroke risk factors, admission serum glucose, and other laboratory data were recorded as previously described. The National Institutes of Health Stroke Scale (NIHSS) scores, The Trial of ORG10172 in Acute Stroke Treatment classification, the posterior circulation Alberta Stroke Program Early Computed Tomography Score (pc-ASPECTS) and the modified thrombolysis in cerebral infarction scale, in which a grade of 2b or 3 indicates successful reperfusion after EVT, were recorded as previously described. We defined admission hyperglycemia as an admission serum glucose $\geq$ 7.8 mmol/L, as described in previous studies [8, 9].

Outcome Measures

The main outcome was defined as an mRS score (range 0–6, with 0 indicating no disability, and 6 indicating death) of 0–3 at 90 days. Other clinical outcomes were defined as an mRS score of 0–2 or 0–1 at 90 days. Safety outcomes included 90-day mortality and symptomatic intracerebral hemorrhage (sICH) within 48 h, as confirmed by neuroimaging (CT or MRI). sICH was defined according to the Heidelberg Bleeding Classification [13].

Statistical Analysis

We compared patients with hyperglycemia on admission to those without hyperglycemia on admission. Continuous data were provided as mean (SD) or median (IQR) and compared using Student's *t* test or nonparametric tests. Categorical data were provided as proportions and compared using the chi-square test or Fisher exact test. For the main outcome and other clinical outcomes, we used a multivariable logistic regression analysis model and adjusted for the following confounders: age, sex, hypertension, atrial fibrillation, severity of stroke onset, initial NIHSS scores, stroke etiology, and occlusion site. We calculated the odds ratio (OR) with 95% confidence intervals (CI) to indicate statistical precision. For sensitivity analysis, we examined the admission hyperglycemia and clinical outcomes relationship on a subset of the population achieving successful reperfusion, or after excluding patients with diabetes mellitus, because previous studies have shown that these patients have worse outcomes in the presence of hyperglycemia [11, 14].

We used continuous measures of admission glucose as the independent variable in an adjusted multivariable logistic regression model. To explore the likelihood of non-linearity between blood glucose and clinical outcomes at 90 days (mRS 0–3, mRS 0–2, mortality,

sICH), glucose was modeled as a restricted cubic spline. We chose 3 knots within the restricted cubic spline function at the 10%, 50%, and 90% percentiles. The reference point was the median value of admission blood glucose levels. Then, we performed restricted cubic spline modeling with adjustment for the following confounders: age, hypertension, atrial fibrillation, severity of stroke onset, initial NIHSS scores, and stroke etiology. We explored the potential nonlinear relationship of admission blood glucose with clinical outcomes.

The differences in area under the curve values of receiver operating characteristic curves were compared using the DeLong test [15], and we used the Kaplan–Meier method to compare mortality in patients with and without hyperglycemia at presentation. During the 1-year follow-up, the log-rank test was used to compare the survival curves of the groups. A subgroup analysis for heterogeneity of hyperglycemia effect was performed, with subgroups defined according to age (≤ 65 or > 65 years), sex, severity of stroke onset (mild to moderate or severe), baseline NIHSS score (< 27 or ≥ 27), stroke etiology (LAA, CE or others), and occlusion site (BA distal, BA middle, BA proximal, and VA-V4).

The significance level was set to $P < 0.05$, and all hypothesis testing was two-sided. We did not perform imputation for missing data, since these were minimal. Statistical analyses were performed using SPSS (v.26.0) and R software (v.4.1.0).

RESULTS

Patient Characteristics

Of the 647 patients treated with EVT in the BASILAR Registry, we excluded 102 patients for missing admission glucose levels. In total, 242 of 545 (44.4%) patients had hyperglycemia on admission (Figure S1 in Supplementary Material).

The patients' baseline characteristics are described in Table 1. The median age was 65 years (IQR, 56–73), and the median blood glucose level was 7.36 (IQR, 6.10–9.66) mmol/L. Patients with hyperglycemia on admission had a higher median NIHSS scores at baseline (28 vs. 25; $P = 0.009$) and higher systolic blood pressure (152 vs. 145; $P < 0.001$). Hyperglycemic patients more often had a history of diabetes mellitus (39.3% vs. 7.9%; $P < 0.001$) and hypertension (76.4% vs. 64%; $P = 0.002$). Patients with hyperglycemia had higher admission blood glucose and glycated hemoglobin than those in the normoglycemic group. The rate of intravenous thrombolysis was similar in both groups. Other baseline clinical manifestations and risk factors did not differ between groups.

Hyperglycemia and Outcome

The study outcomes are presented in Fig. 1A and Table 2. Figure 1A shows the mRS distribution between 2 groups of all the patients with hyperglycemia on admission compared with normoglycemia patients. With adjusted covariates, the multivariable logistic regression analysis showed that admission hyperglycemia was associated with reduced favorable outcome [mRS 0–3; 25.2% vs. 40.6%; adjusted odds ratio (aOR), 0.52, 95% CI 0.35–0.79; $P = 0.002$]. Likewise, admission hyperglycemia was negatively correlated with good outcome (mRS 0–2; 20.2% vs. 35.0%; OR, 0.50; 95% CI 0.33–0.77; $P = 0.001$) and excellent outcome (mRS 0–1; 12.0% vs. 29.7%; OR, 0.33; 95% CI 0.20–0.54; $P < 0.001$). Mortality at 90 days was higher for patients with hyperglycemia on admission (58.7% vs. 33.3%; aOR, 2.67, 95% CI 1.82–3.91; $P < 0.001$). There were no differences in the rates of sICH between groups (8.4% vs. 6.3%; aOR, 1.02, 95% CI 0.51–2.05; $P = 0.952$) (Table 2). The sensitivity analyses showed that, in the subset of patients with successful reperfusion or in the subset of patients without preexisting diabetes mellitus, they essentially yielded similar results (Fig. 1B, C; Table 2).

When we stratified by severity of admission glucose levels, we found that severe admission hyperglycemia was a stronger predictor for poor outcome than mild hyperglycemia (Figure S2 in Supplementary Material). Also, there was a significant difference ($P < 0.001$, log-rank test) in

Table 1 Baseline characteristics

Variables	All patients 545	No admission hyperglycemia 303	Admission hyperglycemia 242	*P* value
Age, years, median (IQR)	65 (56–73)	64.00 (56–72)	65 (57–74)	0.265
Sex, male, *n* (%)	406 (74.5)	235 (77.6)	171 (70.7)	0.083
SBP, median (IQR)	149 (133–166)	145 (130–160)	152 (139–174)	< 0.001
Smoking, *n* (%)	191 (35.0)	113 (37.3)	78 (32.2)	0.254
NIHSS baseline (median (IQR))	27 (16–33)	25 (15–32)	28 (18–34)	0.009
pc-ASPECTS baseline (median (IQR))	8 (7–9)	8 (7–9)	8 (7–9)	0.083
Medical history, *n* (%)				
Hypertension	379 (69.5)	194 (64.0)	185 (76.4)	0.002
Diabetes mellitus	119 (21.8)	24 (7.9)	95 (39.3)	< 0.001
Atrial fibrillation	117 (21.5)	59 (19.5)	58 (24.0)	0.244
Cerebral infarction	118 (21.7)	66 (21.8)	52 (21.5)	1
Biochemical variables, (median (IQR))				
Triglyceride (median (IQR)), mmol/l	1.21 (0.80–1.82)	1.16 (0.79–1.65)	1.31 (0.84–2.06)	0.103
Total cholesterol (median (IQR)), mmol/l	4.54 (3.80–5.54)	4.48 (3.80–5.34)	4.75 (3.82–5.80)	0.029
Admission glucose (median (IQR)), mmol/l	7.36 (6.10–9.66)	6.25 (5.61–6.98)	10.11 (8.52–12.57)	< 0.001
HbA1C (median (IQR))	5.90 (5.50–6.60)	5.70 (5.40–6.10)	6.30 (5.80–7.80)	< 0.001
Stroke etiology, *n* (%)				0.186
LAA	349 (64.0)	196 (64.7)	153 (63.2)	
CE	149 (27.3)	76 (25.1)	73 (30.2)	
Other causes	47 (8.6)	31 (10.2)	16 (6.6)	
Occlusion location, *n* (%)				0.094
BA distal	184 (33.8)	107 (35.3)	77 (31.8)	
BA middle	162 (29.7)	99 (32.7)	63 (26.0)	
BA proximal	96 (17.6)	48 (15.8)	48 (19.8)	
VA-V4	103 (18.9)	49 (16.2)	54 (22.3)	
Anesthesia, *n* (%)	330 (61.2)	193 (64.3)	137 (57.3)	0.116
Intravenous thrombolysis, *n* (%)	98 (18.0)	48 (15.8)	50 (20.7)	0.179
Successful reperfusion, *n* (%)	444 (81.5)	259 (85.5)	185 (76.4)	0.01

Table 1 continued

Variables	All patients 545	No admission hyperglycemia 303	Admission hyperglycemia 242	*P* value
Time variables, median, (IQR), min				
OTP time	326 (221–496)	323 (219–500)	328 (226–491)	0.921
OTR time	442 (328–621)	445 (327–623)	439.00 (337–618)	0.86

CE cardio-embolism, *EVT* endovascular treatment, *IQR* interquartile range, *LAA* large artery atherosclerosis, *mRS* modified Rankin Scale, *NIHSS* National Institutes of Health Stroke Scale, *OTP*, onset to puncture, *OTR* onset to recanalization, *pc-ASPECTS* posterior circulation Alberta Stroke Program Early Computed Tomography Score, *PC-CS score* posterior circulation collateral system score, *SBP* systolic blood pressure, *sICH* Symptomatic intracranial hemorrhage, *TIA* transient ischemic attack, *VA* vertebral artery

survival rate between groups during the follow-up of 1 year (Figure S3 in Supplementary Material).

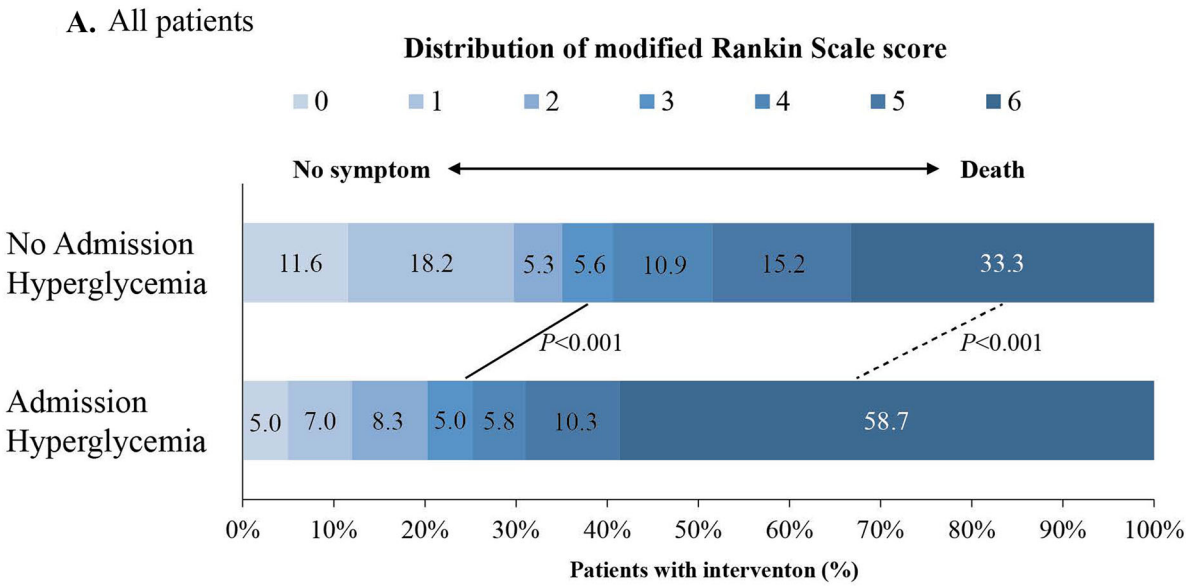
Glucose as a Continuous Variable and Outcome

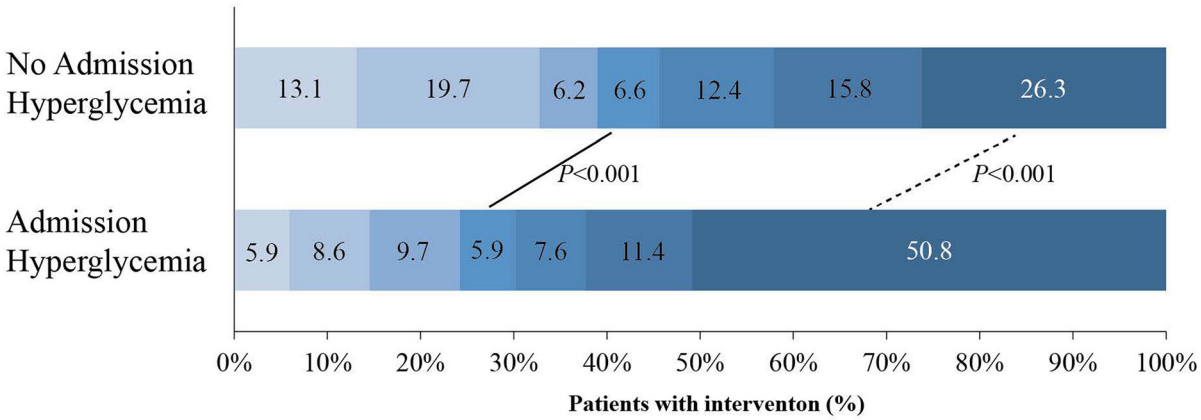
By using a regression model with a restricted cubic spline, we found an association between admission blood glucose and clinical outcomes. Figure 2 assesses admission blood glucose as a restricted cubic spline rather than as a categorical variable. There was evidence of a nonlinear relationship between admission blood glucose and favorable outcome (mRS 0–3) ($P_{\text{non-linear}} = 0.043$, Fig. 2A). The restricted cubic spline for the favorable outcome (mRS 0–3) was negatively sloped, and there was a similar nonlinear relationship between admission blood glucose and good outcome (mRS 0–2) ($P_{\text{non-linear}} = 0.039$, Fig. 2B). Additionally, there was a nonlinear relationship between admission blood glucose and mortality ($P_{\text{non-linear}} = 0.025$, Fig. 2C). The restricted cubic spline for the mortality was positively sloped, and there was no nonlinear relationship between admission blood glucose and sICH ($P_{\text{non-linear}} = 0.661$, Fig. 2D).

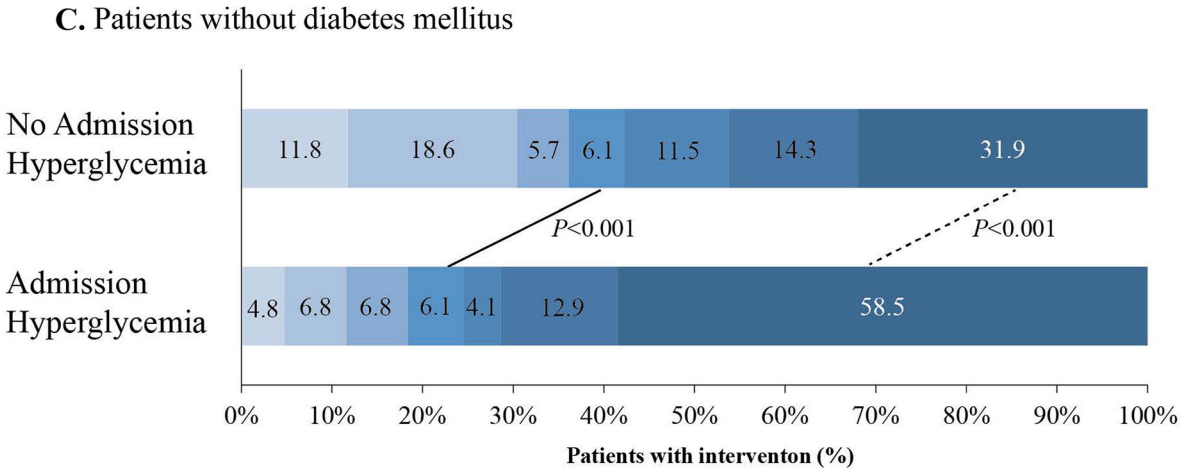
Additionally, we evaluated the association of other glucose parameters and clinical outcomes after EVT. The admission HbA1c level was not associated with the outcomes (mRS 0–3, mRS 0–2, and mRS 0–1) but associated with mortality after EVT, and there was significant difference in the area under the curve values of the receiver operating characteristic for mRS 0–3, mRS 0–2, mRS 0–1, and mortality between admission blood glucose and the HbA1c level parameter (Table S1; Figure S4 in Supplementary Material). In the multivariable logistic regression analysis, with admission blood glucose level and HbA1c level as continuous variables, the admission blood glucose level was a significant negative predictor of functional outcomes, However, this association was not found in the HbA1c level. These two glucose parameters were also associated with mortality at 3 months (Table S1 in Supplementary Material).

Subgroup Analyses

A subgroup analysis was performed to investigate the relationship between the 2 groups and 90-day favorable outcome (mRS 0–3). The cutoff values and subgroup categories were based on the median values, including those based on age, sex, severity of stroke onset, baseline NIHSS score, stroke etiology, and occlusion site. The results showed no significant heterogeneity


A. All patients
Distribution of modified Rankin Scale score
0
1
2
3
4
5
6
No symptom
Death
No Admission Hyperglycemia
11.6
18.2
5.3
5.6
10.9
15.2
33.3
P<0.001
P<0.001
Admission Hyperglycemia
5.0
7.0
8.3
5.0
5.8
10.3
58.7
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
Patients with interventon (%)


B. Patients with successful reperfusion
No Admission Hyperglycemia
13.1
19.7
6.2
6.6
12.4
15.8
26.3
P<0.001
P<0.001
Admission Hyperglycemia
5.9
8.6
9.7
5.9
7.6
11.4
50.8
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
Patients with interventon (%)


C. Patients without diabetes mellitus
No Admission Hyperglycemia
11.8
18.6
5.7
6.1
11.5
14.3
31.9
P<0.001
P<0.001
Admission Hyperglycemia
4.8
6.8
6.8
6.1
4.1
12.9
58.5
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
Patients with interventon (%)

◀**Fig. 1** The distribution of the modified Rankin scale scores at 90 days. Clinical outcomes at day 90 follow-up in patients in the admission hyperglycemia group vs. no admission hyperglycemia group. **A** All patients; **B** patients with successful reperfusion; **C** patients without diabetes mellitus. *BAO* basilar artery occlusion, *EVT* endovascular treatment

across any of the prespecified subgroups (Figure S5 in Supplementary Material).

DISCUSSION

To our knowledge, this study is the first to highlight the association between admission hyperglycemia and functional outcomes in ABAO patients treated with EVT. Our study confirms the notion that admission hyperglycemia is an independent predictor of worse functional outcomes and mortality in ABAO patients treated with EVT; however, no similar association was found in sICH. Further analysis showed a non-linear association between admission glucose levels and poor functional outcomes and mortality.

Published studies of admission hyperglycemia in stroke patients treated with EVT often focus on the anterior circulation ischemic stroke [9, 11, 16]. However, less attention has been paid to ischemic stroke in the posterior circulation or basilar artery, with few literature and sample sizes or proportions generally small, the majority of which examined smaller numbers of ABAO stroke patients [8, 10]. Our findings bolster and expand on those of previous studies, as this prospective cohort study is the largest yet to report on the relationship of admission glucose exclusively in ABAO patients treated uniformly with EVT. In our results, about 40 % of the patients had admission hyperglycemia, which is a high proportion

Table 2 Clinical outcomes at 90 days

Outcome	No admission hyperglycemia (n = 303), n (%)	Admission hyperglycemia (n = 242), n (%)	Model 1[a]		Model 2[b]		Model 3[c]	
			Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Favorable outcome, mRS 0–3	123 (40.6)	61 (25.2)	0.52 (0.35–0.79)	0.002	0.55 (0.36–0.86)	0.009	0.43 (0.26–0.70)	0.001
Good outcome, mRS 0–2	106 (35.0)	49 (20.2)	0.50 (0.33–0.77)	0.001	0.54 (0.34–0.86)	0.009	0.37 (0.22–0.64)	< 0.001
Excellent outcome, mRS 0–1	90 (29.7)	29 (12.0)	0.33 (0.20–0.54)	< 0.001	0.37 (0.22–0.63)	< 0.001	0.28 (0.15–0.52)	< 0.001
Mortality	101 (33.3)	142 (58.7)	2.67 (1.82–3.91)	< 0.001	2.67 (1.72–4.15)	< 0.001	3.01 (1.92–4.74)	< 0.001
sICH	19 (6.3)	20 (8.4)	1.02 (0.51–2.05)	0.952	0.68(0.28–1.64)	0.391	0.95 (0.42–2.16)	0.894

mRS modified Rankin Scale, *OR* odds ratio, *CI* confidence interval, *IQR* interquartile range, *sICH* symptomatic intracranial hemorrhage

[a]Model 1 adjusted for age, sex, hypertension, atrial fibrillation, severity of stroke onset, initial NIHSS scores, stroke etiology and occlusion site

[b]Model 2 excluded patients without successful reperfusion and adjusted for confounding factors in model 1

[c]Model 3 excluded patients without diabetes mellitus and adjusted for confounding factors in model 1

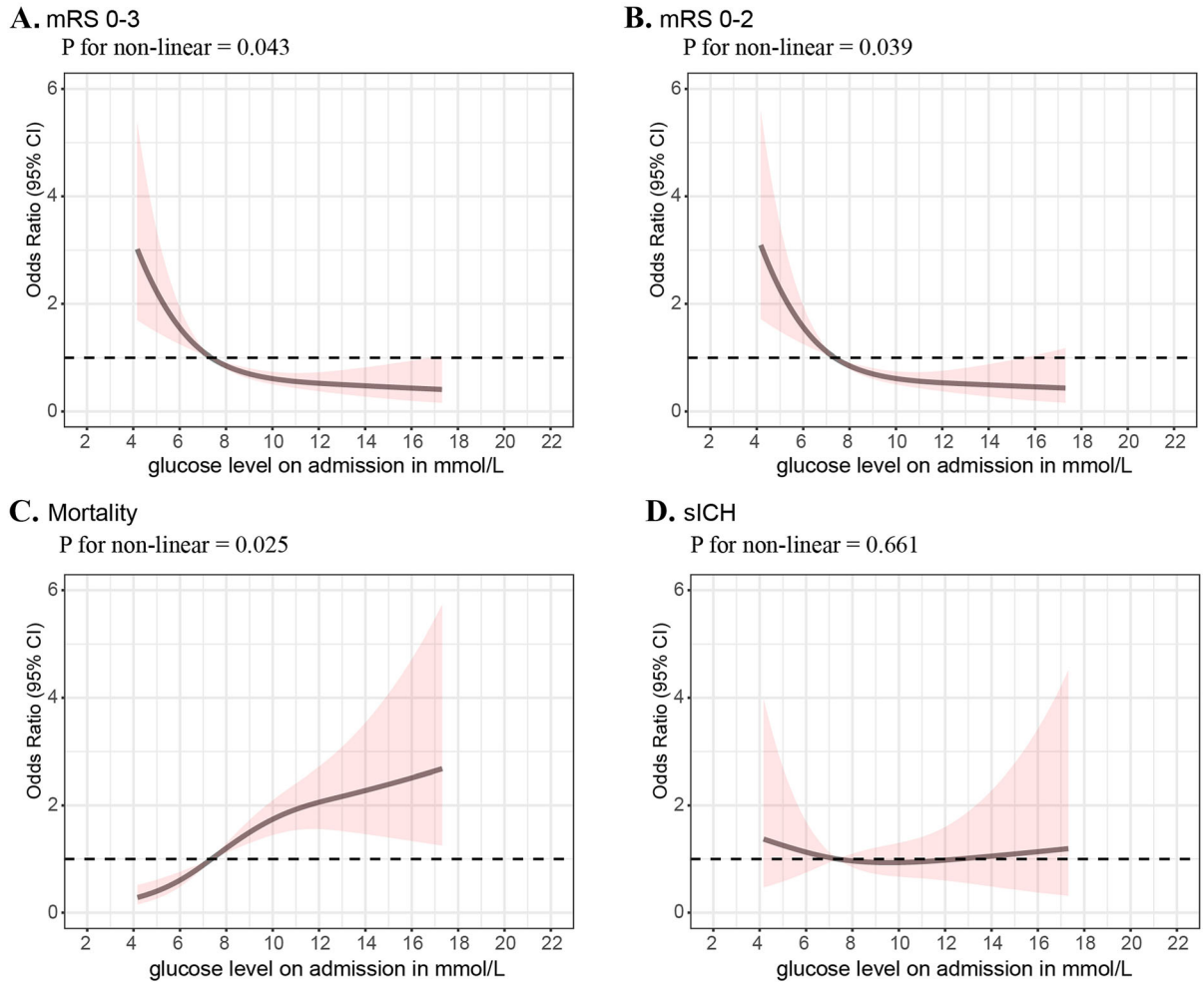


Fig. 2 Admission blood glucose as a continuous variable and the odds ratio of clinical outcomes (mRS 0–3, mRS 0–2, mortality and sICH) at 90 days. The association between admission blood glucose and clinical outcomes including 95% CI is shown. Data were fitted using a multivariable logistic regression model of restricted cubic spline with 3 knots (at the 10th, 50th, and 90th percentiles) adjusting for covariates. The reference point was the median value of admission blood glucose levels (7.36 mmol/L). *Black curves* indicate the adjusted odds ratio and *red shading* indicates the 95% CI bands. **A** mRS 0–3; **B** mRS 0–2; **C** mortality; **D** sICH

compared to previous studies [8, 9, 11]. Published studies of baseline hyperglycemia often report 3-month outcomes or discharge clinical outcomes; we also report the additional 1-year clinical outcomes.

Previous studies have used different cutoff levels to define hyperglycemia (from 7.8 to 10 mmol/l) [3, 11, 17]; however, all of them have suggested an increased risk of worse outcome with elevated blood glucose levels. Our results are in line with those of previous studies that explored the association between blood glucose on admission and functional outcomes in ABAO patients after EVT.

A subgroup analysis of the HERMES (the highly effective reperfusion using multiple endovascular devices collaboration) study [18] showed that higher glucose levels on admission are associated with worse functional outcome, and that glucose levels changed the treatment effect of EVT, with smaller benefit for patients with glucose levels higher than 5.5 mmol/L.

The post hoc analysis of SWIFT (Solitaire flow restoration device vs. the Merci Retriever in patients with AIS) trial [19] demonstrated that admission hyperglycemia was an independent predictor of excellent outcome (defined as mRS 0–1) in patients treated with EVT. However, admission hyperglycemia or admission blood glucose levels were not associated with good outcome (defined as mRS 0–2), complete reperfusion, sICH, and mortality at 90 days. Another post hoc analysis of the MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) trial [16] demonstrated that increased glucose on admission did not modify the effect of IAT in patients with acute ischemic stroke due to intracranial proximal arterial occlusion of the anterior circulation. There were contradictory findings from these studies and the role of hyperglycemia as a predictor after EVT is still ambiguous.

Pulmonary infection occurred more frequently in patients with admission hyperglycemia. The association between hyperglycemia and the occurrence of infections has previously been described in patients with acute ischemic stroke [9, 20]. However, our results did not show evidence that the onset of post-stroke infection mediated or explained the association between admission hyperglycemia and poor functional outcome. It still remains unclear whether post-stroke infection explains the higher risks of worse outcomes.

HbA1c (glycated hemoglobin) is a well-established marker for blood glucose levels and is widely used to assess the average glucose during the last 3 months in patients to monitor diabetes mellitus damage. HbA1c has also been analyzed as a predictor in patients treated with EVT in anterior circulation. Previous studies have evaluated the effects of increasing levels of HbA1c on clinical outcome after EVT and showed reduced functional independence, increased sICH, and increased mortality [21, 22]. Similar results were also reported in our BASILAR registry subgroup analysis [23].

In our study, with blood glucose as a continuous variable, a nonlinear relationship was observed between admission blood glucose and clinical outcomes. Before EVT as a routine clinical strategy, Poppe et al. described a nonlinear association between admission hyperglycemia and functional outcome and sICH in stroke patients treated with IVT [3]. A post hoc analysis of the POINT (Platelet Oriented Inhibition in New TIA and Minor Ischemic Stroke) trial suggests that there was evidence of a nonlinear relationship between serum glucose and subsequent stroke risk [24]. Recently, two previous studies have also reported a J-shaped nonlinear association between admission glucose and functional outcomes in patients with acute ischemic stroke [9, 25]. However, we did not find a typical J-shaped association between glucose and functional outcome in our study, which may be due to the limited number of patients.

If there is a causal relationship between hyperglycemia and clinical outcomes after stroke, whether or not glucose lowering had a positive impact on outcome in patients with stroke. To date, no evidence supports the concept that ensuring strict post-stroke normoglycemia improves outcome. The THIS (Treatment of Hyperglycemia in Ischemic Stroke) trial [26] hinted a benefit of aggressive glucose lowering treatment; however, only 46 patients were enrolled in this pilot study. The GIST-UK (Glucose Insulin in Stroke UK Trial) trial [27] was stopped early and was underpowered, but it showed no difference in clinical outcomes between patients randomly assigned to receive glucose–potassium–insulin or saline as a continuous intravenous infusion for 24 h. The lack of clinical benefit may be related to starting treatment after stroke relatively late (median 14 h) and the small mean reduction in blood glucose achieved in the treatment group (0.57 mmol/L).

The recent randomized SHINE (Stroke Hyperglycemia Insulin Network Effort) trial [28] compared intensive glucose lowering with standard treatment in 1151 AIS patients with hyperglycemia, and there was no difference in outcome between the 2 groups. However, in this study, only a small proportion (13%) of patients underwent EVT, while the authors did not provide a subgroup analysis limited to patients treated with EVT. In agreement with our observations, the SHINE trial did not find a

difference in the incidence of ICH between the groups.

Limitations

We acknowledge that our study has several limitations. First, it is an observational cohort study and our data are prone to possible bias and shortcomings, and further clinical trials are needed to determine whether patients treated with EVT may benefit from early intensive glucose-lowering therapy. Second, our results are based on just a single admission glucose level, and there was no continuous blood glucose monitoring data. However, use of a single baseline glucose level presumably underestimates potential damage, because patients with the highest admission glucose levels would most likely have been treated earlier and more aggressively with glucose-lowering therapies. Third, the method of blood glucose determination was not uniform, with either capillary blood or venous blood glucose measurements used at different sites. Fourth, we have no additional information about blood glucose level management during hospitalization or after discharge. And fifth, due to the time of onset in our enrolled population, a lower proportion of patients received intravenous thrombolytic therapy before EVT in our study compared with other studies.

CONCLUSIONS

Our study suggests that admission hyperglycemia is associated with an increased risk of poor functional outcomes and mortality in patients with ABAO treated with EVT. It is apparent that admission hyperglycemia rapidly identifies patients at higher risk for poor clinical outcomes in whom glucose levels should be closely monitored.

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Compliance with Ethics Guidelines. This study involves human participants and was approved by Xinqiao Hospital Affiliated to Army Medical University. ID: 201308701. Participants gave informed consent to participate in the study before taking part. The study was conducted in accordance with the 1964 declaration of Helsinki.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Martini SR, Kent TA. Hyperglycemia in acute ischemic stroke: a vascular perspective. J Cereb Blood Flow Metab. 2007;27:435–51.

2. Williams LS, Rotich J, Qi R, Fineberg N, Espay A, Bruno A, et al. Effects of admission hyperglycemia on mortality and costs in acute ischemic stroke. Neurology. 2002;59:67–71.

3. Poppe AY, Majumdar SR, Jeerakathil T, Ghali W, Buchan AM, Hill MD. Admission hyperglycemia predicts a worse outcome in stroke patients treated with intravenous thrombolysis. Diabetes Care. 2009;32:617–22.

4. Desilles JP, Meseguer E, Labreuche J, Lapergue B, Sirimarco G, Gonzalez-Valcarcel J, et al. Diabetes mellitus, admission glucose, and outcomes after stroke thrombolysis: a registry and systematic review. Stroke. 2013;44:1915–23.

5. Costalat V, Lobotesis K, Machi P, Mourand I, Maldonado I, Heroum C, et al. Prognostic factors related to clinical outcome following thrombectomy in ischemic stroke (recost study). 50 patients prospective study. Eur J Radiol. 2012;81:4075–82.

6. Desilles JP, Syvannarath V, Ollivier V, Journé C, Delbosc S, Ducroux C, et al. Exacerbation of thromboinflammation by hyperglycemia precipitates cerebral infarct growth and hemorrhagic transformation. Stroke. 2017;48:1932–40.

7. Badhiwala JH, Nassiri F, Alhazzani W, Selim MH, Farrokhyar F, Spears J, et al. Endovascular thrombectomy for acute ischemic stroke: a meta-analysis. JAMA. 2015;314:1832–43.

8. Goyal N, Tsivgoulis G, Pandhi A, Dillard K, Katsanos AH, Magoufis G, et al. Admission hyperglycemia and outcomes in large vessel occlusion strokes treated with mechanical thrombectomy. J Neurointerv Surg. 2018;10:112–7.

9. Rinkel LA, Nguyen TTM, Guglielmi V, Groot AE, Posthuma L, Roos Y, et al. High admission glucose is associated with poor outcome after endovascular treatment for ischemic stroke. Stroke. 2020;51:3215–23.

10. Yazawa Y, Ohira T, Itabashi R, Uchida K, Sakai N, Yamagami H, et al. Association of admission hyperglycemia with clinical outcomes in japanese patients with acute large vessel occlusion stroke: a post hoc analysis of the recovery by endovascular salvage for cerebral ultra-acute embolism japan registry 2. Cerebrovasc Dis. 2021;50:12–9.

11. Kim JT, Liebeskind DS, Jahan R, Menon BK, Goyal M, Nogueira RG, et al. Impact of hyperglycemia according to the collateral status on outcomes in mechanical thrombectomy. Stroke. 2018;49:2706–14.

12. Zi W, Qiu Z, Wu D, Li F, Liu H, Liu W, et al. Assessment of endovascular treatment for acute basilar artery occlusion via a nationwide prospective registry. JAMA Neurol. 2020;77:561–73.

13. von Kummer R, Broderick JP, Campbell BC, Demchuk A, Goyal M, Hill MD, et al. The Heidelberg bleeding classification: classification of bleeding events after ischemic stroke and reperfusion therapy. Stroke. 2015;46:2981–6.

14. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. Stroke. 2001;32:2426–32.

15. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;44:837–45.

16. Osei E, den Hertog HM, Berkhemer OA, Fransen PSS, Roos Y, Beumer D, et al. Admission glucose and effect of intra-arterial treatment in patients with acute ischemic stroke. Stroke. 2017;48:1299–305.

17. Robbins NM, Swanson RA. Opposing effects of glucose on stroke and reperfusion injury: acidosis, oxidative stress, and energy metabolism. Stroke. 2014;45:1881–6.

18. Chamorro Á, Brown S, Amaro S, Hill MD, Muir KW, Dippel DWJ, et al. Glucose modifies the effect of endovascular thrombectomy in patients with acute stroke. Stroke. 2019;50:690–6.

19. Kim JT, Jahan R, Saver JL. Impact of glucose on outcomes in patients treated with mechanical thrombectomy: a post hoc analysis of the solitaire flow restoration with the intention for thrombectomy study. Stroke. 2016;47:120–7.

20. Zonneveld TP, Nederkoorn PJ, Westendorp WF, Brouwer MC, van de Beek D, Kruyt ND. Hyperglycemia predicts poststroke infections in acute ischemic stroke. Neurology. 2017;88:1415–21.

21. Diprose WK, Wang MTM, McFetridge A, Sutcliffe J, Barber PA. Glycated hemoglobin (hba1c) and outcome following endovascular thrombectomy for ischemic stroke. J Neurointerv Surg. 2020;12:30–2.

22. Choi KH, Kim JH, Kang KW, Kim JT, Choi SM, Lee SH, et al. Hba1c (glycated hemoglobin) levels and clinical outcome post-mechanical thrombectomy in patients with large vessel occlusion. Stroke. 2018: Strokeaha118021598.

23. Yue F, Wang Z, Pu J, Zhang M, Liu Y, Han H, et al. Hba1c and clinical outcomes after endovascular treatment in patients with posterior circulation large vessel occlusion: a subgroup analysis of a nationwide registry (basilar). Ther Adv Neurol Disord. 2020;13:1756286420981354.

24. Mac Grory B, Piccini JP, Yaghi S, Poli S, De Havenon A, Rostanski SK, et al. Hyperglycemia, risk of subsequent stroke, and efficacy of dual antiplatelet therapy: a post hoc analysis of the point trial. J Am Heart Assoc. 2022;11: e023223.

25. Ntaios G, Egli M, Faouzi M, Michel P. J-shaped association between serum glucose and functional outcome in acute ischemic stroke. Stroke. 2010;41: 2366–70.

26. Bruno A, Kent TA, Coull BM, Shankar RR, Saha C, Becker KJ, et al. Treatment of hyperglycemia in ischemic stroke (this): a randomized pilot trial. Stroke. 2008;39:384–9.

27. Gray CS, Hildreth AJ, Sandercock PA, O'Connell JE, Johnston DE, Cartlidge NE, et al. Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: the UK glucose insulin in stroke trial (GIST-UK). Lancet Neurol. 2007;6: 397–406.

28. Johnston KC, Bruno A, Pauls Q, Hall CE, Barrett KM, Barsan W, et al. Intensive vs standard treatment of hyperglycemia and functional outcome in patients with acute ischemic stroke: the shine randomized clinical trial. JAMA. 2019;322:326–35.