

ORIGINAL RESEARCH

# Fasting Blood-Glucose Level and Clinical Outcome in Anterior Circulation Ischemic Stroke of Different Age Groups After Endovascular Treatment

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**Objective:** We aimed to analyze the association between fasting blood-glucose (FBG) level and 3-month functional outcome in anterior circulation ischemic stroke in different age groups after endovascular treatment (EVT).

Methods: We retrospectively analyzed the consecutive patients with acute ischemic stroke (AIS) receiving EVT from our department between July 2015 and March 2021. The patients were categorized into the older (≥60 years) and younger (<60 years) groups, and patients in each age group were dichotomized into favorable versus unfavorable outcomes according to the 3-month modified Rankin Scale (mRS) score.

**Results:** A total of 504 patients (286 males and 218 females) were included in our study. Three hundred ninety-two patients (77.8%) belonged to the group aged  $\geq$ 60 years, and 112 (22.2%) belonged to the group aged  $\leq$ 60 years. At the end of the study, 222 (56.6%) patients developed unfavorable outcomes in the older group and 31 (27.7%) showed unfavorable outcomes in the younger group. FBG level of the younger patients was significantly lower than that of older patients. In the older group, FBG level independently predicted a 3-month clinical unfavorable outcome with an odds ratio of 1.242 (95% confidence interval, 1.096–1.407; p = 0.001). However, the association was not found in the younger group (p = 0.376).

**Conclusion:** Higher FBG level is an independent risk factor for 3-month unfavorable outcome in the AIS patients aged  $\geq$ 60 years receiving EVT, but no similar effect was seen in the group aged  $\leq$ 60 years.

**Keywords:** fasting blood-glucose, hyperglycemia, acute ischemic stroke, endovascular treatment, outcome

#### Introduction

Acute ischemic stroke (AIS) is an important public health concern due to the high mortality and disability rates in China, <sup>1,2</sup> with an increase in the number of younger stroke patients. <sup>3</sup> Endovascular treatment (EVT) is considered to be an effective treatment for emergent large vessel occlusion stroke in the anterior circulation. <sup>4</sup> Previous clinical studies demonstrate that admission and fasting hyperglycemia are associated with poorer functional outcomes in AIS patients receiving EVT. <sup>5–7</sup> The possible mechanisms have been proposed to explain the relationship between hyperglycemia and unfavorable outcomes following ischemic stroke, including impaired blood–brain barrier, disordered cerebral microvasculature, increased inflammatory responses, and aggravated reperfusion injury. <sup>8–11</sup>

Some scholars have proposed that admission blood-glucose is affected by different physiologic statuses, such as feeding or using hypoglycemic agents before stroke. Fasting blood-glucose (FBG) can be more reliable in evaluating glucose metabolism and predicting 90-day outcomes better than admission blood-glucose in patients with AIS. Cao et al's study demonstrates that FBG is a powerful predictor related to the prognosis of AIS treated with intravenous thrombolysis, independent of admission blood-glucose. The MR CLEAN pretrial cohort shows that impaired FBG

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(>5.5 mmol/L) in the first week of admission is associated with poor functional outcome at discharge after EVT of ischemic stroke.<sup>7</sup> A recent study finds that fasting hyperglycemia on the next day after EVT in patients with AIS is an independent risk factor for unfavorable outcome.<sup>6</sup>

However, previous studies do not group stroke patients according to age to explore the relationship between FBG and the prognosis of AIS undergoing EVT. Age may affect the risk of stroke and glucose metabolism. <sup>13–16</sup> In respect to insulin sensitivity and glucose effectiveness, either a reduction or no change has been reported in healthy subjects with increasing age. <sup>17,18</sup> We wondered whether FBG predicted outcomes of AIS treated with EVT in younger or older patients. Therefore, our study aims to investigate the association between FBG level and clinical outcome in the anterior circulation ischemic stroke of different age groups after EVT.

### **Methods**

## Subjects

We retrospectively reviewed the consecutive patients with acute anterior circulation stroke patients receiving EVT between July 2015 and March 2021 at our department. The study was approved by the Ethics Committee of the First Affiliated Hospital of Wannan Medical College (201900039). Due to the retrospective nature, patient consent was waived. Patients were included if they met the following criteria: (1) age ≥18 years; (2) modified Rankin Scale (mRS) score before stroke <2; (3) occlusion of the internal carotid artery (ICA) or MCA was confirmed by computed tomographic angiography/magnetic resonance angiography/digital subtraction angiography (DSA); and (4) patients undergoing EVT. The flow chart of the inclusion of the study population is shown in Figure 1.

## Clinical Information and Laboratory Assays

The clinical information about demographic data, medical history (hypertension, diabetes mellitus, and atrial fibrillation), the Trial of ORG 10,172 in the Acute Stroke Treatment (TOAST) classification, baseline National Institutes of Health

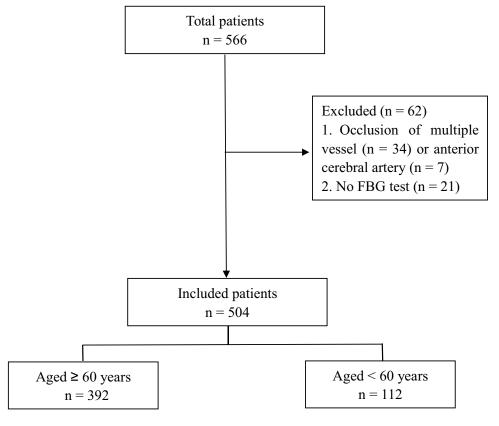


Figure I Inclusion flow chart.

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Stroke Scale (NIHSS) score, baseline Alberta Stroke Program Early computed tomography (ASPECT) score, perioperative variables (time from stroke onset to puncture [OTP], collateral circulation and recanalization status), and post-stroke functional outcome were collected.

TOAST classification was used to identify subtypes of ischemic stroke based on their etiology. NIHSS and ASPECT scores were used to assess stroke severity and early ischemic change on admission, respectively. Collateral circulation was evaluated according to retrograde contrast opacification of the vessels within the occluded area on delayed DSA images and classified by the criteria as follows: grade 0 (no reconstitution in the occluded area or the collaterals reached less than 1/3 of the occluded area), grade 1 (the collaterals reached less than 2/3 of the occluded area), grade 2 (the collaterals reached more than 2/3 of the occluded area). Poor collateral circulation was defined as grade 0 or 1, and good collateral circulation was defined as grade 2. Recanalization status after EVT was evaluated based on modified Thrombolysis in Cerebral Infarction (mTICI) grading. Unsuccessful recanalization was defined as an mTICI score ranging from 0 to 2a, and successful recanalization was defined as an mTICI score ranging from 2b to 3. The clinical outcome of the patients was determined by the mRS at 3-month after stroke. The mRS score ≤2 was defined as the favorable outcome, and the mRS score ≥3 was defined as the unfavorable outcome.

The blood samples were drawn by nurses on the next day after EVT and overnight fasting, and FBG was examined using the glucose oxidase method in the laboratory department. The normal FBG level was defined as 3.9–6.1mmol/L.

## Statistical Analysis

Statistical Package for the Social Sciences (SPSS) version 22.0 was used for all statistical analyses. The patients were categorized into the older ( $\geq$ 60 years) and younger (<60 years) groups, and patients in each age group were dichotomized into favorable (mRS score 0–2) versus unfavorable outcomes (mRS score 3–6) according to the 3-months mRS score. The normally distributed continuous variables were presented as mean  $\pm$  standard deviation (SD), and the nonnormally distributed continuous variables were presented as median (interquartile range [IQR]). Comparison of variables between groups was done using t-tests, nonparametric tests, Chi-square tests, or Fisher's exact tests as appropriate. Multivariate binary logistic regression was used to calculate Odds Ratios (OR) and the 95% confidence intervals (CI) for the association between unfavorable outcomes and the variables with p < 0.05 from the univariate analysis. A receiver operating characteristic curve analysis was performed between FBG and unfavorable outcome in the group aged  $\geq$ 60 years.

#### Results

A total of 504 patients (286 males and 218 females) were included in our study. Three hundred and ninety-two patients (77.8%) belonged to the group aged ≥60 years, and 112 (22.2%) belonged to the group aged <60 years. At the end of the study, 222 (56.6%) patients developed unfavorable outcomes in the older group and 31 (27.7%) showed unfavorable outcomes in the younger group. The demographics and clinical characteristics of patients (total and stratified by age group) are summarized in Table 1.

In the younger (<60 years) group, there was a significant difference between the patients with unfavorable and favorable outcome in TOAST classification (large-artery atherosclerosis, 32.3% vs 54.3%; cardioembolic, 41.9% vs 19.8%; undetermined or others, 25.8% vs 25.9%; p = 0.038) and occlusion site (ICA, 61.3% vs 30.9%; MCA 38.7% vs 69.1%; p = 0.003). The patients with an unfavorable outcome had higher baseline NIHSS score (16.00 [12.00–20.00] vs 13.00 [10.00–16.00], p = 0.006), lower baseline ASPECT score (8.00 [7.00–9.00] vs 9.00 [8.00–10.00], p = 0.001), higher prevalence of poor collateral circulation (grade 0, 22.6% vs 6.2%; grade 1, 48.4% vs 17.3%; grade 2, 29.0% vs 76.5%; p < 0.001), lower rate of successful recanalization (67.7% vs 90.1%; p = 0.004) and higher level of FBG (6.06 [5.13–9.02] vs 5.39 [4.83–6.58], p = 0.016) compared with those with favorable outcome (Table 2).

Multivariate logistic regression analysis between variables (p < 0.05) and 3-month functional outcomes in the younger group is listed in Table 3. FBG was not independently associated with outcome after adjusting Toast classification, occlusion site, baseline NIHSS score, ASPECT score, collateral circulation, and successful recanalization (OR 1.106, 95% CI 0.884–1.384, p = 0.376).

In the older ( $\ge$ 60 years) group, the patients with unfavorable outcome were more likely to be older (74.50 [69.00–79.00] vs 72.00 [66.00–76.00], p < 0.001) compared with those with favorable outcome. There was a significant

Table I The Demographics and Clinical Characteristics by Age Groups

Parameters	All Patients (n = 504)	≥60 Years (n = 392)	<60 Years (n = 112)	р
Age (years)	70.00 (62.00–76.00)	73.00 (67.00–78.00)	53.00 (49.00 -56.00)	< 0.001
Male, n (%)	286 (56.7)	207 (52.8)	79 (70.5)	0.001
Medical history, n (%)	(****)	(		
Hypertension	336 (66.7)	276 (70.4)	60 (53.6)	0.001
Diabetes mellitus	71 (14.1)	59 (15.1)	12 (10.7)	0.245
Atrial fibrillation	269 (53.4)	242 (61.7)	27 (24.1)	< 0.001
TOAST classification, n (%)	, ,			< 0.001
Large-artery atherosclerosis	144 (28.6)	90 (23.0)	54 (48.2)	
Cardioembolic	301 (59.7)	272 (69.4)	29 (25.9)	
Undetermined or others	59 (11.7)	30 (7.7)	29 (25.9)	
Occlusion site, n (%)				0.771
ICA	204 (40.5)	160 (40.8)	44 (39.3)	
MCA	300 (59.5)	232 (59.2)	68 (60.7)	
Baseline NIHSS score	14.00 (12.00-18.00)	15.00 (12.00-18.00)	14.00 (11.00-17.00)	0.022
Baseline ASPECT score	8.00 (8.00-10.00)	8.00 (8.00-9.00)	9.00 (8.00-10.00)	0.003
OTP (minutes)	280.00 (223.00–339.75)	280 (223.00–330.00)	276.50 (222.75–388.00)	0.294
Collateral circulation, n (%)				0.009
Grade 0	92 (18.3)	80 (20.4)	12 (10.7)	
Grade I	153 (30.4)	124 (31.6)	29 (25.9)	
Grade 2	259 (51.4)	188 (48.0)	71 (63.4)	
mTICI, 2b/3, n (%)	407 (80.8)	313 (79.8)	94 (83.9)	0.334
Unfavorable outcome	253 (50.2)	222 (56.6)	31 (27.7)	< 0.001
FBG (mmol/L)	6.08 (5.10–7.92)	6.31 (5.24–8.01)	5.52 (4.88–6.89)	0.002

Note: The values are presented as n (%), and median (interquartile range).

Abbreviations: ASPECT, Alberta Stroke Program Early CT; FBG, fasting blood-glucose; ICA, internal carotid artery; MCA, middle carotid artery; mTICI, modified thrombolysis in cerebral infarction; NIHSS, National Institutes of Health Stroke Scale; OTP, symptoms onset to groin puncture time; TOAST, the Trial of ORG 10172 in Acute Stroke Treatment.

difference between the patients with unfavorable and favorable outcome in TOAST classification (large-artery atherosclerosis, 17.1% vs 30.6%; cardioembolic, 76.1% vs 60.6%; undetermined or others, 6.8% vs 8.8%; p = 0.003) and occlusion site (ICA, 47.3% vs 32.4%; MCA 52.7% vs 67.6%; p = 0.003). History of hypertension (74.8% vs 64.7%, p = 0.030), diabetes mellitus (18.9% vs 10.0%, p = 0.014) and atrial fibrillation (69.4% vs 51.8%, p < 0.001), higher baseline NIHSS score (16.00 [13.00–19.00] vs 13.00 [11.00–16.00], p < 0.001), lower baseline ASPECT score (8.00 [7.00–9.00] vs 9.00 [8.00–10.00], p < 0.001), higher rate of poor collateral circulation (grade 0, 33.3% vs 3.5%; grade 1, 33.8% vs 28.8%; grade 2, 32.9% vs 67.6%; p < 0.001), lower rate of successful recanalization (72.5% vs 89.4%, p < 0.001), higher level of FBG (7.11 [5.81–9.14] vs 5.54 [4.82–6.95], p < 0.001) were significantly associated with more unfavorable outcome (Table 2).

Multivariate logistic regression analysis showed that baseline NIHSS score (OR 1.097, 95% CI 1.028–1.172, p = 0.005), ASPECT score (OR 0.761, 95% CI 0.631–0.919, p = 0.004), collateral circulation (grade 0 vs grade 1, OR 0.180, 95% CI 0.068–0.477, p = 0.001; grade 0 vs grade 2, OR 0.116, 95% CI 0.045–0.303, p < 0.001), the rate of successful recanalization (OR 0.430, 95% CI 0.219–0.845, p = 0.014) and FBG (OR 1.242, 95% CI 1.096–1.407, p = 0.001) were independently associated with unfavorable outcome in the group aged  $\geq 60$  years (Table 4).

The receiver operating characteristic (ROC) curve of FBG in predicting the 3-months unfavorable outcome of the older group is demonstrated in Figure 2. The optimal cutoff point for FBG to predict the outcome of the older patients with AIS after EVT was 5.680 mmol/L (sensitivity of 79.3% and specificity of 57.6%). The area under the curve (AUC) for the ability of FBG level to predict unfavorable outcomes in the patients with age  $\geq$ 60 years was 0.719 (95% CI 0.668–0.770, p < 0.001).

Table 2 Comparison of Clinical Characteristics in Those with Favorable versus Unfavorable Outcome of the Different Age Groups

Parameters	Aged ≥60 Years		р	Aged <	Aged <60 Years	
	Favorable Outcome (n = 170)	Unfavorable Outcome (n = 222)		Favorable Outcome (n = 81)	Unfavorable Outcome (n = 31)	
Age (years)	72.00 (66.00–76.00)	74.50 (69.00–79.00)	< 0.001	53.00 (49.00–56.50)	53.00 (48.00–56.00)	0.527
Male, n (%)	99 (58.2)	108 (48.6)	0.060	61 (75.3)	18 (58.1)	0.073
Medical history, n (%)						
Hypertension	110 (64.7)	166 (74.8)	0.030	42 (51.9)	18 (58.1)	0.555
Diabetes mellitus	17 (10.0)	42 (18.9)	0.014	9 (11.1)	3 (9.7)	0.826
Atrial fibrillation	88 (51.8)	154 (69.4)	< 0.001	16 (19.8)	11 (35.5)	0.082
TOAST classification, n (%)			0.003			0.038
Large-artery atherosclerosis	52 (30.6)	38 (17.1)		44 (54.3)	10 (32.3)	
Cardioembolic	103 (60.6)	169 (76.1)		16 (19.8)	13 (41.9)	
Undetermined or others	15 (8.8)	15 (6.8)		21 (25.9)	8 (25.8)	
Occlusion site, n (%)			0.003			0.003
ICA	55 (32.4)	105 (47.3)		25 (30.9)	19 (61.3)	
MCA	115 (67.6)	117 (52.7)		56 (69.1)	12 (38.7)	
Baseline NIHSS score	13.00 (11.00–16.00)	16.00 (13.00-19.00)	< 0.001	13.00 (10.00-16.00)	16.00 (12.00–20.00)	0.006
Baseline ASPECT score	9.00 (8.00-10.00)	8.00 (7.00–9.00)	< 0.001	9.00 (8.00-10.00)	8.00 (7.00–9.00)	0.001
OTP (minutes)	300.00 (230.00–330.00)	270.00 (210.00–330.00)	0.458	275.00 (222.50-420.00)	280.00 (222.00–360.00)	0.982
Collateral circulation, n (%)			< 0.001			< 0.001
Grade 0	6 (3.5)	74 (33.3)		5 (6.2)	7 (22.6)	
Grade I	49 (28.8)	75 (33.8)		14 (17.3)	15 (48.4)	
Grade 2	115 (67.6)	73 (32.9)		62 (76.5)	9 (29.0)	
mTICI, 2b/3, n (%)	152 (89.4)	161 (72.5)	< 0.001	73 (90.1)	21 (67.7)	0.004
FBG (mmol/L)	5.54 (4.82–6.95)	7.11 (5.81–9.14)	< 0.001	5.39 (4.83–6.58)	6.06 (5.13–9.02)	0.016

Note: The values are presented as n (%), and median (interquartile range).

Abbreviations: ASPECT, Alberta Stroke Program Early CT; FBG, fasting blood-glucose; ICA, internal carotid artery; MCA, middle carotid artery; mTICI, modified thrombolysis in cerebral infarction; NIHSS, National Institutes of Health Stroke Scale; OTP, symptoms onset to groin puncture time; TOAST, the Trial of ORG 10172 in Acute Stroke Treatment.

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**Table 3** Multivariate Logistic Regression for 90-Day Unfavorable Outcome in the Group Aged <60 Years

Parameters	Unfavorable Outcome		
	OR	95% CI	Р
TOAST classification			
Large-artery atherosclerosis (reference)			
Cardioembolic	4.284	1.025-17.906	0.046
Undetermined or others	1.860	0.422-8.206	0.412
Occlusion site, n (%)			
ICA (reference)			
MCA	0.269	0.883	0.030
Baseline NIHSS score	1.050	0.920-1.199	0.469
Baseline ASPECT score	0.631	0.426-0.935	0.022
Collateral circulation			
Grade 0 (reference)			
Grade I	1.004	0.173-5.833	0.997
Grade 2	0.157	0.026-0.970	0.046
mTICI, 2b/3	0.202	0.052-0.777	0.020
FBG (mmol/L)	1.106	0.884-1.384	0.376

**Abbreviations**: ASPECT, Alberta Stroke Program Early CT; CI, confidence interval; FBG, fasting blood-glucose; ICA, internal carotid artery; MCA, middle carotid artery; mTICI, modified thrombolysis in cerebral infarction; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; TOAST, the Trial of ORG 10172 in Acute Stroke Treatment.

**Table 4** Multivariate Logistic Regression for 90-Day Unfavorable Outcome in the Group Aged ≥60 Years

Parameters	Unfavorable Outcome			
	OR	95% CI	р	
Age	1.031	0.991-1.073	0.126	
Hypertension	1.057	0.614-1.818	0.842	
Diabetes mellitus	1.262	0.567-2.809	0.569	
Atrial fibrillation	1.212	0.563-2.608	0.623	
TOAST classification				
Large-artery atherosclerosis (reference)				
Cardioembolic	1.265	0.537-2.980	0.591	
Undetermined or others	1.681	0.602-2.691	0.322	
Occlusion site, n (%)				
ICA (reference)				
MCA	0.651	0.384-1.105	0.112	
Baseline NIHSS score	1.097	1.028-1.172	0.005	
Baseline ASPECT score	0.761	0.631-0.919	0.004	
Collateral circulation				
Grade 0 (reference)				
Grade I	0.180	0.068-0.477	0.001	
Grade 2	0.116	0.045-0.303	< 0.001	
mTICI, 2b/3	0.430	0.219-0.845	0.014	
FBG (mmol/L)	1.242	1.096-1.407	0.001	

**Abbreviations**: ASPECT, Alberta Stroke Program Early CT; CI, confidence interval; FBG, fasting blood-glucose; ICA, internal carotid artery; MCA, middle carotid artery; mTICI, modified thrombolysis in cerebral infarction; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; TOAST, the Trial of ORG 10172 in Acute Stroke Treatment.

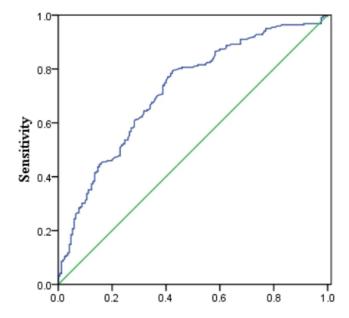


Figure 2 Receiver-operating characteristic (ROC) curve showed predictive fasting blood-glucose for unfavorable outcome in the group aged ≥ 60 years.

## **Discussion**

So far, only a few studies have explored the role of impaired FBG after EVT.  $^{6,7}$  This is the first study to investigate the association of FBG level with clinical outcome in anterior circulation AIS of different age groups after EVT. We found that higher FBG level increased the risk of unfavorable outcomes independently of established risk factors, such as collateral circulation, successful recanalization, NIHSS, and ASPECT score on admission in the patients with age  $\geq 60$  years, but this association was not detected in the group aged < 60 years. FBG level of the younger patients was significantly lower than that of older patients. However, a history of diabetes mellitus did not predict unfavorable outcomes in younger or older patients.

Previous studies revealed an association between blood glucose levels and the prognosis of ischemic stroke. <sup>19–23</sup> A study of intravenous thrombolysis showed FBG was a powerful predictor associated with the 90-day outcome of AIS independent of diabetes mellitus history. <sup>12</sup> The pretrial cohort of the Multicenter Randomized Clinical trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) found that impaired fasting glucose (IFG) defined as fasting glucose >5.5 mmol/L in the first week after EVT was associated with unfavorable outcomes at discharge. <sup>7</sup> Recent research of Wnuk and his colleagues revealed that fasting hyperglycemia (fasting glycemia >5.5 mmol/L) on the next day after EVT in AIS patients was an independent risk factor for poorer functional outcome. <sup>6</sup> The results of the above studies were similar to those of the older group in our study. However, in the previous literature, all AIS patients were considered as a whole and were not analyzed by age group. The age of the patient was found to be an important factor affecting the prognosis of stroke. Therefore, our study attempted to stratify with age and explore the relationship between FBG level and functional outcome of AIS receiving EVT.

There was some evidence that glucose tolerance deteriorates with age, <sup>13,15,16,18</sup> but other data showed that glucose-stimulated insulin secretion did not significantly alter with age. <sup>17,24</sup> Our study indicated no difference between the older (≥60 years) and younger (<60 years) groups in terms of diabetes mellitus history, but the FBG level of the older patients was significantly higher than that of younger patients. Interestingly, increased FBG level may predict an unfavorable outcome in the older patients after EVT, but no similar effect was seen in the younger patients. We speculated that the result is due to the different characteristics of AIS in different age groups. <sup>3</sup> There was a significant difference in TOAST classification between the older and younger groups. Younger patients had a higher proportion of stroke of undetermined and of other determined etiology, and previous results were generally consistent with our data. <sup>25–27</sup> The older group had more patients with unfavorable outcomes, and higher prevalence of hypertension and atrial fibrillation, higher NIHSS scores, lower rate of collateral circulation and ASPECT scores than the younger group. AIS in the young population

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accounted for a small proportion of total AIS, and we also considered that the size of younger patients in our study was limited to identifying the association between FBG and prognosis of stroke after EVT in this subgroup, therefore larger studies of younger patients with AIS are needed.

Moreover, the association of FBG after EVT with unfavorable outcomes in the group aged  $\geq$ 60 years was independent of the history of diabetes. FBG may reflect the interaction of hormones involved in the stress response with concomitant insulin resistance in the case of acute diseases. Previous studies have confirmed that hyperglycemia may lead to increased oxidative stress, inflammatory response, and endothelial dysfunction, resulting in reperfusion injury to the brain tissue. Our result suggested that strict blood glucose management might be required in the AIS patients aged  $\geq$  60 years receiving EVT.

Inevitably, our study has some limitations. First, our study was limited by monocentric design, and the number of patients receiving EVT was insufficient to allow more detailed age groups. Second, we only measured FBG on the next day after admission and did not dynamically monitor FBG during hospitalization. Finally, we did not take into consideration the influence of hypoglycemic drugs used after ischemic stroke.

## **Conclusions**

Our study found that a higher FBG level is an independent risk factor for 3-month unfavorable outcome in the patients aged  $\geq$ 60 years receiving EVT, but no similar effect was seen in the group aged  $\leq$ 60 years. In the future study, we will explore whether appropriate glucose management after EVT benefits older AIS patients.

## **Data Sharing Statement**

The data used to support the findings of this study are available upon reasonable request.

## **Ethical Approval**

Our study was carried out in compliance with the Declaration of Helsinki and approved by the ethics committee of the First Affiliated Hospital of Wannan Medical College (NO. 201900039). Due to the retrospective nature, patient consent was waived. All individual information was strictly kept confidential and anonymous in the manuscript.

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#### **Disclosure**

The authors declare no conflicts of interest in this work nor regarding the publication of this article.

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