

HbA1c and clinical outcomes after endovascular treatment in patients with posterior circulation large vessel occlusion: a subgroup analysis of a nationwide registry (BASILAR)

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Abstract

Background and aims: Recently, several clinical trials have shown that increased glycated hemoglobin (HbA1c) level is correlated with poor clinical outcomes in ischemic stroke patients after thrombolysis and possibly after mechanical thrombectomy. However, the effect of HbA1c on posterior circulation large vessel occlusion (PCLVO) patients treated with endovascular thrombectomy (EVT) remains unclear. This multicenter study assessed the association between the HbA1c levels and clinical outcomes in patients with PCLVO after EVT.

Methods: We studied 385 PCLVO ischemic stroke patients included in the EVT for acute basilar artery occlusion study (BASILAR). Patients were divided into a high HbA1c level group (HbA1c >6.5%) and a low HbA1c level group (HbA1c ≤6.5%). The efficacy outcome was a 90-day favorable functional outcome (modified Rankin Scale 0–3). The safety outcomes included symptomatic intracerebral hemorrhage and mortality at 90 days after EVT.

Results: The frequency of a favorable outcome in patients with an HbA1c ≤6.5% was significantly higher than that in the HbA1c >6.5% group (41.2% versus 26.2%, $p = 0.001$). In multivariate analysis with adjusted confounders, high HbA1c levels and favorable outcomes were significantly negatively correlated. There was also a significant association between high HbA1c levels and mortality after 3 months. The negative effects of high HbA1c levels on functional status after 3 months were exacerbated in patients aged ≥65 years.

Conclusion: Our multicenter study suggests that a higher serum HbA1c level (HbA1c >6.5%) is an independent predictor of a 90-day poor outcome and mortality in patients with PCLVO after EVT, particularly in those aged ≥65 years.

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Introduction

Hyperglycemia in patients with acute ischemic stroke (AIS) is a well-established predictor of poor clinical outcomes. It occurs in approximately one-third of AIS patients.¹ A significant association was reported between hyperglycemia at admission

and adverse prognosis in patients with emergent large vessel occlusion after mechanical thrombectomy.² Hyperglycemia not only can aggravate ischemic brain injury by enhancing intracellular acidosis in the penumbra and increasing free radical formation but also can damage cerebral

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autoregulation and the blood–brain barrier, leading to ischemia–reperfusion injury.^{3,4}

However, serum glucose fluctuates during the day, for reasons that include exercise, the level of blood insulin, diet, and medical treatment.⁵ Inflammatory responses and an acute stress reaction may elevate the serum glucose levels, which could be negative prognostic factors.^{1,6,7} By contrast, glycated hemoglobin (HbA1c), a widely used glycemic control parameter, reflects the average blood glucose level over several months before the examination and is less susceptible to recent changes.⁵ Recent researches have shown that higher HbA1c levels may increase the risk of ischemic stroke and new ischemic lesions in patients with AIS.^{8–10} Other studies have reported an independent association between a higher HbA1c level and poor prognosis after intravenous thrombolysis.¹¹ However, only a few studies with a small sample size and single-center studies have investigated the relationship between HbA1c and clinical outcomes in patients who had undergone endovascular treatment.^{12,13} To the best of our knowledge, this association has not been examined in patients with acute posterior circulatory endovascular treatment (EVT).

In our multicenter prospective cohort study, we aimed to analyze the relationship between the HbA1c levels and clinical outcomes in patients with posterior circulation occlusion of large vessels (PCLVO) after EVT.

Methods

Study population

Our patients were selected from the EVT for acute basilar artery occlusion study (BASILAR), a nationwide prospective cohort study including 47 comprehensive stroke centers in China that tested the efficacy and safety of EVT in patients with AIS due to basilar artery occlusion. All patients or their legally authorized representatives provided signed informed consent and their HbA1c levels were systematically measured before admission. BASILAR was approved by the China Ethics Committee of Registering Clinical Trials (approval number CHiECRCT-20180023) and is registered on the Chinese Clinical Trial Registry (<http://www.chictr.org.cn;ChiCTR1800014759>). The details of this registration study have been published previously.¹⁴

The main inclusion criteria were as follows: (1) age ≥ 18 years; (2) presentation of estimated time of PCLVO ≤ 24 h; (3) presence of PCLVO on magnetic resonance angiography (MRA), computed tomographic angiography (CTA), or digital subtraction angiography; (4) EVT performed within 24 h of estimated time of PCLVO; (5) performance of tests to determine the HbA1c levels; and (6) informed consent was signed.

Patients were excluded when they (1) had a pre-morbid Modified Rankin Scale (mRS) > 2 ; (2) evidence of cerebral hemorrhage by neuroimaging; (3) incomplete clinical data, including laboratory data; and (4) pregnant or lactating women and those patients with a serious, terminal illness.

Treatments

Patients received standard medical treatment after excluding intracranial hemorrhage by non-contrast computed tomography (CT). The use of recombinant tissue plasminogen activator (rt-PA) or urokinase, anticoagulation, and antiplatelet drugs were in accordance with the guidelines for the management of AIS.^{15,16} Patients were treated with EVT using stent retrievers, balloon angioplasty thromboaspiration, stenting, intra-arterial thrombolysis, or multiple combinations of these approaches within 24 h of the estimated time of PCLVO.

Data collection

We recorded the following data for analysis: baseline information, laboratory data, risk factors for stroke, imaging performance, and EVT characteristics. Details of the data are available in Tables 1 and 2.

Patients were divided into two groups according to their plasma HbA1c levels, measured at admission. The high HbA1c level group was defined as a HbA1c $> 6.5\%$, which meets the current criteria for diagnosis of diabetes.⁵ The low HbA1c level group consisted of patients with HbA1c $\leq 6.5\%$. The degree of recanalization was evaluated at the end of the procedure. Successful reperfusion after EVT was defined as modified Thrombolysis in Cerebral Infarction (mTICI) scores of 2b or 3.¹⁷ The patients also underwent non-contrast CT to identify intracerebral hemorrhage. CTA or MRA was performed within 48 h after EVT to determine vessel patency. Relevant imaging data were evaluated by the imaging core laboratory.

Table 1. Baseline clinical and biochemical characteristics, according to HbA1c levels.

	HbA1c ≤6.5% <i>n</i> = 255	HbA1c >6.5% <i>n</i> = 130	<i>p</i> value ^a
Age, years, mean ± SD	64.7 ± 11.5	62.4 ± 11.1	0.033
Men, <i>n</i> (%)	190 (74.5)	99 (76.2)	0.724
History of risk factors, <i>n</i> (%)			
Hypertension	165 (64.7)	108 (83.1)	<0.001
DM	20 (7.8)	103 (79.2)	<0.001
Dyslipidemia	85 (33.3)	56 (43.1)	0.061
Atrial fibrillation	52 (20.4)	23 (17.7)	0.527
Cerebral infarction	48 (18.8)	34 (26.2)	0.097
Smoking	102 (40.0)	50 (38.5)	0.77
TIA	4 (1.6)	2 (1.5)	0.982
SBP, mmHg, mean ± SD	148.7 ± 27.0	154.1 ± 23.1	0.028
Biochemical variables, mean ± SD			
Total cholesterol, mmol/L	4.7 ± 1.4	4.8 ± 1.5	0.964
LDL-C, mmol/L	3.0 ± 1.2	2.9 ± 1.0	0.626
Triglyceride, mmol/L	1.4 ± 1.0	2.1 ± 2.7	0.477
HDL-C, mmol/L	1.2 ± 0.3	1.1 ± 0.3	0.994
Admission serum glucose, mmol/L	7.3 ± 2.2	11.0 ± 3.4	<0.001
TOAST classification, <i>n</i> (%)			0.465
LAA	170 (66.7)	96 (73.8)	
CE	67 (26.3)	27 (20.8)	
SOE	5 (2.0)	3 (2.3)	
SUE	13 (5.1)	4 (3.1)	
Initial NIHSS	22.9 ± 10.2	24.4 ± 9.7	<0.001
Initial pc-ASPECTS	8.0 ± 1.6	7.6 ± 1.8	<0.001

^aContinuous variables were compared between groups using Student *t* tests. The χ^2 test was used for non-continuous variables.
CE, cardioembolism; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LAA, large artery atherosclerosis; LDL-C, low-density lipoprotein cholesterol; NIHSS, National Institutes of Health Stroke Scale; pc-ASPECTS, posterior circulation Alberta Stroke Program Early CT Score; SBP, systolic blood pressure; SOE, stroke of other determined cause; SUE, stroke of undetermined cause; TIA, transient ischemic attack; TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

Table 2. Procedural-related characteristics, according to HbA1c levels.

	HbA1c ≤6.5% n = 255	HbA1c >6.5% n = 130	p value
Occlusion site, n (%)			0.108
BA distal	77 (30.2)	34 (26.2)	
BA middle	79 (31.0)	36 (27.7)	
BA proximal	50 (19.6)	26 (20.0)	
V4	43 (16.9)	34 (26.2)	
PCA	6 (2.4)	0 (0)	
mTICI, n (%)			0.109
mTICI 0–2a	40 (15.7)	29 (22.3)	
mTICI 2b–3 ^a	215 (84.3)	101 (77.7)	
Anesthesia, n (%) ^b			0.214
General	80 (31.6)	49 (38.0)	
Local	173 (68.4)	80 (62.0)	
ASITN/SIR, n (%)			0.991
ASITN/SIR 0–1	145 (56.9)	74 (56.9)	
ASITN/SIR 2–4 ^c	110 (43.1)	56 (43.1)	
Time variables, min, mean ± SD			
Onset to puncture time	419.3 ± 306.3	422.1 ± 459.9	0.023
Onset to recanalization time	535.0 ± 316.0	541.3 ± 462.9	0.001
Puncture to recanalization time	115.7 ± 64.9	119.3 ± 69.3	<0.001
Intravenous thrombolysis, n (%)	40 (15.7)	23 (17.7)	0.615
Intracerebral hemorrhage, n (%)	6 (2.4)	1 (0.8%)	0.271

^aA TICI score of 2b or 3 indicates complete recanalization.

^bData were not available in three patients (two patients in HbA1c ≤6.5% group and one patient in HbA1c >6.5%).

^cAn ASITN/SIR score of 2–4 indicates favorable collateral compensation.

ASITN/SIR, American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology; BA, basilar artery; HbA1c, glycated hemoglobin; mTICI, modified thrombolysis in cerebral infarction; PCA, posterior cerebral artery; V4, V4 segment of vertebral artery.

Outcome measurements

The efficacy clinical outcome was assessed by the mRS scores at 90 days. A favorable functional outcome was defined as a mRS score between 0 and 3 (indicating the ability to walk without assistance, 0–3 is preferred over 0–2 for posterior stroke, which carries a worse prognosis than those of anterior circulation).

The safety clinical outcomes included symptomatic intracerebral hemorrhage (sICH) and mortality at 90 days after EVT. sICH was defined as a newly observed intracranial hemorrhage leading to an increase of ≥4 points on the National Institutes of Health Stroke Scale (NIHSS) score before worsening or increase of ≥2 points in one category.

Statistical analysis

Data analyses were performed using SPSS 22.0 (IBM Corp., Armonk, NY, USA). Differences between the two groups were tested using the χ^2 test for categorical values and the *t*-test or Fisher's exact test for continuous values. We defined a *p* value <0.05 as statistically significant.

The assessment of the odds ratios (ORs) and 95% confidence intervals (CIs) for clinical outcomes used a multivariable logistic regression analysis. We adjusted the variables based on clinical significance, including age, systolic blood pressure (SBP), NIHSS score, onset to puncture time, occlusion site, American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology score, and posterior circulation Alberta Stroke Program Early CT Score (pc-ASPECTS). Subgroups included mTICI (0–2a or 2b–3), pc-ASPECTS ≤ 7 or $7 < \text{pc-ASPECTS} \leq 10$, NIHSS score (≤ 25 or > 25), sex, and age (≤ 65 or > 65 years). We also analyzed the heterogeneity of the HbA1c effect within subgroups.

Results

Patient characteristics

Our multicenter prospective study examined the data of 385 patients with PCLVO treated with EVT after AIS. The data were obtained from the BASILAR database in China. There were 255 patients with a HbA1c level $\leq 6.5\%$ and 130 patients with a HbA1c level $> 6.5\%$. All patients had follow-ups at 3 months. Twenty-seven patients (21.8%) had no history of diabetes mellitus (DM) in the high HbA1c level group, but should be diagnosed as occult DM.⁵ We found that hypertension, SBP, serum glucose level at admission, and initial NIHSS scores were higher in patients with HbA1c levels $> 6.5\%$ and initial pc-ASPECTS were lower in this group. Table 1 presents the associations between the HbA1c levels and biochemical and clinical characteristics.

Characteristics of endovascular procedures

Intravenous thrombolysis was performed in 40 patients (15.7%) with a HbA1c level $\leq 6.5\%$ and in 23 patients (17.7%) with a HbA1c level $> 6.5\%$. Basilar artery occlusion was found in 206 patients (80.7%) in the HbA1c $\leq 6.5\%$ group and

in 96 patients (73.8%) in the HbA1c $> 6.5\%$ group. Poor collateral flow (American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology 0–1) was found in 145 patients (56.9%) with a HbA1c $\leq 6.5\%$ and 74 patients (56.9%) with a HbA1c $> 6.5\%$. Successful reperfusion (mTICI 2b or 3) was achieved in 316 patients. Onset to puncture time, onset to recanalization time, puncture to recanalization time, and initial NIHSS scores were higher in the high HbA1c level group. Table 2 describes the procedural characteristics.

Efficacy outcomes

There were 139 patients who had a favorable outcome (mRS of 0 to 3). The frequency of favorable outcomes in patients with a HbA1c $\leq 6.5\%$ was significantly higher than that in the HbA1c $> 6.5\%$ group (41.2% versus 26.2%, *p* = 0.001; Figure 1). In a multivariate analysis with adjusted confounders, high HbA1c levels and favorable outcomes were found to be significantly negatively correlated (OR, 0.52; 95% CI, 0.28 – 0.94; *p* = 0.032; Table 3).

Safety outcomes

In the multivariable analysis, there was also a significant association between the high HbA1c levels and mortality after 3 months (OR, 2.89; 95% CI, 1.68–4.99; *p* < 0.001). We found no correlation between the high HbA1c levels and sICH.

Subgroup analyses

There was significant heterogeneity between the patients aged <65 years and patients aged ≥ 65 years in OR for favorable outcome in subgroup analyses. In the age subgroup, a high HbA1c level in those aged ≥ 65 years was associated with lower odds for favorable outcome at 3 months than in the <65 years group. Heterogeneity was not affected by the high HbA1c levels in the other prespecified subgroups. Subgroup analysis is shown in Figures 2 and 3.

Discussion

This multicenter cohort study, to the best of our knowledge, is the first to examine the association between the HbA1c levels and functional outcomes among PCLVO patients treated with EVT. Our data indicated that the higher HbA1c levels

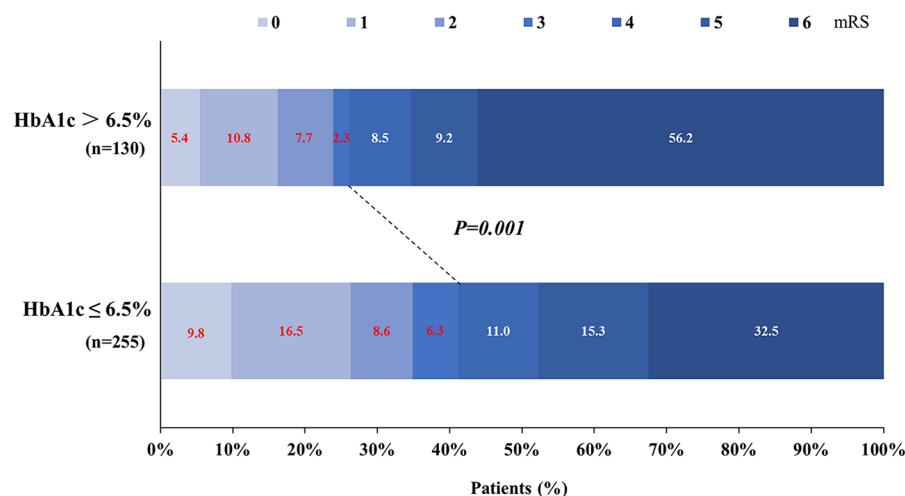


Figure 1. Primary outcomes according to glycosylated hemoglobin (HbA1c) levels. Distribution of modified Rankin Scale (mRS) scores at 3 months in patients treated with endovascular treatment.

Table 3. Association between high HbA1c levels (HbA1c >6.5%) and outcomes.

Clinical outcomes	HbA1c ≤6.5% n = 255 n (%)	HbA1c >6.5% n = 130 n (%)	Adjusted OR ^a (95% CI)	p value ^b
Efficacy outcomes at 3 months				
Good outcome, mRS, 0–3	105 (41.2)	34 (26.2)	0.52 (0.28–0.94)	0.032
Safety outcomes				
3-month mortality	83 (32.5)	73 (56.2)	2.89 (1.68–4.99)	<0.001
Symptomatic intracranial hemorrhage ^c	12 (4.8)	10 (7.9)	1.59 (0.62–4.05)	0.330

^aThe multiple logistic regression test was used to analyze ORs. Adjusted variables: age, systolic blood pressure, National Institutes of Health Stroke Scale, onset to puncture time, occlusion site, American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology, Alberta Stroke Program Early CT Score.

^bThe Bonferroni correction method was applied to multiple comparisons using a p value <0.05/number of comparisons as a threshold for statistical significance.

^cData were not available in seven patients (four patients in HbA1c ≤6.5% group and three patients in HbA1c >6.5%). CI, confidence interval; HbA1c, glycosylated hemoglobin; mRS, modified Rankin Scale; OR, odds ratio.

(>6.5%) were associated with a poor functional outcome and higher mortality at 3 months. The correlation remained statistically significant after adjusting for confounding factors.

High HbA1c levels reflect a chronic hyperglycemia status and abnormal glucose metabolism.¹⁸ Compared with acute hyperglycemia, chronic hyperglycemia might be less related to inflammatory and stress responses.¹ Given the link between

chronic hyperglycemia and the mechanism of injury to the nervous system in AIS patients,^{12,19,20} previous studies have emphasized the importance of intensive pre-stroke glycemic control, which may lead to better outcomes after performing reperfusion therapies.^{13,21} Our results regarding the HbA1c levels and clinical outcome also supported this view. In our study, there were some patients with HbA1c levels >6.5% who were not diagnosed with diabetes according to the present

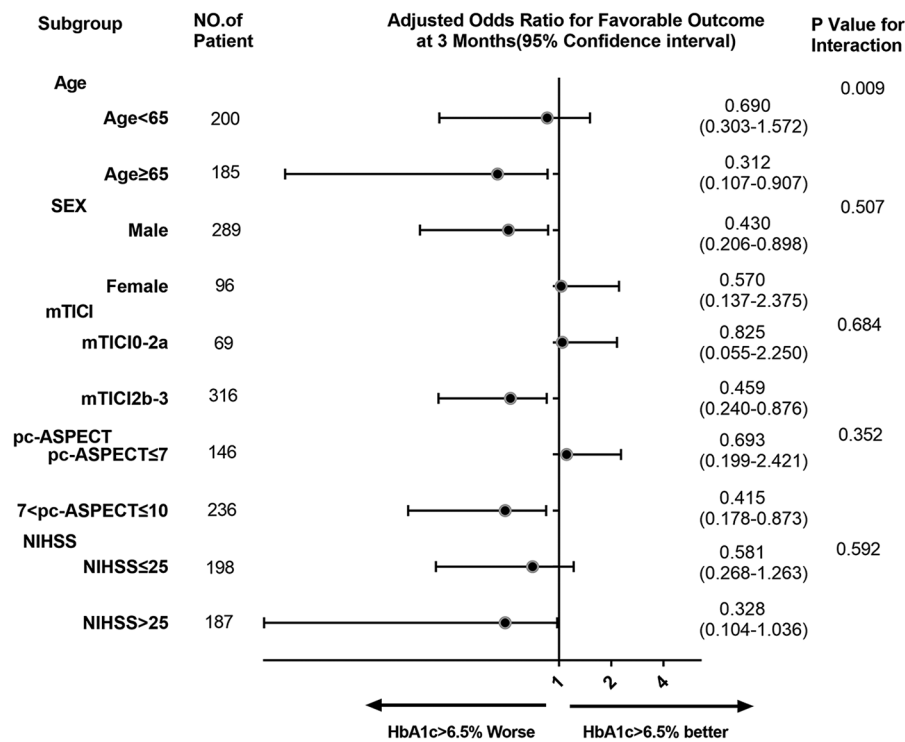


Figure 2. Subgroup analyses of primary outcomes. The forest plot shows the differences in odds ratios for favorable outcomes (defined as modified Rankin Scale score of 0–3) at 3 months in the prespecified subgroups. Adjusted variables: age, systolic blood pressure, National Institutes of Health Stroke Scale (NIHSS), puncture to recanalization time, occlusion site, American Society of Interventional and Therapeutic Neuroradiology/ Society of Interventional Radiology, posterior circulation Alberta Stroke Program Early CT Score (pc-ASPECTS). CT, computed tomography; HbA1c, glycated hemoglobin; mTICI, modified Thrombolysis in Cerebral Infarction.

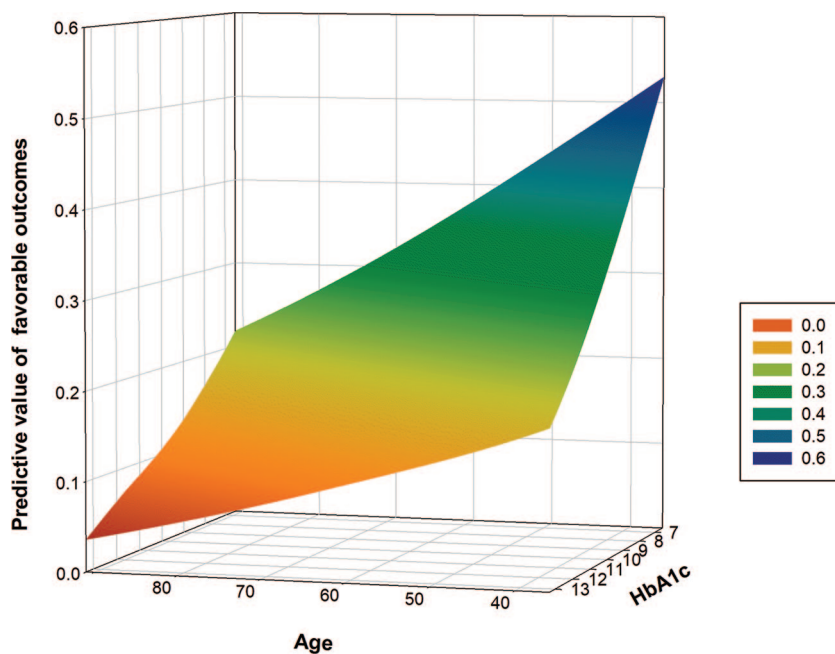


Figure 3. Association between age and predictive value of favorable outcomes in the high glycated hemoglobin (HbA1c) level group.

standards before stroke.²² A previous study by O'Sullivan *et al.*²³ found a higher mortality rate in undiagnosed than in already diagnosed patients with DM after emergency vascular surgical procedures. This may suggest that the regular serum glucose control and testing are necessary for a better prognosis in diagnosed and undiagnosed patients with DM.¹²

Previous researchers have reported that higher HbA1c levels were correlated with worse clinical outcomes in patients with AIS after intravenous rt-PA.^{11,24} Compared with intravenous rt-PA, EVT treatment for AIS had a higher reperfusion rate and did not increase the mortality rates or the risk for sICH.^{25,26} Therefore, recent studies have investigated the association between HbA1c levels and clinical outcomes, and found that high HbA1c levels had a negative effect on clinical outcomes.^{12,13} Our findings were consistent with those obtained from previous studies on functional outcome. However, our study further highlighted the effect of HbA1c levels on posterior circulation large vessel occlusion treated with EVT.

A previous study on cardiovascular disease showed that high HbA1c was associated with increased all-cause mortality.²⁷ However, recent findings regarding the relationship between the HbA1c levels and mortality after ischemic stroke were controversial. Specifically, some reports have suggested that there was no association, while others have revealed a detrimental effect in patients with high HbA1c levels.^{28,29} In the present study, we found that high HbA1c level was a significant predictive factor of 3 months mortality in patients with PCLVO after EVT (OR, 2.89; 95% CI, 1.68–4.99; $p < 0.001$). This discrepancy may be attributed to the different study populations. Further researches are needed in the future to define this association.

In our study, successful reperfusion (mTICI, 2b or 3) was achieved in 215 (84.3%) and 101 (77.7%) patients in the HbA1c $\leq 6.5\%$ and HbA1c $> 6.5\%$ groups, respectively. Although the recanalization rates appeared to be higher in the normal HbA1c level group, the difference between the two groups was not statistically significant ($p = 0.109$). Thomas *et al.*³⁰ found that the futile recanalization was significantly higher in the posterior than in the anterior circulation.

These findings may suggest that the protective effect of normoglycemia does not seem to be attributed to high recanalization rates.

A previous post hoc analysis of the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution Study 2 trial demonstrated that age was an independent predictor of adverse functional outcomes.³¹ Similarly, our observations also suggested that the negative effects of higher HbA1c levels on the functional status at the 3 month follow-up were exacerbated in patients aged ≥ 65 years. These results may suggest that more caution should be taken in elderly patients treated with EVT, especially in those with PCLVO.

Limitations

Our study had some limitations. First, as it was an observational study, there may be inevitable biases. However, our prospective data collection from multiple centers minimized the risk of bias. Although we have adjusted for confounding factors in a multivariate analysis, unmeasured residual confounding factors may still exist. Moreover, because of the lack of data on diabetes typing and fasting glucose, we were unable to analyze their effects on the patients' prognosis.

Conclusion

In summary, a high HbA1c level may be an independent predictor of poor prognosis at 3 months in patients with PCLVO after EVT. These findings may help physicians to identify the PCLVO patients that may benefit more or less from EVT. Further confirmation of this finding or potential methods to reduce this risk should be examined in a well-designed prospective, randomized trial.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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