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ORIGINAL RESEARCH

Association of Admission HbA1c Levels and Clinical Outcomes in Patients with Large Vessel Occlusion Following Endovascular Treatment: A Secondary Analysis of RESCUE BT Trial

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Background: This study aimed to analyze the association of HbA1c levels and outcomes in patients with large vessel occlusion (LVO) undergoing endovascular treatment (EVT).

Methods: Patients with recorded HbA1c values were enrolled from The Endovascular Treatment With vs Without Tirofiban for Patients with Large Vessel Occlusion Stroke (RESCUE BT) trial. We defined the high HbA1c levels as a plasma level of HbA1c > 6.5%. The primary outcome was good outcome (defined as a modified Rankin Scale score (mRS) of 0–2) at 90 days, secondary outcomes included other clinical outcomes (excellent outcome, mRS 0–1) at 90 days, mortality at 90 days, symptomatic intracerebral hemorrhage (sICH) within 48h, and any intracerebral hemorrhage (ICH).

Results: Among the 560 patients with HbA1c values, 133 (23.7%) patients were in the HbA1c > 6.5% group, and 427 (76.3%) patients were in the HbA1c ≤ 6.5% group. In multivariable analysis, the HbA1c > 6.5% group showed a significant negative association with good outcomes at 90 days (mRS 0–2; adjusted odds ratio [aOR], 0.57; 95% CI 0.37–0.88; *P* = 0.01), and the HbA1c > 6.5% group was significantly associated with increased mortality (aOR, 2.06; 95% CI 1.20–3.54; *P* = 0.009). There were no significant differences in the incidence of sICH between the two groups. Additionally, the subgroup analysis showed an interaction effect between high HbA1c levels and age.

Conclusion: Our results demonstrated that elevated HbA1c levels were associated with poor clinical outcomes in LVO patients who underwent EVT.

Keywords: HbA1c levels, acute ischemic stroke, large vessel occlusion, endovascular treatment, RESCUE BT trial

Introduction

Hyperglycemia is a familiar predictor of poor outcomes in patients with acute ischemic stroke (AIS).[1,2] Previous studies have showed that admission hyperglycemia was associated with poor functional outcomes and increased mortality in AIS patients treated with intravenous thrombolysis (IVT).[3,4] Moreover, admission hyperglycemia is also an independent predictor of worse clinical outcomes in patients with large vessel occlusion (LVO) treated with endovascular treatment

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(EVT).[5–7] This may be attributed to the fact that hyperglycemia can worsen ischemic brain injury by promoting free radical formation and exacerbating intracellular acidosis in the ischemic penumbra.[8] In addition, hyperglycemia can contribute to neurovascular damage and blood-brain barrier disruption, ultimately leading to reperfusion injury following successful recanalization.[9] Considering these pathophysiological mechanisms, hyperglycemia may negatively impact the clinical outcomes of patients with AIS undergoing reperfusion therapy. Admission hyperglycemia may reflect preexisting impaired glucose metabolism or stress hyperglycemia in AIS patients, both of which could negatively affect prognosis.[1] Therefore, to better evaluate the impact of hyperglycemia on AIS, it is essential to assess blood glucose levels over an extended period prior to AIS, rather than relying solely on admission hyperglycemia or stress hyperglycemia.

Glycated hemoglobin (HbA1c) is a proven marker of elevated glucose levels and is widely used to estimate a patient's average blood glucose levels over the past three months and providing valuable insights into diabetic vascular complications.[10,11] HbA1c is a marker of chronic hyperglycemia and increased levels are associated with worse outcome following AIS or hemorrhagic transformation patients in some previous studies.[12–14] Moreover, only a few studies have explored the relationship between HbA1c levels and clinical outcomes in patients with AIS undergoing IVT or EVT.[4,15–17] However, these studies are predominantly single-center or small sample size studies with a low level of evidence. To date, no relevant multicenter prospective cohort studies or randomized controlled trials (RCTs) have been reported.

In this context, using the data from The Endovascular Treatment With versus Without Tirofiban for Patients with Large Vessel Occlusion Stroke (RESCUE BT) Trial.[18] We performed a secondary analysis of RESCUE BT trial to evaluate the association of HbA1c levels and clinical outcomes following EVT in patients with large vessel occlusion.

Methods

Study Design and Patients Selection

This study used the data from The Endovascular Treatment With versus Without Tirofiban for Patients with Large Vessel Occlusion Stroke (RESCUE BT) Trial, which was a multicenter, randomized, double-blind, placebo-controlled trial involving 948 consecutive patients with confirmed proximal intracranial LVO stroke within 24 hours from October 2018 to October 2021 in 55 stroke centers in China. Patients with AIS caused by anterior circulation LVO stroke were randomly assigned, in a 1:1 ratio, to either the tirofiban group or the placebo group prior to undergoing endovascular treatment. All patients were subsequently prepared for and received endovascular treatment. Detailed information regarding the study protocol and patient eligibility criteria for the RESCUE BT trial has been previously published.[19] RESCUE BT trial was registered on the Chinese Clinical Trial Registry (Registration number: ChiCTR-INR-17014167). Approval for the protocol was obtained from the institutional review boards of each center. Written informed consent was secured from all patients or their legally authorized representatives before randomization. In the overall trial population, 388 patients with missing HbA1c values were excluded from this subgroup analysis, leaving a total of 560 patients included in the final analysis (Figure S1).

Data Collection

Baseline characteristics, including demographics, stroke risk factors, admission National Institutes of Health Stroke Scale (NIHSS) scores, and Alberta Stroke Program Early Computed Tomography Score (ASPECTS), as well as stroke etiology classified according to the Trial of ORG10172 in Acute Stroke Treatment (TOAST) criteria, were documented as previously described. Laboratory parameters, including admission glucose and glycated hemoglobin (HbA1c) levels, were also recorded. High HbA1c levels was defined as plasma levels exceeding 6.5%, which meets the current diagnostic criteria for diabetes mellitus.[15,20] Additional laboratory data were documented according to previously established protocols. The procedure-related time was recorded.

Outcome Measures

The primary measure of clinical effectiveness was the modified Rankin Scale (mRS) score of 0 to 2 at 90 days (mRS 0–2), indicating a good outcome. The mRS is an ordinal scale ranging from 0 (no symptoms) to 6 (death). An additional clinical outcome was defined as an mRS score of 0 to 1 at 90 days (mRS 0–1), indicating an excellent outcome. Safety

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outcomes included mortality at 90 days and symptomatic intracerebral hemorrhage (sICH) within 48 hours, verified by neuroimaging (CT or MRI). sICH was defined based on the Heidelberg Bleeding Classification.[21]

Statistical Analysis

Statistical comparisons were performed using Chi-square test or Fisher exact test for categorical and binary variables. For continuous variables, Student's *t*-test was applied to normally distributed data, while the Mann–Whitney *U*-test was used for non-normally distributed variables. Unless otherwise specified, baseline characteristics and outcomes are presented as medians with interquartile ranges (IQRs) for continuous variables and frequencies (percentages) for categorical variables. For the clinical outcomes in all patients set and successful reperfusion patients set, we performed a multivariable logistic regression analysis model, statistical associations were quantified using odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) to indicate precision of the estimates. Based on their clinical significance and the results of prior studies, adjustments were performed for the following covariates: age, sex, hypertension, atrial fibrillation, TIA, baseline ASPECTS, stroke etiology, and Puncture to recanalization time.

The multivariable logistic regression models were constructed with HbA1c levels as a continuous predictor variable, adjusting for potential confounders. To investigate potential non-linear associations between HbA1c levels and 90-day clinical outcomes, restricted cubic spline model (RCS) was employed. In the RCS model, adjustments were made for the following covariates: age, sex, hypertension, atrial fibrillation, TIA, baseline ASPECTS, stroke etiology, and Puncture to recanalization time. To evaluate the robustness of the relationship between HbA1c levels and clinical outcomes, we conducted a sensitivity analysis using stratified analyses across various HbA1c categories. In addition, A subgroup analysis for heterogeneity of HbA1c effect were performed to examine whether the association between HbA1c levels and good outcome (mRS 0–2) was consistent across various baseline characteristics. Also, the differences between areas under the receiver operating characteristic curves (AUCs) were assessed using the DeLong test.[22]

Statistical analyses were performed using SPSS version 25 (IBM, Armonk, NY, USA) and R version 4.4.2 (https://www.r-project.org). The level of statistical significance was set at a two-tailed *P*-value of less than 0.05. Patients with missing essential data were excluded from our analysis; hence, no imputation of missing data was performed.

Result

Baseline Characteristics

Among the 560 patients with HbA1c value in RESCUE BT trial, 133 (23.7%) patients were in the high HbA1c levels group (HbA1c > 6.5%), and 427 (76.3%) patients were in the normal HbA1c levels group (HbA1c ≤ 6.5%). The median age was 68 years (IQR, 57–75), with a median blood glucose level of 6.92 mmol/L (IQR, 5.78–8.73), a baseline NIHSS score of 16 (IQR, 12–19), and a baseline ASPECTS of 8 (IQR, 7–9). Patients in the high HbA1c levels group had higher systolic blood pressure (SBP) compared to the normal HbA1c levels group (150 mmHg versus 144 mmHg; $P < 0.001$). Additionally, a higher proportion of patients in the high HbA1c levels group had a history of diabetes mellitus (88.0% versus 8.9%; $P < 0.001$) and hypertension (68.4% versus 53.9%; $P = 0.004$). Admission blood glucose levels were also higher in the high HbA1c levels group. A detailed comparison of baseline characteristics is presented in Table 1.

HbA1c and Outcomes

The clinical outcomes are summarized in Figure 1 and Table 2. Figure 1 shows the mRS distribution, comparing patients in the high HbA1c levels group with those in the normal HbA1c levels group. In the multivariable logistic regression analysis, with adjusted covariates, the high HbA1c levels group showed a significant negative correlation, with good outcomes at 90 days after AIS in patients treated with EVT (mRS 0–2; 50.4% versus 37.6%; adjusted odds ratio [aOR], 0.57; 95% CI 0.37–0.88; $P = 0.01$). The number of patients with an excellent outcome (mRS 0–1) was lower in the high HbA1c levels group than in the normal HbA1c levels group, but no statistical significance was found (mRS 0–1; 35.1% versus 26.3%; aOR, 0.66; 95% CI 0.41–1.05; $P = 0.08$). Mortality at 90 days occurred more often in the high HbA1c levels group than in the normal HbA1c levels group (14.1% versus 21.1%; aOR, 2.06; 95% CI 1.20–3.54; $P = 0.009$).

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Table 1 Baseline Characteristics

Variables	All patients	HbA1c ≤6.5% (normal HbA1c levels group)	HbA1c >6.5% (high HbA1c levels group)	*P* value
Number of patients	**(n=560)**	**(n=427)**	**(n=133)**	
Age, y, median (IQR)	68.00 (57–75)	68.00 (57–75)	67.00 (58–74)	0.532
Sex, male, n (%)	316 (56.4)	246 (57.6)	70 (52.6)	0.362
Baseline SBP, median (IQR)	145 (129–162)	144 (127–160)	150 (135–169)	0.002
Baseline NIHSS, median (IQR)	16 (12–19)	16 (12–19)	16 (12–19)	0.66
Baseline ASPECTS, median (IQR)	8 (7–9)	8 (7–9)	8 (7–9)	0.542
Medical history, n (%)				
Hypertension	321 (57.3)	230 (53.9)	91 (68.4)	0.004
Hyperlipidemia	84 (15.0)	57 (13.3)	27 (20.3)	0.069
Diabetes mellitus	155 (27.7)	38 (8.9)	117 (88.0)	<0.001
TIA	7 (1.2)	6 (1.4)	1 (0.8)	0.885
Atrial fibrillation	191 (34.1)	155 (36.3)	36 (27.1)	0.05
Smoking	110 (19.6)	81 (19.0)	29 (21.8)	0.472
History antiplatelet (%)	44 (7.9)	32 (7.5)	12 (9.0)	0.698
Pre-stroke mRS score (%)				0.723
0	514 (91.8)	393 (92.0)	121 (91.0)	
1	35 (6.2)	25 (5.9)	10 (7.5)	
2	11 (2.0)	9 (2.1)	2 (1.5)	
Stroke etiology, n (%)				0.015
LAA	251 (44.8)	177 (41.5)	74 (55.6)	
CE	248 (44.3)	202 (47.3)	46 (34.6)	
Other causes	61 (10.9)	48 (11.2)	13 (9.8)	
Glucose parameters, median (IQR)				
Admission glucose, mmol/L	6.92 (5.78–8.73)	6.44 (5.60–7.52)	10.64 (8.40–13.49)	<0.001
HbA1C, %	5.90 (5.50–6.41)	5.70 (5.40–6.00)	7.90 (7.13–9.40)	<0.001
SHR, %	1.17 (1.00–1.37)	1.14 (0.99–1.31)	1.31 (1.09–1.60)	<0.001
Occlusion site, n (%)				0.883
ICA intracranial	122 (21.8)	91 (21.3)	31 (23.3)	
MCA-M1	358 (63.9)	275 (64.4)	83 (62.4)	
MCA-M2	80 (14.3)	61 (14.3)	19 (14.3)	
Time variables, median, (IQR), min				
Onset to puncture time	377 (257–595)	377 (257–597)	382 (260–592)	0.543
Puncture to recanalization time	65 (40–102)	67 (42–104)	62 (39–99)	0.47
Group, n (%)				0.129
Tirofiban	289 (51.6)	228 (53.4)	61 (45.9)	
Placebo	271 (48.4)	199 (46.6)	72 (54.1)	

Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CE, cardio-embolism; HbA1c, glycated hemoglobin; ICA, internal carotid artery; IQR, interquartile range; LAA, large artery atherosclerosis; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; SHR, stress hyperglycemia ratio; TIA, Transient Ischemic Attack.

There were no significant differences in the frequencies of sICH and any ICH between the two groups (Table 2). Additionally, the analysis revealed that among the subset of patients who achieved successful reperfusion, they essentially yielded similar outcomes (Figure 1B; Table 2).

HbA1c as a Continuous Variable and Outcomes

Restricted cubic spline regression analysis was employed to examine the association between HbA1c levels and clinical outcomes. Figure 2 depicts the analysis of HbA1c as a continuous variable using restricted cubic splines, rather than categorical stratification. Our findings demonstrated linear associations between HbA1c levels and all clinical endpoints (good outcome [mRS 0–2], excellent outcome [mRS 0–1], mortality, and sICH), with no evidence of non-linear relationships (Figure 2).

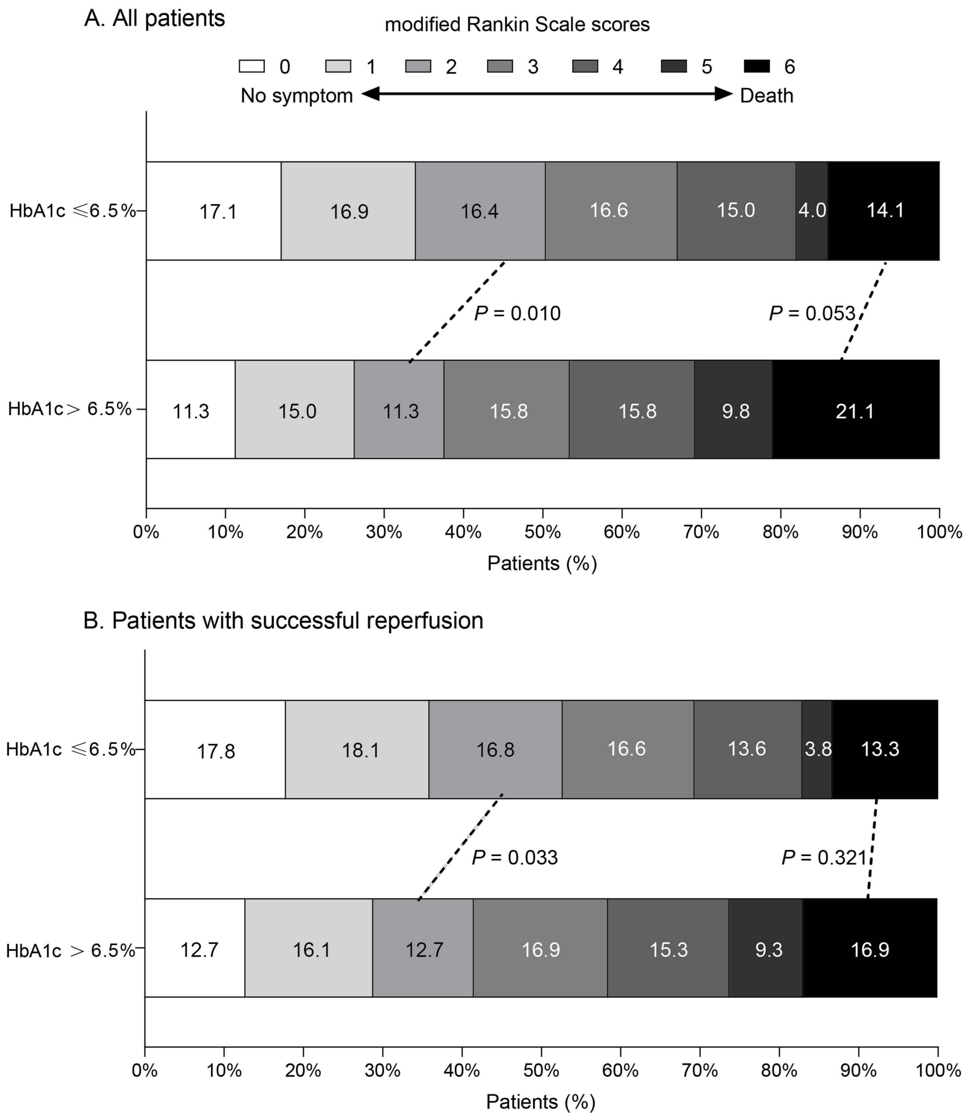

Figure 1 Clinical outcome at 90 days. The distribution of the modified Rankin scale scores at 90 days. Comparison of clinical outcomes between high HbA1c levels group (> 6.5%) and normal HbA1c levels group (≤ 6.5%) at 90 days Follow-up. (**A**) All patients; (**B**) Patients with successful reperfusion.
Abbreviation: HbA1c, glycated hemoglobin.

Furthermore, we evaluated the association of other glucose parameters and clinical outcomes following EVT. There was no significant difference in the area under the curve (AUC) values of the receiver operating characteristic (ROC) curves for predicting excellent outcomes (mRS 0–1), mortality, and sICH between HbA1c levels and the other glucose

Table 2 Clinical Outcome at 90 days

Clinical outcomes	HbA1c ≤6.5% (normal HbA1c levels group)	HbA1c >6.5% (high HbA1c levels group)	Unadjusted OR (95% CI)	P value	Adjusted OR[a] (95% CI)	P value
All patients	**(n=427), n (%)**	**(n=133), n (%)**				
mRS 0 to 2, (Good outcome)	215 (50.4)	50 (37.6)	0.59 (0.40–0.89)	0.01	0.57 (0.37–0.88)	0.01
mRS 0 to 1, (Excellent outcome)	150 (35.1)	35 (26.3)	0.66 (0.43–1.02)	0.06	0.66 (0.41–1.05)	0.08
Mortality	60 (14.1)	28 (21.1)	1.63 (0.99–2.69)	0.05	2.06 (1.20–3.54)	0.009
sICH	31 (7.3)	8 (6.0)	1.05 (0.56–1.99)	0.88	0.89 (0.39–2.05)	0.79
Any ICH	124 (29.0)	45 (33.8)	1.25 (0.83–1.89)	0.29	1.48 (0.96–2.30)	0.08

(*Continued*)

Table 2 (Continued).

Clinical outcomes	HbA1c ≤6.5% (normal HbA1c levels group)	HbA1c >6.5% (high HbA1c levels group)	Unadjusted OR (95% CI)	P value	Adjusted OR[a] (95% CI)	P value
Patients with successful reperfusion status	**(n=398), n (%)**	**(n=118), n (%)**				
mRS 0 to 2, (Good outcome)	210 (52.8)	49 (41.5)	1.57 (1.04–2.38)	0.03	1.74 (1.11–2.71)	0.02
mRS 0 to 1, (Excellent outcome)	148 (37.2)	34 (28.8)	1.46 (0.94–2.29)	0.10	1.56 (0.97–2.51)	0.07
Mortality	53 (13.3)	20 (16.9)	0.75 (0.43–1.32)	0.32	0.58 (0.32–1.05)	0.07
sICH	27 (6.8)	7 (5.9)	1.15 (0.49–2.72)	0.74	1.02 (0.41–2.50)	0.97
Any ICH	110 (27.6)	38 (32.2)	0.80 (0.52–1.25)	0.34	0.69 (0.43–1.11)	0.13

Notes: [a]Adjusted for age, sex, hypertension, atrial fibrillation, TIA, baseline ASPECTS, stroke etiology and Puncture to recanalization time.
Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; HbA1c, glycated hemoglobin; ICH, intracranial hemorrhage; mRS, modified Rankin Scale; OR, odds ratio; CI, confidence interval; sICH, symptomatic intracranial hemorrhage; TIA, transient ischemic attack.

parameters (Figure S2). In the multivariable logistic regression analysis, admission serum glucose levels and SHR levels were identified as significant negative predictors of good outcome (mRS 0–2), along with HbA1c levels (aOR: 0.89; 95% CI: 0.84–0.95; $P < 0.001$ and aOR: 0.45; 95% CI: 0.26–0.78; $P = 0.004$, respectively), these glucose parameters also showed significant associations with mortality at 90 days. Nevertheless, none of these glucose parameters demonstrated a significant association with sICH (Table S1).

Subgroup Analyses and Sensitivity Analysis

Subgroup analyses were conducted to examine the association between the two groups and good outcomes (mRS 0–2) at 90 days. Median values from the study cohort were utilized to establish the cutoff thresholds and define subgroup categories, including stratifications based on age, sex, hypertension, atrial fibrillation, baseline ASPECTS, and stroke etiology. In the subgroup analyses, significant heterogeneity was observed in the OR for good outcomes (mRS 0–2) associated with HbA1c levels between patients younger than 68 years and those aged 68 years or older. HbA1c levels > 6.5% in patients aged ≤ 68 years were associated with significantly lower odds of achieving a favorable outcome at 90 days compared to those aged > 68 years. The effect of elevated HbA1c levels remained consistent across all other prespecified variables, with no significant heterogeneity detected (Figure 3).

In the sensitivity analysis performed, which was based on different HbA1c levels, elevated HbA1c levels were negatively correlated with both good and excellent outcomes 3 months (mRS 0–2, mRS 0–1) compared with the reference group with HbA1c ≤ 6.5% (Figure S3). Elevated HbA1c levels (HbA1c >6.5%) were significantly associated with an increased risk of 90-day mortality. However, no significant difference in sICH was observed between patients with HbA1c >6.5% and those with HbA1c ≤ 6.5% (Figure S3).

Discussion

In the secondary analysis of the RESCUE BT trial, this study highlighted the association of HbA1c levels on clinical outcomes in patients with LVO following EVT. Our results demonstrated that elevated HbA1c levels were significantly and negatively associated with good outcomes in LVO patients who underwent EVT, in which HbA1c levels of > 6.5% were associated with increased mortality at 90 days, but not sICH. The results also showed linear associations between HbA1c levels and outcomes, with no evidence of non-linear relationships. Additionally, the subgroup analysis showed an interaction effect between high HbA1c levels and age. These findings indicate that suboptimal glycemic control prior to acute LVO significantly adversely affects clinical outcomes following EVT.

Previous study has reported that over 20% of patients with acute ischemic stroke experience acute hyperglycemia, regardless of whether they have been diagnosed with DM.[23] However, a multicenter randomized trial involving patients with acute hyperglycemic ischemic stroke, predominantly with DM, revealed that intensive insulin therapy, compared to standard treatment, failed to improve functional outcomes.[24] Several previous studies have shown that acute

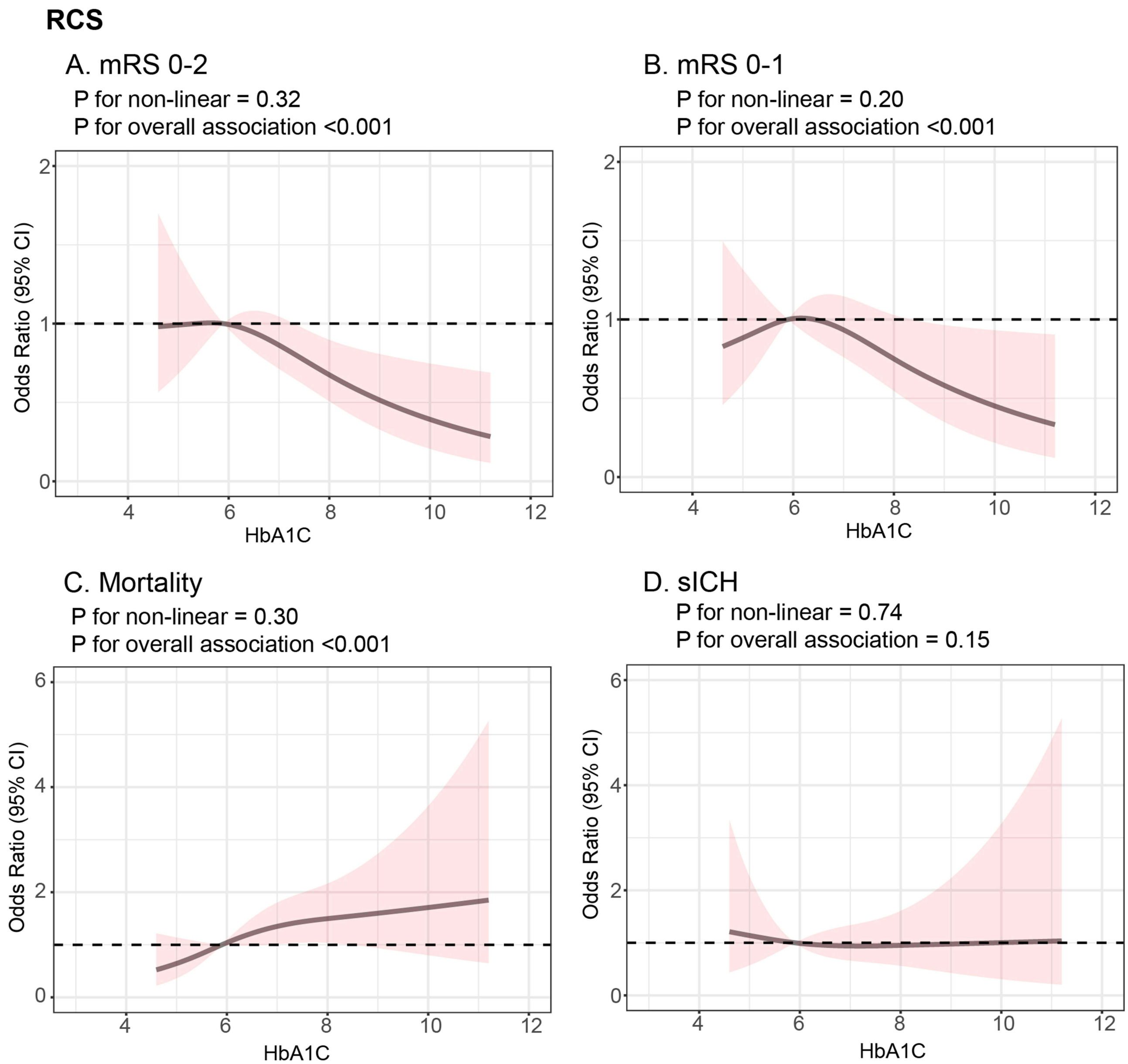

Figure 2 HbA1c as a continuous variable and the odds ratio of clinical outcomes (mRS 0–2, mRS 0–1, mortality and sICH) at 90 days. The association between HbA1c levels and clinical outcomes, including the 95% CI, was analyzed. Data were modeled using a multivariable regression model with a RCS incorporating three knots, adjusted for covariates. The median HbA1c level (6.5%) was used as the reference point. The black solid line represents the adjusted odds ratio, while the red shaded area indicates the 95% CI bands. (**A**) mRS 0–2; (**B**) mRS 0–1; (**C**) mortality; (**D**) sICH.

Abbreviations: CI, confidence interval; HbA1c, glycated hemoglobin; mRS, modified Rankin scale scores; RCS, restricted cubic spline; sICH, symptomatic intracerebral hemorrhage.

hyperglycemia at admission is associated with an increased risk of poor functional outcomes in patients with acute ischemic stroke undergoing EVT.[7,25,26] Additionally, other studies have indicated that acute stress hyperglycemia is negatively associated with functional outcomes following mechanical thrombectomy.[27,28] Previous studies have investigated the impact of chronic hyperglycemia on clinical outcomes in AIS patients receiving standard medical treatment or IVT.[14,17] However, the same association in LVO patients following EVT remains largely unexplored, limited researches have explored the association between chronic hyperglycemia and prognosis in patients after EVT; additionally, these studies are characterized by single-center design, or small sample sizes, and consequently, a low level of clinical evidence.[15,16]

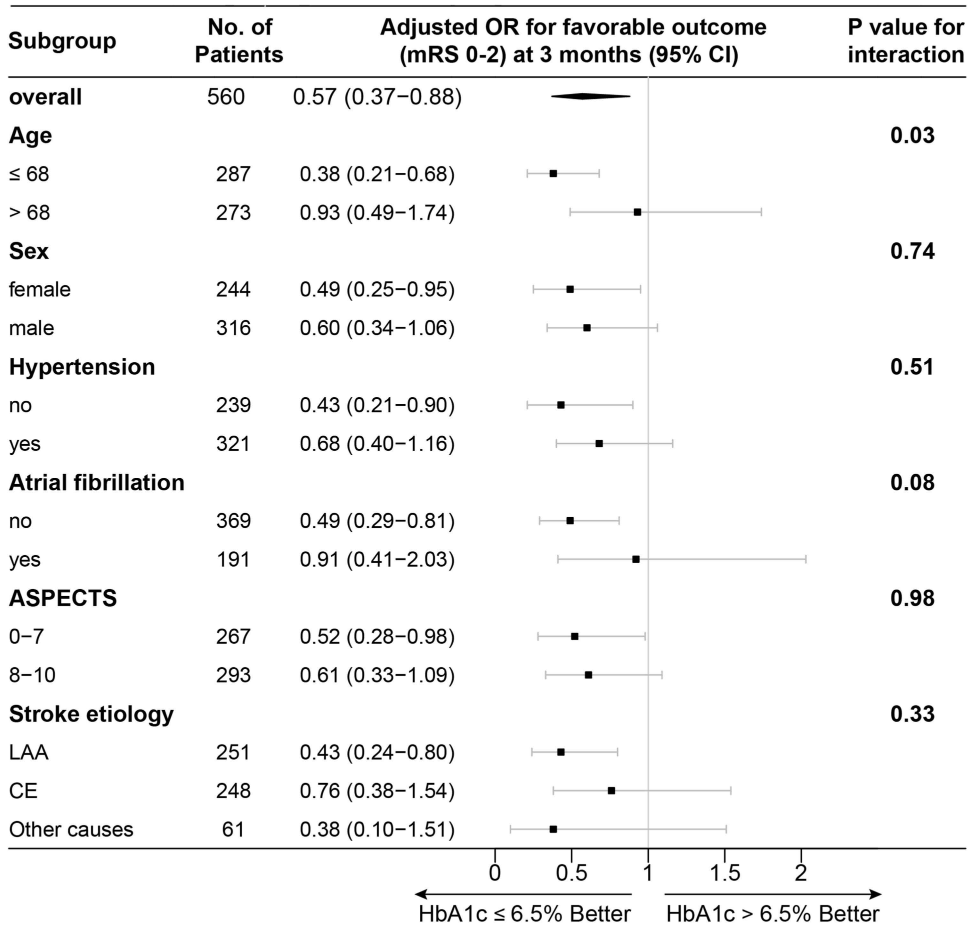

Figure 3 Subgroup analyses of good outcome (mRS 0–2). The forest plot illustrates the differences in odds ratios for achieving a good outcome (mRS 0–2) at 90 days across the subgroups. Adjusted variables: age, sex, hypertension, atrial fibrillation, baseline ASPECTS, and stroke etiology.
Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CE, cardio-embolism; CI, confidence interval; HbA1c, glycated hemoglobin; LAA, large artery atherosclerosis; mRS, modified Rankin scale scores; OR, odds ratio.

HbA1c serves as a robust biochemical indicator, accurately representing the average glucose concentration during the past 3 months and signaling underlying disturbances in glucose metabolism and chronic hyperglycemia. Chronic hyperglycemia causes cerebrovascular damage through mechanisms that may be independent of the thrombosis inflammatory changes of stress hyperglycemia. Persistent elevation of blood glucose (chronic hyperglycemia) induces oxidative stress and promotes excessive mitochondrial superoxide production, subsequently activating glucose-dependent metabolic cascades that lead to vascular dysfunction and damage.[13] Chronic hyperglycemia promotes the formation of advanced glycation end products through protein modification, which subsequently accelerates the development of long-term complications, facilitates plaque accumulation, and exacerbates atherosclerotic processes.[17] These pathological events significantly elevate the risk of cerebrovascular recurrence, thereby increasing the likelihood of adverse clinical outcomes and mortality.[15] In this context, prolonged exposure to pathologically elevated glucose levels triggers both vascular and metabolic perturbations, consequently impairing reparative neovascularization capacity and diminishing the functional plasticity of neural circuits.[29]

Previous studies have showed that the association between admission glucose levels and poor outcome was J-shaped curve, this indicates that there is a nonlinear relationship between acute hyperglycemia and poor clinical outcomes.[7,25] Similarly, several studies investigating the relationship between stress hyperglycemia ratio and clinical outcomes have demonstrated a significant nonlinear association, confirming the complex interplay between these parameters.[27] Recently, A nonlinear relationship was observed between HbA1c levels and post-stroke cognitive impairment (PSCI). Specifically, when HbA1c exceeded 8.2%, higher HbA1c levels were positively associated with an increased risk of PSCI.[30]

Moreover, in AIS patients with diabetes who underwent IVT, each 1% increment in HbA1c was associated with an elevated mortality risk.[4] However, the existence of such nonlinear relationships in patients undergoing EVT remains to be elucidated. Our study pioneered the investigation of potential nonlinear associations between HbA1c levels and clinical outcomes in AIS patients following EVT, utilizing data from the RESCUE BT trial. Through restricted cubic spline analysis, we found no evidence of nonlinear relationships between HbA1c levels and adverse clinical outcomes, mortality, or sICH.

A recent study demonstrated that in age-stratified analyses, elevated HbA1c levels were associated with significantly lower odds of favorable outcomes at 3-month follow-up in patients aged ≥ 65 years compared to those aged < 65 years.[31] However, another study suggests that among younger adult group, the higher HbA1c level was related to short-and long-term functional loss in patients with the small vessel occlusion subtype.[32] Our findings demonstrated similar effects on functional outcomes in the younger patient group (aged ≤ 68 years). We believed that elevated HbA1c levels in young patients with acute ischemic stroke indicate an underlying history of chronic metabolic dysfunction and significant vascular injury. Poor long-term glycemic control not only exacerbates acute brain injury and impedes neurological recovery but is also frequently associated with unhealthy lifestyle choices and suboptimal chronic disease management in this population. Consequently, a high HbA1c level is linked to poorer outcomes in young stroke patients, underscoring the critical importance of early detection and proactive management of diabetes and vascular risk factors, even among younger individuals. Advanced age represents a critical predictor of adverse outcomes in both ischemic and hemorrhagic stroke, the impact of elevated HbA1c levels on adverse outcomes appears to be attenuated in elderly patients.[32,33] Consequently, the adverse prognostic implications of elevated HbA1c levels following stroke may not be readily apparent in elderly patients with pre-existing hyperglycemia. Our findings are in alignment with findings from previous research.

Prior investigation has demonstrated that admission hyperglycemia neither influenced the likelihood of successful reperfusion nor did achieved reperfusion modify the association between glycemic status and functional outcomes in patients following EVT.[7] Another report indicated that stress hyperglycemia serves as a predictor of futile recanalization in patients who achieved successful recanalization following mechanical thrombectomy.[28] However, one study revealed that elevated HbA1c levels showed no significant association with successful reperfusion, as defined by mTICI of 2b-3.[16] Additionally, subgroup analysis from previous study indicated that elevated HbA1c levels were associated with significantly lower odds of favorable outcomes following AIS in patients who achieved recanalization compared to those who did not.[15] In our study, in successful recanalization population subset, we observed that elevated HbA1c levels were negatively associated with favorable clinical outcomes in successful recanalization subset.

This study had several limitations, and our findings should be interpreted within the context of its design. First, this study used the data from the RESCUE BT trial, this was a post hoc analysis of randomized controlled trial, although baseline data revealed no significant differences in HbA1c values between the Tirofiban and Control groups. However, selection bias seemed inevitable in the patients. Second, our study lacked comprehensive information about patients' previous antidiabetic medication regimens and the specific treatments employed to manage post-stroke hyperglycemia. Despite its limitations, this study still provides some of the best available evidence regarding the association between HbA1c levels and clinical outcomes in patients with LVO following EVT.

Conclusions

In summary, our finding suggests that the elevated HbA1c level is associated with poor clinical outcomes at 90 days. Our results indicate that HbA1c may function as a significant predictive marker for clinical outcomes in patients with LVO stroke following EVT, while also facilitating timely implementation of preventive interventions. Further research is warranted to assess the potential integration of HbA1c into clinical decision support tools for EVT.

Data Sharing Statement

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

Ethics Approval

The study was approved by the ethics committee of the Xinqiao Hospital, Army Medical University, in Chongqing, China (ID number: 2019-003-01). All patients or their legally authorized representatives provided signed, informed consent. The study was conducted in accordance with the Declaration of Helsinki.

Author Contributions

Drs. Fei Gao, Xiaolin Tan, and Linyu Li contributed equally. Drs. Wenjie Zi and Zhenying Shang were corresponding authors. 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; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; 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

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