Clinical Trial/Experimental Study

Medicine

OPEN

# Influencing factors of early dramatic recovery of neurological function after intravenous thrombolysis in patients with branch atheromatous disease

Yuanyuan Meng, MM[a], Yanjun Zhao, MM[b], Ruixia Wang, MM[c], Jiangshan Wen, MM[d], Tianping Tang, MD[a,*]

**Abstract**

**Background:** Intravenous thrombolysis can significantly improve the neurological function of patients with acute ischemic stroke. However, the expected early dramatic recovery (EDR) of neurological function after thrombolysis is not achieved in some patients with branch atheromatous disease (BAD). Here we evaluated the factors associated with EDR after thrombolysis in BAD patients.

**Methods:** We conducted a retrospective study on 580 consecutive BAD patients. All patients met the diagnostic criteria of BAD and received intravenous recombinant tissue-type plasminogen activator (rt-PA). EDR was defined when the improvement of National Institutes of Health Stroke Scale (NIHSS) score was >8 points within 2 or 24 hours after rt-PA, or the total NIHSS score was 0 or 1. The factors associated with EDR were analyzed with multivariate logistic regression analysis.

**Results:** Among 580 patients, the incidence of EDR was 35.2% (204 cases). Compared with patients without EDR, patients with EDR had lower incidence of diabetes (15.7% vs 29.3%, $P < .001$), lower NIHSS scores at 2 and 24 hours after rt-PA ($P < .001$), less cerebral hemorrhage (0% vs 5.3%, $P = .001$), and shorter onset to treatment time (OTT) ($P < .001$). Multivariate logistic regression analysis in propensity score-matched cohort showed that EDR was associated with OTT (adjusted OR = 0.994; 95% CI, 0.989–0.999) and NIHSS score after rt-PA (adjusted OR = 0.768; 95% CI, 0.663–0.890). Notably, diabetes (adjusted OR = 0.477, 95% CI, 0.234–0.972) was an independent factor related to EDR of neurological function in BAD patients. In the subgroup analysis, a lower incidence of diabetes (adjusted OR = 0.205, 95% CI: 0.059–0.714, $P = .013$) and a lower NIHSS score after thrombolysis in patients with paramedian pontine infarction (adjusted OR = 0.809, 95% CI: 0.656–0.997, $P = .047$) were significantly associated with EDR.

**Conclusion:** Diabetes is not conducive to EDR of neurological function in patients with BAD, especially in patients with paramedian pontine infraction. Low NIHSS score and short OTT after thrombolysis may be closely related to EDR after intravenous thrombolysis.

**Abbreviations:** BAD = branch atheromatous disease, DWI = diffusion weighted imaging, EDR = early dramatic recovery, mRS = modified Rankin Scale, NIHSS = National Institutes of Health Stroke Scale, OR = odds ratio, OTT = onset to treatment time, rt-PA = recombinant tissue-type plasminogen activator.

**Keywords:** branch atheromatous disease, early dramatic recovery, parapontine median artery, thrombolysis.

## 1. Introduction

Branch atheromatous disease (BAD) is described as an acute cerebral infarction in the blood supply area of the perforating artery. It is caused by the atherosclerotic plaque occluding the opening of the perforating artery. It is a common type of acute ischemic stroke, especially in Asian population. However, 20 years after the concept was proposed, the concept of BAD has not attracted clinical attention due to few pathological studies

*The authors have no conflicts of interest to disclose.*

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

*Informed consent was obtained from patients. This study was approved by the Ethics of Committee of Shengli Oilfield Central Hospital.*

*[a] Department of Neurology, Shengli Oilfield Central Hospital, Dongying, China, [b] Department of Rehabilitation, Weifang People's Hospital, Weifang, China, [c] Department of Neurology, The Second Hospital of Tianjin Medical University, Tianjin, China, [d] Department of Critical Care Medicine, Zibo Central Hospital, Zibo, China.*

** Correspondence: Tianping Tang, Department of Neurology, Shengli Oilfield Central Hospital, No. 31 Jinan Road, Dongying 257034, China (e-mail: jipan_1900@163.com).*



*How to cite this article: Meng Y, Zhao Y, Wang R, Wen J, Tang T. Influencing factors of early dramatic recovery of neurological function after intravenous thrombolysis in patients with branch atheromatous disease. Medicine 2023;102:19(e33658).*

*Received: 29 November 2022 / Received in final form: 6 April 2023 / Accepted: 10 April 2023*

*http://dx.doi.org/10.1097/MD.0000000000033658*

on BAD. Additionally, the vascular imaging examination still cannot visualize the wall of perforating arteries, resulting in bottlenecks in BAD-related research. With the leap of imaging technology in the past 10 years, BAD has attracted attention again. Epidemiological studies have found that the prevalence of BAD is as high as 10.4% to 18.3%.[1] In the acute phase of BAD, it is of great importance to maintain blood pressure and cerebral perfusion, and to administer active antiplatelet and intensive lipid-lowering therapy. However, some patients with BAD induced infarction are prone to repeated symptom fluctuations, and the long-term prognosis is still poor.[1–3] Due to the special anatomical location of the perforating artery, mechanical thrombectomy is usually not suitable for patients with BAD. So far, the treatment strategy for BAD is still controversial.

Intravenous thrombolysis with recombinant tissue-type plasminogen activator (rt-PA) is still the most important measure to improve cerebral perfusion. The symptoms of BAD patients vary in severity, and BAD patients have large heterogeneity in response to thrombolytic therapy. It is reported that BAD patients could benefit from intravenous thrombolytic therapy.[4] However, other studies found that intravenous thrombolysis could neither improve the clinical outcomes of BAD patients nor prevent the deterioration of neurological function in the early stage.[3,5] Therefore, it is unclear whether intravenous rt-PA can promote the early dramatic recovery (EDR) in patients with BAD induced infarction. Although the predictors of neurological deterioration in patients with branch artery infarction have been identified,[6] the factors that can predict the EDR of neurological function in patients with BAD are not clear. Since EDR can improve the long-term prognosis, identifying these predictive factors will help clinicians predict the early clinical outcome and long-term prognosis after intravenous thrombolysis.[7]

In this study, we analyzed the influencing factors of EDR of neurological function after intravenous thrombolysis in patients with BAD. Our findings may provide evidence for how to safely and effectively administer thrombolytic therapy in patients with acute BAD.

## 2. Materials and methods

### 2.1. Study subjects

This is a retrospective study. The BAD patients who were hospitalized in the Second Hospital of Tianjin Medical University, Weifang People's Hospital, Zibo Central Hospital, and Shengli Oilfield Central Hospital from January 2016 to April 2022 were consecutively included. Inclusion criteria: patients received rt-PA within 4.5 hours after the onset of ischemic stroke symptoms; patient with definite diagnosis of BAD; patients diagnosed by diffusion weighted imaging (DWI). BAD induced infarction was defined as follows[3,8–10]: infarction involved more than 3 axial slices on DWI in the blood supply area of the lenticulostriate artery or the infarction involved the blood supply area of the parapontine median artery (extending from the midline to the veutro of pons), with the lesion generally not exceeding the midline; No evidence of cerebral infarction caused by large parent arterial disease (>50% stenosis or occlusion) and other definite causes (such as immune or infectious vasculitis, cardiogenic cerebral embolism, fat embolism, abnormal platelet and coagulation function, etc.). Exclusion criteria: Patients with stenosis of the great vessels ≥ 50%; Patients with unstable plaques in the intracranial aorta, external carotid artery and vertebral artery that can cause arterial-arterial embolism; Patients cortical infarction, watershed infarction or multiple cerebral infarctions on DWI; Patients with cerebral infarction caused by other definite causes, such as immune or infectious vasculitis, cardiogenic cerebral embolism, fat embolism, abnormal platelet and coagulation function, etc.). Informed consent was obtained from patients. This study was approved by the Ethics of Committee of Shengli Oilfield Central Hospital.

### 2.2. Treatment

All patients received standard dose (0.9 mg/kg) of rt-PA (alteplase) within 4.5 hours after acute stroke. At 24 hours after thrombolysis and when intracerebral hemorrhage was excluded by CT scan, the patients received 100 mg aspirin and 75 mg clopidogrel. Antiplatelet therapy was terminated when there was symptomatic intracerebral hemorrhage.

### 2.3. Data collection

The basic clinical characteristics of all participants were collected, including age, sex, body mass index, blood pressure, onset to treatment time (OTT), National Institutes of Health Stroke Scale (NIHSS) baseline score, and NIHSS score at 2 and 24 hours after rt-PA treatment. The potential vascular risk factors were also collected, including hypertension, dyslipidemia, diabetes, ischemic stroke history, smoking and drinking habits. In addition, the fasting blood glucose, mean platelet volume, low density lipoprotein, uric acid and triglycerides were measured and collected.

### 2.4. Clinical outcomes

EDR was defined when the NIHSS score was improved by > 8 points within 2 or 24 hours after rt-PA treatment, or the total NIHSS score was 0 or 1.[11] The long-term clinical prognosis was evaluated by the modified Rankin Scale (mRS) at 3 months of onset. In mRS, an ordered stratification of 7 points was used, with 0 indicating no symptoms and 6 indicating death. Symptomatic intracerebral hemorrhage was defined as space occupying hematoma in the brain after thrombolysis, and NIHSS score increased by ≥ 4 points compared with baseline.[12]

### 2.5. Statistical analysis

The data were analyzed by SPSS statistical software (version 26.0; IBM, Armonk, NY). The Shapiro–Wilk normality test was used to test the normal distribution of continuous variables. The measurement data of normal distribution are expressed as mean ± standard deviation, and those of skew distribution are expressed as median and interquartile range. Categorical variables are expressed as frequency and percentage. The *t* test, Pearson-$\chi^2$ test and Mann–Whitney *U* test were used to compare the differences of baseline data. Multivariate logistic regression analysis was performed to identify independent predictors of EDR. The variables included in the multivariate analysis included diabetes, NIHSS score at 2 and 24 hours after rt-PA treatment, and OTT. The results were expressed by odds ratio (OR) and 95% confidence interval (CI). Propensity score matching at 1:1 ratio was used to balance the differences in baseline characteristics between the 2 groups with different clinical outcomes and to minimize the effect of selection bias. Significant difference was set at $P < .05$.

## 3. Results

### 3.1. Baseline characteristics

From January 2016 to April 2022, there were a total of 2362 patients with acute ischemic stroke who were treated in the Second Hospital of Tianjin Medical University, Weifang People's Hospital, Zibo Central Hospital, and Shengli Oilfield Central Hospital, including 851 women (36.03%) and 1511 men (63.97%). According to the inclusion criteria, a total of 580 patients were finally included (Fig. 1). Based on the incidence of EDR, these patients were divided into EDR group (n = 204) and non EDR group (n = 376). There was no significant difference in age, sex, incidence of silent brain infarct, biochemical data (such as blood pressure, blood glucose, and blood lipid) and vascular risk factors

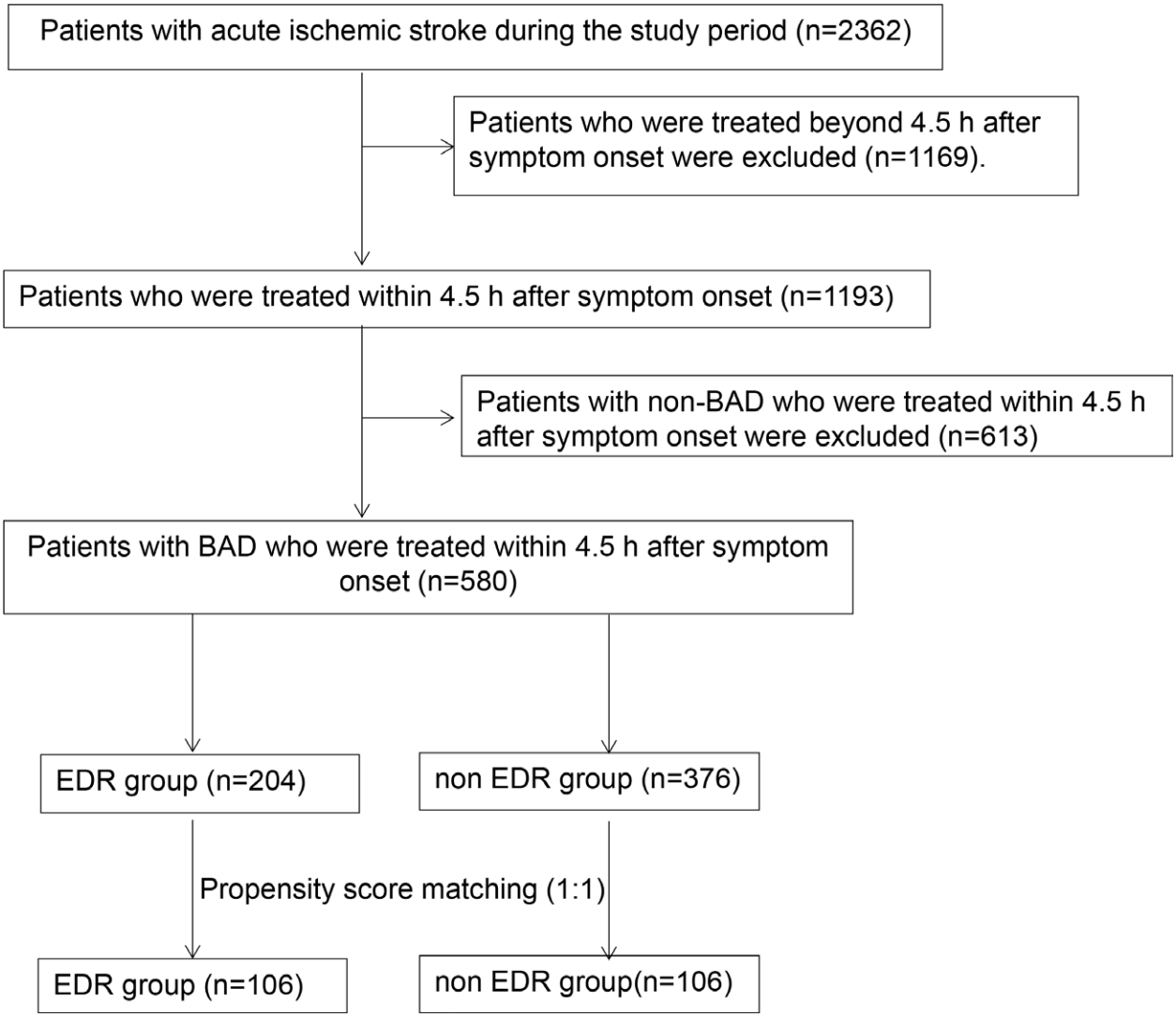


**Figure 1.** Flowchart of patient enrollment. BAD = branch atheromatous disease, EDR = early dramatic recovery.

(such as history of hypertension, dyslipidemia, history of ischemic stroke, drinking history, smoking habits, etc.) between EDR group and non EDR group ($P > .05$) (Table 1). The proportion of patients with diabetes history in non EDR group was significantly higher than that in EDR group ($P < .05$). The OTT was also significantly different between the 2 groups. Twenty patients (3.44%) suffered from cerebral hemorrhage after intravenous thrombolysis. The non EDR group had significantly higher percentage of intracerebral hemorrhage (5.3%), symptomatic intracerebral hemorrhage (2.7%), and asymptomatic intracerebral hemorrhage (2.7%). A total of 106 pairs of subjects were successfully matched through propensity score matching. After matching, OTT was significantly shorter in the EDR group than in the non-EDR group ($P = .005$). Furthermore, there were significantly higher percentages of intracerebral hemorrhage (7.5% vs 0%; $P = .004$) and diabetes (16.0% vs 27.3%; $P = .046$) in the non-EDR group.

### 3.2. Clinical outcomes

Patients in the EDR group benefited more from intravenous thrombolysis as they had significantly lower NIHSS scores at 2 hours (median, 0 vs 3, $P < .001$) and 24 hours (median, 0 vs 3, $P < .001$) after rt-PA than non EDR group (Table 2). After 3 months of follow-up, the number of patients in EDR group with mRS score 0 to 1 was 186 (91.2%) and in non EDR group was 200 (53.2%). The number of patients in EDR group with mRS score 0 to 2 was 197 (96.6%) and in non EDR group was 254 (67.6%). The mRS score at 3 months was significantly lower in EDR group than in non EDR group ($P < .05$). Based on infarction site, we further grouped patients into those with lenticulostriate artery infarction (n = 137) and those with site at paramedian pontine infarction (n = 67) (Table 3). Their baseline characteristic comparison showed that there were significant differences in hyperlipidemia ($P = .020$) and low-density lipoprotein cholesterol ($P = .025$).

### 3.3. Analysis of EDR influencing factors in patients with BAD

Univariate analysis results showed that diabetes (OR = 0.450, 95% CI: 0.290–0.697, $P = .001$), 2 hours NIHSS score (OR = 0.731, 95% CI: 0.671–0.795, $P < .001$), 24 hours NIHSS score (OR = 0.545, 95% CI: 0.481–0.618, $P < .001$), and OTT (OR = 0.987, 95% CI: 0.983–0.990, $P < .001$) were closely associated with EDR of BAD patients. In multivariate logistic regression analysis (Table 4), patients had lower post-thrombotic NIHSS score (OR = 0.496, 95% CI: 0.412–0.596, $P < .001$) and shorter OTT (OR = 0.989, 95% CI: 0.985–0.993, $P < .001$) were more likely to achieve EDR of neurological function. Diabetes (OR = 0.517, 95% CI: 0.306–0.874,

**Table 1**

**The demographics and clinical characteristics of patients with branch atheromatous disease.**

| | Unmatched cohort | | | Matched cohort | | |
|---|---|---|---|---|---|---|
| **Variables** | **EDR group (N = 204)** | **Non EDR group (N = 376)** | ***P*** | **EDR group (N = 106)** | **Non EDR group (N = 106)** | ***P*** |
| Age, mean ± SD, yr | 63.19 ± 11.46 | 62.66 ± 12.13 | .609 | 64.09 ± 11.07 | 64.34 ± 11.68 | .875 |
| Male, n (%) | 140 (68.6) | 256 (68.1) | .534 | 75 (70.8) | 78 (73.6) | .646 |
| History of ischemic stroke, n (%) | 31 (15.2) | 67 (17.8) | .421 | 18 (17.0) | 16 (15.1) | .708 |
| Hypertension, n (%) | 123 (60.3) | 231 (61.4) | .788 | 60 (56.6) | 65 (61.3) | .485 |
| Diabetes, n (%) | 32 (15.7) | 110 (29.3) | <.001 | 17 (16.0) | 29 (27.3) | .046 |
| Hyperlipidemia, n (%) | 15 (7.35) | 17 (4.52) | .154 | 5 (4.7) | 2 (1.9) | .249 |
| Smoking, n (%) | 71 (34.8) | 148 (39.4) | .280 | 31 (29.2) | 24 (22.6) | .273 |
| Drinking history, n (%) | 59 (28.9) | 85 (22.6) | .093 | 27 (25.5) | 24 (22.6) | .630 |
| SBP, mean ± SD, mm Hg | 151.35 ± 22.23 | 152.98 ± 20.42 | .373 | 150.79 ± 20.69 | 156.60 ± 19.37 | .056 |
| DBP, mean ± SD, mm Hg | 88.03 ± 15.62 | 88.30 ± 12.51 | .822 | 87.72 ± 13.59 | 86.92 ± 12.33 | .657 |
| TC, mean ± SD, mmol/L | 4.59 ± 0.97 | 4.74 ± 1.17 | .098 | 4.49 ± 1.13 | 4.73 ± 1.00 | .102 |
| TG, mean ± SD, median (IQR), mmol/L | 1.20 (0.88, 1.76) | 1.27 (0.91, 2.02) | .132 | 1.21 (0.85, 1.78) | 1.38 (0.91, 2.03) | .293 |
| LDL-C, mean ± SD, mmol/L | 2.79 ± 0.81 | 2.83 ± 0.92 | .602 | 2.69 ± 0.86 | 2.85 ± 0.81 | .166 |
| Baseline blood glucose, mean ± SD, mmol/L | 6.80 (5.70,8.50) | 7.10 (6.00,8.80) | .065 | 6.10 (5.40,8.52) | 7.10 (5.97,8.79) | .009 |
| Uric acid, mean ± SD, mmol/L | 310.06 ± 79.04 | 309.11 ± 87.88 | .754 | 312.84 ± 76.62 | 293.42 ± 87.09 | .086 |
| MPV, median (IQR), fL | 9.20 ± 0.96 | 9.15 ± 0.99 | .578 | 9.22 ± 0.94 | 9.19 ± 1.09 | .870 |
| Onset to treatment time, median (IQR) | 137.13 ± 55.69 | 181.01 ± 57.62 | <.001 | 147.93 ± 53.38 | 169.98 ± 60.72 | .005 |
| Baseline NIHSS score, median (IQR) | 4 (2.2, 8) | 4 (2, 8) | .229 | 3 (2, 5) | 3 (2, 5) | .469 |
| Intracerebral hemorrhage, n (%) | 0 (0) | 20 (5.3) | .001 | 0 (0) | 8 (7.5) | .004 |
| Symptomatic intracerebral hemorrhage, n (%) | 0 (0) | 10 (2.7) | .019 | 0 (0) | 4 (3.8) | .043 |
| Asymptomatic intracerebral hemorrhage, n (%) | 0 (0) | 10 (2.7) | .019 | 0 (0) | 4 (3.8) | .043 |
| Silent brain infarct, n (%) | 75 (36.8) | 169 (44.9) | .057 | 41 (38.7) | 58 (54.7) | .332 |
| Infarction site | | | | | | |
| The lenticulostriate artery, n (%) | 137 (67.2) | 249 (66.2) | .820 | 76 (71.7) | 71 (66.9) | .456 |
| The paramedian pontine artery, n (%) | 67 (32.8) | 127 (33.8) | .820 | 30 (28.3) | 35 (33.0) | .456 |

The measurement data of normal distribution are expressed as mean ± standard deviation (SD), and those of skew distribution are expressed as median and interquartile range (IQR). Categorical variables are expressed as frequency and percentage.

DBP = diastolic blood pressure, EDR = early dramatic recovery, LDL-C = low-density lipoprotein cholesterol, MPV = mean platelet volume, NIHSS = National Institutes of Health Stroke Scale, SBP = systolic blood pressure, TC = total cholesterol, TG = triglyceride.

**Table 2**

**Clinical outcomes.**

| **Variables** | **EDR group (N = 204)** | **Non EDR group (N = 376)** | **$z/\chi^2$** | ***P*** |
|---|---|---|---|---|
| NIHSS score at 2 h after rt-PA, median (IQR) | 0 (0,1) | 3 (1,5) | −12.433 | <.001 |
| NIHSS score at 24 h after rt-PA, median (IQR) | 0 (0,1) | 3 (2,6) | −14.406 | <.001 |
| Number of patients with mRS score 0–1 at 3 mo | 186 (91.2%) | 200 (53.2%) | 85.720 | <.001 |
| Number of patients with mRS score 0–2 at 3 mo | 197 (96.6%) | 254 (67.6%) | 64.378 | <.001 |
| mRS score at 3 mo, median (IQR) | 0 (0,1) | 2 (1,3) | −12.313 | <.001 |

The measurement data of normal distribution are expressed as mean ± standard deviation (SD), and those of skew distribution are expressed as median and interquartile range (IQR). Categorical variables are expressed as frequency and percentage.

EDR = early dramatic recovery, mRS = modified Rankin Scale, NIHSS = National Institutes of Health Stroke Scale, rt-PA = recombinant tissue-type plasminogen activator.

*P* = .014) was an unfavorable risk factor for EDR. In the subgroup analysis (Table 4), shorter OTT (OR = 0.989, 95% CI: 0.985–0.993, *P* < .001) and lower NIHSS score after thrombolysis (OR = 0.496, 95% CI: 0.412–0.596, *P* < .001) was significantly associated with EDR in patients with lenticulostriate artery infarction. A lower incidence of diabetes (OR = 0.362, 95% CI: 0.151–0.866, *P* = .022) and a lower NIHSS score after thrombolysis in patients with paramedian pontine infarction (OR = 0.480, 95% CI: 0.340–0.675, *P* < .001) was significantly associated with EDR. Patients with lenticulostriate artery infarction were more likely to achieve EDR than patients with paramedian pontine infarction (Fig. 2).

To minimize the effect of selection bias, a propensity score-matched analysis was performed. BAD patients with EDR had a lower incidence of diabetes (OR = 0.477, 95% CI: 0.234–0.972, *P* = .042) (Table 4). Multivariate logistic regression analysis in propensity score-matched cohort showed that the lower NIHSS score after thrombolysis (OR = 0.768, 95% CI: 0.663–0.890, *P* < .001) and the shorter OTT (OR = 0.994, 95% CI: 0.989–0.999, *P* = .006) were independently associated with EDR (Table 4). Diabetes was a risk factor for paramedian pontine infarction (OR = 0.205, 95% CI: 0.059–0.714, *P* = .013).

## 4. Discussion

The concept of BAD has been proposed for more than 30 years, in which the atherosclerosis in the perforating arteries (mainly the lenticulostriate artery and the paramedian pontine artery) themselves or their openings cause lumen stenosis or occlusion, leading to a single cerebral infarction deep in the brain.[13] Cerebral infarction due to BAD is more common in Asia, especially in China.[14] In recent years, some scholars have demonstrated that the fluctuation or progression of neurological function is closely related to BAD,[15,16] wherein the fluctuation of neurological function mainly involves the progression of motor deficits, which usually leads to severe disability. Unfortunately, only a few studies are focused on the treatment of BAD. The NINDS trial showed that alteplase was the most effective drug for improving clinical outcomes of ischemic stroke.[17] Wu et al[16] demonstrated that rt-PA infusion within 4.5 hours after the onset of symptoms significantly improved the

**Table 3**

**Baseline characteristics of patients with early dramatic recovery (N = 162).**

| Variables | Lenticulostriate artery infarction (N = 137) | Paramedian pontine infarction (N = 67) | $t/z/\chi^2$ | *P* |
|---|---|---|---|---|
| Age, mean ± SD, yr | 62.77 ± 11.55 | 64.03 ± 11.29 | 0.735 | .463 |
| Male, n (%) | 99 (72.3) | 45 (67.2) | 0.563 | .453 |
| History of ischemic stroke, n (%) | 21 (15.3) | 10 (14.9) | 0.006 | .940 |
| Hypertension, n (%) | 93 (67.9) | 37 (55.2) | 3.119 | .077 |
| Diabetes, n (%) | 21 (15.3) | 12 (17.9) | 0.221 | .638 |
| Hyperlipidemia, n (%) | 6 (4.4) | 9 (13.4) | 5.414 | .020 |
| Smoking, n (%) | 51 (37.2) | 20 (29.9) | 1.079 | .299 |
| Drinking history, n (%) | 38 (27.7) | 21 (31.3) | 0.285 | .594 |
| SBP, mean ± SD, mm Hg | 150.41 ± 23.41 | 153.27 ± 19.62 | 0.863 | .389 |
| DBP, mean ± SD, mm Hg | 88.13 ± 16.34 | 87.82 ± 14.14 | –0.133 | .894 |
| TC, mean ± SD, mmol/L | 4.49 ± 0.89 | 4.77 ± 1.10 | 1.917 | .057 |
| TG, median (IQR), mmol/L | 1.20 (0.86, 1.76) | 1.21 (0.91, 1.704) | –0.964 | .335 |
| LDL-C, mean ± SD, mmol/L | 2.70 ± 0.68 | 2.97 ± 1.01 | 2.253 | .025 |
| Baseline blood glucose, median (IQR), mmol/L | 6.50 (5.71, 8.55) | 6.90 (5.70, 8.20) | –0.729 | .466 |
| Uric acid, mean ± SD, mmol/L | 305.07 ± 73.73 | 320.27 ± 88.64 | 1.292 | .198 |
| MPV, median (IQR), fL | 9.26 ± 0.96 | 9.08 ± 0.96 | –1.264 | .208 |
| Onset to treatment time, mean ± SD, min | 137.80 ± 52.16 | 135.76 ± 62.7 | –0.245 | .806 |
| Baseline NIHSS score, median (IQR) | 4 (2, 8) | 5 (2, 11) | –1.922 | .055 |
| NIHSS score at 2 h after rt-PA, median (IQR) | 0 (0, 1) | 0 (0, 2) | –0.731 | .465 |
| NIHSS score at 24 h after rt-PA, median (IQR) | 0 (0, 1) | 0 (0, 1) | –0.758 | .448 |
| Silent brain infarct | 50 (36.5) | 25 (37.3) | 0.013 | .909 |

The measurement data of normal distribution are expressed as mean ± standard deviation (SD), and those of skew distribution are expressed as median and interquartile range (IQR). Categorical variables are expressed as frequency and percentage.

DBP = diastolic blood pressure, LDL-C = low-density lipoprotein cholesterol, MPV = mean platelet volume, NIHSS = National Institutes of Health Stroke Scale, rt-PA = recombinant tissue-type plasminogen activator, SBP = systolic blood pressure, TC = total cholesterol, TG = triglyceride.

**Table 4**

**Multivariate logistic regression analysis models for prediction of early dramatic recovery.**

| | Binary logistic regression analysis | | | |
|---|---|---|---|---|
| | Unmatched cohort adjusted OR (95% CI) | *P* | Matched cohort adjusted OR (95% CI) | *P* |
| Branch atheromatous disease | | | | |
| Diabetes | 0.517 (0.306–0.874) | .014 | 0.477 (0.234–0.972) | .042 |
| NIHSS score at 24 h after rt-PA | 0.496 (0.412–0.596) | <.001 | 0.768 (0.663–0.890) | <.001 |
| Onset to treatment time | 0.989 (0.985–0.993) | <.001 | 0.994 (0.989–0.999) | .017 |
| Lenticulostriate artery infarction | | | | |
| Onset to treatment time | 0.981 (0.986–0.992) | <.001 | 0.989 (0.982–0.995) | .001 |
| NIHSS score at 24 h after rt-PA | 0.449 (0.534–0.636) | <.001 | 0.719 (0.600–0.863) | <.001 |
| Paramedian pontine infarction | | | | |
| Diabetes | 0.362 (0.151–0.866) | .022 | 0.205 (0.059–0.714) | .013 |
| Onset to treatment time | 0.993 (0.986–0.999) | .028 | 0.789 (0.667–0.934) | .006 |
| NIHSS score at 24 h after rt-PA | 0.480 (0.340–0.675) | <.001 | 0.809 (0.656–0.997) | .047 |

NIHSS = National Institutes of Health Stroke Scale, rt-PA = recombinant tissue-type plasminogen activator.

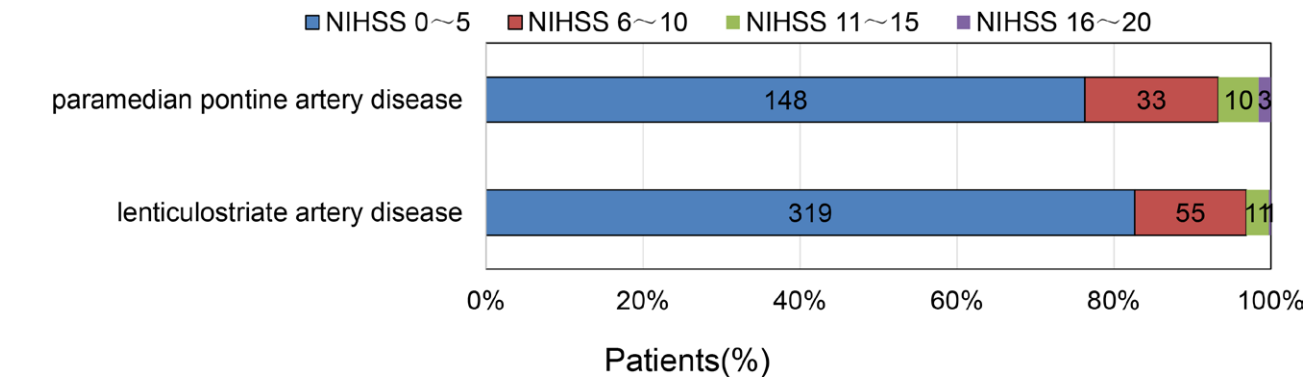


**Figure 2.** Distribution of National Institutes of Health Stroke Scale (NIHSS) scores at 24 h after rt-PA in patients with lenticulostirate artery infarction and paramedian pontine infarction. The higher the patient's NIHSS score, the more severe the disability.

early improvement rate of clinical symptoms in hyperacute BAD patients. The current study (n = 580) showed that intravenous alteplase administered within 4.5 hours of stroke onset increased EDR (35.2%) and more patients had favorable outcomes, which is consistent with a recent study.[18]

Previously, the large sample, randomized and controlled studies have shown that the incidence of cerebral hemorrhage after intravenous thrombolysis ranged from 5.2% to 20.7%.[17,19,20] In our study, the incidence of cerebral hemorrhage was 3.44%, which was far lower than that in the NINDS study (10.6%). In addition, the CT images of cerebral hemorrhage showed no or slight space occupying effect of the hematoma. In this study, we only analyzed patients with cerebral hemorrhage within 24 hours after thrombolysis, and the population thrombolysis was limited to patients with BAD. In addition, our study suggested that neither cerebral hemorrhage nor symptomatic cerebral hemorrhage affected the early neurological function after thrombolysis. This also indicates that only hematoma with obvious space occupying effect can lead to deterioration of nervous system function and poor prognosis.[21]

Previous retrospective studies showed that women and young adults (<60 years) benefited more from rt-PA administration.[22,23] However, in this study, the proportion of female and the age gap of patients were small, leading to differences in the results. The relationship between OTT and EDR in this study is consistent with earlier findings,[24,25] suggesting that early reperfusion is an important factor in achieving EDR 24 hours after intravenous rt-PA. Since the green channel for acute ischemic stroke has been optimized, we can predict a faster OTT and higher EDR incidence after intravenous thrombolysis. Our findings suggest that patients with higher NIHSS scores were more likely to achieve EDR after intravenous thrombolysis. Intravenous injection of thrombolytic drugs can exert thrombolytic effects on smaller thrombus and can quickly relieve clinical symptoms. The NIHSS score can indirectly reflect the quantitative index of thrombus burden. Therefore, a lower NIHSS score after thrombolysis is a clinical predictor of EDR after intravenous thrombolysis.

Additionally, our finding on the association between diabetes and EDR is consistent with the findings of earlier studies,[26,27] indicating that a history of diabetes is a unfavorable factor in achieving EDR in BAD patients at 24 hours after thrombolysis. However, these previous studies have mainly focused on patients with BAD who were not given intravenous thrombolysis. Our findings further pointed out that nondiabetic patients (adjusted OR = 0.205; 95% CI: 0.059–0.714) more often achieved EDR of neurological function, especially in patients with paramedian pontine infarction. The pathogenesis of diabetes-induced atherosclerotic disease is extremely complex, which mainly involves vascular dysfunction caused by ischemia/hypoxia.[28–30] In addition, metabolic abnormalities (such as oxidative stress, protein kinase C, glycation end products, and polyol pathway) caused by hyperglycemia are also involved in its pathogenesis.[31,32] However, none of these mechanisms could explain the greater susceptibility of the paramedian pontine artery to hyperglycemia induced damage. This should be further investigated in further studies.

There are still some limitations. First, we did not control for differences in clinical therapeutic interventions after intravenous thrombolysis. Second, some variables in the baseline data were unbalanced between the 2 groups. A propensity score matching analysis can only adjust for some confounding factors, not all factors inducing bias. Third, this is a single-center retrospective study. Therefore, further studies are warranted.

## 5. Conclusion

In summary, diabetes is an unfavorable predictor of EDR in patients with BAD, especially in patients with paramedian pontine infarction receiving intravenous thrombolysis. EDR is related to OTT. Patients with lower NIHSS scores after thrombolysis have better effect of intravenous thrombolysis. The clinical prognosis of patients with EDR is better than that of patients without EDR. These factors may provide better predictive ability for intravenous thrombolysis in patients with acute BAD, and ultimately help clinicians optimize the treatment plan.

## Author contributions

**Conceptualization:** Yuanyuan Meng, Tianping Tang.
Data curation: Yuanyuan Meng, Yanjun Zhao, Ruixia Wang, Jiangshan Wen.
Formal analysis: Yuanyuan Meng, Yanjun Zhao, Ruixia Wang, Jiangshan Wen.
Investigation: Yanjun Zhao.
Methodology: Yuanyuan Meng.
Project administration: Tianping Tang.
Software: Yuanyuan Meng.
Supervision: Tianping Tang.
Writing – original draft: Yuanyuan Meng.
Writing – review & editing: Tianping Tang.

## References

[1] Nakase T, Yoshioka S, Sasaki M, et al. Clinical evaluation of lacunar infarction and branch atheromatous disease. J Stroke Cerebrovasc Dis. 2013;22:406–12.
[2] Jeong HG, Kim BJ, Yang MH, et al. Neuroimaging markers for early neurologic deterioration in single small subcortical infarction. Stroke. 2015;46:687–91.
[3] Park MG, Oh EH, Kim BK, et al. Intravenous tissue plasminogen activator in acute branch atheromatous disease: does it prevent early neurological deterioration? J Clin Neurosci. 2016;33:194–7.
[4] Rocha J, Pinho J, Varanda S, et al. Dramatic recovery after IV thrombolysis in anterior circulation ischemic stroke: predictive factors and prognosis. Clin Neurol Neurosurg. 2014;125:19–23.
[5] Nakase T, Yamamoto Y, Takagi M; Japan Branch Atheromatous Disease Registry Collaborators. The impact of diagnosing branch atheromatous disease for predicting prognosis. J Stroke Cerebrovasc Dis. 2015;24:2423–8.
[6] Tsivgoulis G, Saqqur M, Sharma VK, et al.; CLOTBUST-PRO investigators. Timing of recanalization and functional recovery in acute ischemic stroke. J Stroke. 2020;22:130–40.
[7] Bilgic AB, Gocmen R, Arsava EM, et al. The effect of clot volume and permeability on response to intravenous tissue plasminogen activator in acute ischemic stroke. J Stroke Cerebrovasc Dis. 2020;29:104541.
[8] Zhou L, Yao M, Peng B, et al. Atherosclerosis might be responsible for branch artery disease: evidence from white matter hyperintensity burden in acute isolated pontine infarction. Front Neurol. 2018;9:840.
[9] Liao S, Deng Z, Wang Y, et al. Different mechanisms of two subtypes of perforating artery infarct in the middle cerebral artery territory: a high-resolution magnetic resonance imaging study. Front Neurol. 2018;9:657.
[10] Petrone L, Nannoni S, Del Bene A, et al. Branch atheromatous disease: a clinically meaningful, yet unproven concept. Cerebrovasc Dis. 2016;41:87–95.
[11] Jovin TG, Chamorro A, Cobo E, et al.; REVASCAT Trial Investigators. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med. 2015;372:2296–306.
[12] Lansberg MG, Thijs VN, Bammer R, et al.; DEFUSE Investigators. Risk factors of symptomatic intracerebral hemorrhage after tPA therapy for acute stroke. Stroke. 2007;38:2275–8.
[13] Campbell BC, Mitchell PJ, Kleinig TJ, et al.; EXTEND-IA Investigators. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. 2015;372:1009–18.
[14] Hart RG, Sharma M, Mundl H, et al.; NAVIGATE ESUS Investigators. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. N Engl J Med. 2018;378:2191–201.
[15] Uchiyama S, Toyoda K, Kitagawa K, et al.; NAVIGATE ESUS Investigators. Branch atheromatous disease diagnosed as embolic stroke of undetermined source: a sub-analysis of NAVIGATE ESUS. Int J Stroke. 2019;14:915–22.

[16] Wu X, Liu Y, Nie C, et al. Efficacy and safety of intravenous thrombolysis on acute branch atheromatous disease: a retrospective case-control study. Front Neurol. 2020;11:581.
[17] National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333:1581–7.
[18] Agarwal S, Scher E, Lord A, et al. Redefined measure of early neurological improvement shows treatment benefit of alteplase over placebo. Stroke. 2020;51:1226–30.
[19] Hacke W, Kaste M, Bluhmki E, et al.; ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008;359:1317–29.
[20] Graham GD. Tissue plasminogen activator for acute ischemic stroke in clinical practice: a meta-analysis of safety data. Stroke. 2003;34:2847–50.
[21] Yang T, Jing H, Cao Y, et al. The relationship of the type of intracerebral hemorrhage to early disease evolution and long-term prognosis after r-tPA thrombolysis. Clin Appl Thromb Hemost. 2021;27:1076029621992125.
[22] Saposnik G, Di Legge S, Webster F, et al. Predictors of major neurologic improvement after thrombolysis in acute stroke. Neurology. 2005;65:1169–74.
[23] Boddu DB, Srinivasarao Bandaru VC, Reddy PG, et al. Predictors of major neurological improvement after intravenous thrombolysis in acute ischemic stroke: a hospital-based study from south India. Neurol India. 2010;58:403–6.
[24] Mazighi M, Meseguer E, Labreuche J, et al. Dramatic recovery in acute ischemic stroke is associated with arterial recanalization grade and speed. Stroke. 2012;43:2998–3002.
[25] Kim DH, Nah HW, Park HS, et al. Factors associated with early dramatic recovery following successful recanalization of occluded artery by endovascular treatment in anterior circulation stroke. J Clin Neurosci. 2017;46:171–5.
[26] Yamamoto Y, Ohara T, Hamanaka M, et al. Characteristics of intracranial branch atheromatous disease and its association with progressive motor deficits. J Neurol Sci. 2011;304:78–82.
[27] Umemura T, Senda J, Fukami Y, et al. Impact of albuminuria on early neurological deterioration and lesion volume expansion in lenticulostriate small infarcts. Stroke. 2014;45:587–90.
[28] Rask-Madsen C, King GL. Vascular complications of diabetes: mechanisms of injury and protective factors. Cell Metab. 2013;17:20–33.
[29] Merlino G, Smeralda C, Sponza M, et al. Dynamic hyperglycemic patterns predict adverse outcomes in patients with acute ischemic stroke undergoing mechanical thrombectomy. J Clin Med. 2020;9:1932.
[30] Liu Q, Wang S, Cai L. Diabetic cardiomyopathy and its mechanisms: role of oxidative stress and damage. J Diabetes Investig. 2014;5:623–34.
[31] Umemura T, Kawamura T, Hotta N. Pathogenesis and neuroimaging of cerebral large and small vessel disease in type 2 diabetes: a possible link between cerebral and retinal microvascular abnormalities. J Diabetes Investig. 2017;8:134–48.
[32] Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. Lancet Neurol. 2019;18:684–96.