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Factors Associated With Short-Term Neurological Improvement Following Perforating Artery Disease-Related Infarction: A Single-Center Retrospective Cohort Study

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Abstract

Aims/Background: Perforating artery disease (PAD) is a common yet heterogeneous stroke subtype with variable short-term recovery patterns. Identifying early predictors of neurological improvement may facilitate the development of individualized treatment strategies. This study aimed to investigate the independent factors influencing short-term neurological improvement in patients with acute infarction due to PAD. **Methods:** This single-center retrospective cohort study consecutively enrolled 243 inpatients diagnosed with PAD-related acute ischemic stroke between January 2020 and June 2025. PAD was diagnosed based on isolated infarcts within perforating artery territories on diffusion-weighted imaging (DWI), after excluding large-artery stenosis and other definite etiologies. Demographic characteristics, clinical features, laboratory results, and imaging data were collected. The degree of short-term neurological improvement (Δ NIHSS), defined as the difference between admission and day-14 National Institutes of Health Stroke Scale (NIHSS) scores, was used as the dependent variable. These variables were initially screened using univariate linear regression ($p < 0.05$), followed by bidirectional stepwise regression based on the Akaike Information Criterion (AIC) to construct a multivariable linear regression model. Subgroup analyses were performed according to infarct location (anterior vs. posterior circulation), and interaction tests were performed to assess the modifying effect of infarct location on individual factors. **Results:** Multivariable stepwise regression identified fasting glucose ($\beta = -0.205$, 95% confidence interval [CI]: -0.364 to -0.046 , $p = 0.012$), diabetes mellitus ($\beta = -0.180$, -0.339 to -0.022 , $p = 0.026$), total cerebral small vessel disease (CSVD) burden score ($\beta = -0.255$, -0.365 to -0.145 , $p < 0.001$), early neurological deterioration (END; $\beta = -0.238$, -0.347 to -0.128 , $p < 0.001$), and baseline NIHSS score ($\beta = -0.158$, -0.265 to -0.050 , $p = 0.004$) as independent factors associated with Δ NIHSS (adjusted $R^2 = 0.283$). In patients with anterior circulation infarction, diabetes mellitus, total CSVD burden, END, and baseline NIHSS score were independently associated with Δ NIHSS (adjusted $R^2 = 0.355$). In patients with posterior circulation infarction, only total CSVD burden score and END remained significant, while fasting glucose, diabetes mellitus, and baseline NIHSS score did not reach statistical significance (all $p > 0.05$; adjusted $R^2 = 0.290$). Interaction analysis revealed no significant effect modification by infarct location (all $p > 0.05$). **Conclusions:** These findings suggest that early glycemic monitoring, CSVD burden assessment, and END surveillance may facilitate risk stratification, and that underlying microvascular pathology may impair neurorepair capacity in PAD patients. Total CSVD burden and END exhibited the largest effect sizes, followed by fasting glucose, diabetes mellitus, and baseline NIHSS score, all of which are independent predictors. The effects of these factors do not differ significantly between anterior and posterior circulation infarctions.

Keywords: perforating artery disease; infarction; functional recovery; linear regression models

1. Introduction

Perforating artery disease (PAD) constitutes a major etiological subtype of acute ischemic stroke, accounting for approximately 15%–26% of all cases [1]. The pathophysiology of PAD primarily involves two mechanisms: microatheroma at the origin of proximal penetrating arteries (i.e., branch atheromatous disease, BAD) and lipohyalinosis of distal penetrating arteries (i.e., classic lacunar infarction). Although both may present as single subcortical small infarcts on diffusion-weighted imaging (DWI), their clinical courses and prognoses differ considerably. Compared with lipohyalinosis-related lacunar infarctions, BAD-related strokes are more susceptible to early neurological

deterioration (END) and are associated with poorer short-term and long-term functional outcomes [2,3]. Therefore, an in-depth investigation of factors influencing neurological recovery in PAD patients is crucial for early identification of high-risk individuals and for guiding individualized treatment strategies.

Recent studies have extensively explored risk factors associated with poor prognosis in PAD. Clinically, multiple studies have demonstrated that advanced age, hypertension, diabetes mellitus, hyperglycemia, and greater baseline neurological deficit severity (National Institutes of Health Stroke Scale, NIHSS) are closely associated with patient outcomes [2,4]. Kanazawa et al. [2], in an analysis of

201 patients with perforator artery infarction, identified age >69 years as an independent predictor of END. Regarding imaging markers, maximal infarct diameter is considered an important determinant of END and poor functional outcome. BAD is typically defined by an infarct diameter ≥ 15 mm on DWI or involvement of three or more axial slices, with larger infarcts suggesting more extensive involvement of the primary perforator territory and a poorer prognosis [5]. Furthermore, the total cerebral small vessel disease (CSVD) burden, a composite imaging score incorporating white matter hyperintensities, lacunes, cerebral microbleeds, and enlarged perivascular spaces [6], has been shown to independently predict functional recovery following ischemic stroke [7,8]. Huang et al. [7], in a study of acute ischemic stroke patients undergoing endovascular treatment, reported that a moderate-to-severe total CSVD burden was significantly associated with reduced NIHSS improvement at 7 days. CSVD may not only reflect underlying microvascular pathology but also impair post-stroke neurorepair processes by disrupting the integrity and plasticity of neural networks [6].

However, several limitations remain in existing literature. First, most studies focus on the occurrence of END or long-term functional outcomes, such as the 90-day modified Rankin Scale score, whereas less attention has been paid to dynamic changes in short-term neurological improvement (e.g., within two weeks). The degree of short-term neurological improvement (Δ NIHSS) may more sensitively reflect treatment response and early neuroplasticity, thereby providing valuable information to guide early rehabilitation interventions and predict long-term outcomes. Second, PAD-related infarctions can occur in both the anterior circulation (e.g., lenticulostriate arteries) and posterior circulation (e.g., thalamogeniculate arteries and paramedian pontine arteries). Differences in anatomical characteristics and collateral compensatory capacity between these vascular territories may contribute to heterogeneity in prognostic factors. Demir Unal [9], in a comparison of 100 patients with anterior and posterior circulation acute ischemic stroke, demonstrated that anterior circulation infarctions were associated with greater early clinical disability, while the NIHSS was more effective and reliable for assessing anterior circulation strokes. Multiple previous studies have analyzed anterior and posterior circulation infarctions together or focused on a single location, lacking subgroup comparisons and interaction analyses based on infarct location. Third, although the prognostic value of total CSVD burden in ischemic stroke has gained increasing recognition, its independent role in short-term neurological improvement following PAD-related infarction requires further validation.

Against this background, the present study employed a single-center retrospective cohort design and consecutively enrolled patients with MRI-confirmed PAD-related infarction. We systematically evaluated the effects of demo-

graphic characteristics, vascular risk factors, laboratory parameters, and imaging variables on neurological improvement within 14 days after admission (Δ NIHSS). Using multivariable stepwise linear regression, we aimed to identify independent factors associated with short-term neurological improvement in PAD patients; compare the spectrum of influencing factors between anterior and posterior circulation subgroups using stratified analyses and interaction testing; and provide evidence-based support for the early identification of patients with different recovery potentials and the optimization of individualized management strategies.

2. Methods

2.1 Study Population

This was a single-center, retrospective, observational cohort study conducted between January 2020 and June 2025. The study protocol was approved by the Institutional Review Board of Ningbo Zhenhai People's Hospital (Approval No. 2026-007). Due to the retrospective nature of the study and the anonymization of patient data, the requirement for individual informed consent was waived. The study was conducted in accordance with the principles of the Declaration of Helsinki.

The inclusion criteria were as follows: (1) age ≥ 18 years; (2) clinical diagnosis of acute ischemic stroke, with MRI completed within 72 hours of symptom onset (all patients had a known onset time); (3) hospital admission within 7 days of symptom onset (MRI could be performed either before or upon admission); and (4) fulfilment of the imaging diagnostic criteria for PAD on DWI, defined as a single acute infarct within a perforating artery territory on DWI, without $\geq 50\%$ stenosis or occlusion of the corresponding parent artery (e.g., the M1 segment of the middle cerebral artery or the basilar artery) [2,10].

The exclusion criteria were as follows: (1) stroke etiology definitively identified as non-PAD (e.g., cardioembolism, large-artery atherosclerosis, or other determined etiologies); (2) pre-existing significant disability (pre-stroke modified Rankin Scale score ≥ 2); (3) death, discharge against medical advice, or transfer within 14 days after admission, resulting in unavailable outcome assessment; and (4) incomplete data, including missing primary outcome data or key covariates.

2.2 Data Collection

Data were extracted from the electronic medical record system.

Primary Outcome Variable:

Short-term neurological improvement was defined as Δ NIHSS = baseline NIHSS score at admission – NIHSS score on day 14 after admission. NIHSS assessments at admission and on day 14 were performed by certified neurologists who were not involved in the study design or hypothesis generation and were blinded to the clinical and imaging data of the patients.

Potential Predictor Variables:

Demographics and Baseline Characteristics: Age, sex, and admission blood pressure. **Vascular Risk Factors:** Hypertension, diabetes mellitus, hyperlipidemia, current smoking, and history of prior stroke or transient ischemic attack (TIA). Hyperlipidemia was defined according to the Chinese Guidelines for the Prevention and Treatment of Dyslipidemia in Adults (2016 revision) [11] as total cholesterol ≥ 6.2 mmol/L, triglycerides ≥ 2.3 mmol/L, LDL-C ≥ 4.1 mmol/L, HDL-C < 1.0 mmol/L, or current use of lipid-lowering medication. **Stroke Characteristics and Management:** Baseline NIHSS score and early neurological deterioration (END), defined as an increase of ≥ 2 points in the NIHSS score within 72 hours after admission. **Laboratory Parameters:** Fasting glucose, hemoglobin A1c (HbA1c), low-density lipoprotein cholesterol (LDL-C), C-reactive protein (CRP), albumin, and homocysteine. **Imaging Parameters:** Imaging assessments were independently performed by two experienced neurologists trained in neuroimaging evaluation who were blinded to the clinical data. Any disagreements were resolved through consensus; if consensus could not be reached, a third senior neuroimaging expert was consulted for adjudication.

Infarct location was categorized as anterior circulation (lenticulostriate artery territory, internal capsule, and corona radiata), posterior circulation (thalamogeniculate artery territory or paramedian pontine artery territory), or other. Locations classified as ‘other’ included the other thalamic perforator territories (e.g., tuberothalamic artery or paramedian thalamic artery), and infarcts within unclassifiable perforating artery territories. The maximal infarct diameter was measured on DWI as the largest axial diameter (mm) of the acute infarct lesion. The total cerebral small vessel disease (CSVD) burden score (range: 0–4) was assessed using standardized criteria, with one point assigned for each of the following imaging markers: (1) white matter hyperintensities, defined as a Fazekas deep white matter score ≥ 2 or periventricular score ≥ 2 ; (2) presence of ≥ 1 lacune; (3) presence of ≥ 1 cerebral microbleed; and (4) moderate-to-severe enlarged perivascular spaces (grade 2–3) in the basal ganglia. Early rehabilitation was defined as initiation of standardized rehabilitation therapy (including physical therapy and/or occupational therapy) within 72 hours after admission, as documented in the medical records.

2.3 Statistical Analysis

Statistical analyses were performed using R software (version 4.5.2; R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were expressed as mean $\pm$ standard deviation (SD) or median (interquartile range [IQR]), as appropriate, whereas categorical variables were presented as frequency (percentage). The normality of continuous variables was assessed using the Shapiro-Wilk test.

First, univariate linear regression analyses were performed to screen variables associated with Δ NIHSS. Variables with $p < 0.05$ in the univariate analyses were entered into the multivariable analysis. Subsequently, all selected variables were included, and bidirectional stepwise regression based on the Akaike Information Criterion (AIC) was applied to construct the final multivariable linear regression model. To enable comparison of the relative effect sizes of predictors measured on different scales, all continuous and binary predictors, as well as the dependent variable (Δ NIHSS), were standardized as $(x - \text{mean})/\text{SD}$ before fitting the regression models.

Model diagnostics included the following: multicollinearity assessed using the variance inflation factor (VIF), with $\text{VIF} > 5$ considered to indicate significant collinearity; linearity was evaluated using residual-versus-fitted plots and partial residual plots; normality of residuals was assessed using Q-Q plots and the Shapiro-Wilk test; homoscedasticity was examined using the Breusch-Pagan test; and influential observations were identified using Cook’s distance.

For subgroup analyses, multivariable linear regression models were fitted separately for the anterior and posterior circulation groups after excluding patients with ‘other’ infarct locations. The core predictors identified in the overall model were included in each subgroup model. No additional variable selection was performed within subgroups due to the limited sample size, particularly in the posterior circulation group. To evaluate whether infarct location modified the effects of the key predictor variables, a combined linear regression model was constructed using the full dataset after excluding patients with ‘other’ infarct locations. This model included the core variables identified from the overall model as main effects, along with interaction terms between each predictor and infarct location (anterior vs. posterior). All main effects and interaction terms were entered simultaneously into the model. All statistical tests were two-tailed, and $p < 0.05$ was considered statistically significant.

3. Results

3.1 Baseline Characteristics

A total of 243 patients with PAD-related infarction were included in the study. The mean age was 63.8 ± 9.8 years, and 121 patients (49.8%) were male. The proportions of hypertension, diabetes mellitus, hyperlipidemia, current smoking, and prior stroke/TIA were 63.4%, 23.9%, 40.3%, 28.8%, and 11.5%, respectively. The median baseline NIHSS score was 4.0 [IQR, 3.0–6.0], and the incidence of early neurological deterioration was 18.1%.

Laboratory findings showed a median fasting glucose level of 5.8 [IQR, 5.0–6.6] mmol/L, a median HbA1c level of 5.5% [IQR, 5.3–6.0], and a median LDL-C level of 2.7 [IQR, 2.0–3.4] mmol/L. Among the inflammatory and nutritional markers, the median CRP level was 2.8 [IQR, 1.7–

4.1] mg/L, the median albumin level was 40.4 [IQR, 37.4–43.7] g/L, and the median homocysteine level was 9.8 [IQR, 7.7–11.8] μ mol/L. The mean systolic blood pressure was 139.3 $\pm$ 14.4 mmHg, and the mean diastolic blood pressure was 85.3 $\pm$ 9.9 mmHg.

In terms of imaging characteristics, infarct locations were distributed as follows: anterior circulation in 120 patients (49.4%), posterior circulation in 98 patients (40.3%), and other locations in 25 patients (10.3%). The median maximal infarct diameter was 9.4 [IQR, 7.0–12.1] mm, and the median total CSVD burden score was 3.0 [IQR, 2.0–3.0]. The mean Δ NIHSS was 1.5 $\pm$ 3.0. Early rehabilitation was implemented in 141 patients (58.0%). Additional baseline characteristics are detailed in Table 1.

Table 1. Baseline characteristics of the study population.

Characteristic	Overall Cohort (n = 243)
Age, years	63.8 $\pm$ 9.8
Male sex, n (%)	121 (49.8)
Hypertension, n (%)	154 (63.4)
Diabetes mellitus, n (%)	58 (23.9)
Hyperlipidemia, n (%)	98 (40.3)
Current smoking, n (%)	70 (28.8)
Prior stroke/TIA, n (%)	28 (11.5)
Baseline NIHSS score	4.0 [3.0–6.0]
Early neurological deterioration, n (%)	44 (18.1)
Early rehabilitation, n (%)	141 (58.0)
Systolic blood pressure, mmHg	139.3 $\pm$ 14.4
Diastolic blood pressure, mmHg	85.3 $\pm$ 9.9
Fasting glucose, mmol/L	5.8 [5.0–6.6]
Hemoglobin A1c, (%)	5.5 [5.3–6.0]
Low-density lipoprotein cholesterol, mmol/L	2.7 [2.0–3.4]
C-reactive protein, mg/L	2.8 [1.7–4.1]
Albumin, g/L	40.4 [37.4–43.7]
Homocysteine, μ mol/L	9.8 [7.7–11.8]
Infarct location, n (%)	
Anterior circulation	120 (49.4)
Posterior circulation	98 (40.3)
Other	25 (10.3)
Maximal infarct diameter, mm	9.4 [7.0–12.1]
Total CSVD burden score	3.0 [2.0–3.0]

Data are presented as mean $\pm$ SD, median [IQR], or n (%), as appropriate.

Abbreviations: CSVD, cerebral small vessel disease; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack; SD, standard deviation; IQR, interquartile range.

3.2 Univariate Linear Regression Analysis

Univariate linear regression analyses (Table 2) demonstrated that fasting glucose, diabetes mellitus, HbA1c, total CSVD burden score, END, and baseline

NIHSS score were significantly associated with Δ NIHSS (all $p < 0.05$). No significant associations were observed for the remaining variables (all $p > 0.05$).

3.3 Multivariable Analysis

The six variables with $p < 0.05$ in univariate analyses (fasting glucose, diabetes mellitus, HbA1c, total CSVD burden, END, baseline NIHSS score) were entered into the full model. Bidirectional stepwise regression based on the AIC selected a final model that retained five variables (Table 3). Fasting glucose, diabetes mellitus, total CSVD burden, END, and baseline NIHSS score were all independently and negatively associated with Δ NIHSS. The model's adjusted $R^2 = 0.283$, and the overall model was statistically significant (F -test, $p < 0.001$).

Model diagnostics showed all VIFs < 5 , suggesting no evidence of substantial multicollinearity. Residuals were approximately normally distributed (Shapiro-Wilk test, $p = 0.422$), and homoscedasticity was supported by the Breusch-Pagan test ($p = 0.546$). All Cook's distance values were within acceptable limits, indicating no influential observations. Linearity assumptions were supported by residual-versus-fitted plots and partial residual plots, which showed no evidence of nonlinearity.

3.4 Subgroup and Interaction Analyses

After excluding 25 patients with infarcts classified as 'other' locations, separate multivariable linear regression analyses were performed for the anterior circulation subgroup (lenticulostriate territory, $n = 120$) and the posterior circulation subgroup (thalamogeniculate and paramedian pontine artery territories, $n = 98$). The results are presented in Table 4.

Anterior Circulation Subgroup: Diabetes mellitus ($\beta = -0.272$, $p = 0.025$), total CSVD burden score ($\beta = -0.234$, $p = 0.002$), END ($\beta = -0.259$, $p < 0.001$), and baseline NIHSS score ($\beta = -0.192$, $p = 0.005$) were significantly associated with Δ NIHSS. Fasting glucose did not reach statistical significance ($\beta = -0.166$, $p = 0.176$). The model yielded an adjusted R^2 of 0.355.

Posterior Circulation Subgroup: Only total CSVD burden score ($\beta = -0.317$, $p = 0.001$) and END ($\beta = -0.312$, $p = 0.004$) remained significantly associated with Δ NIHSS. Fasting glucose ($\beta = -0.220$, $p = 0.083$), diabetes mellitus ($\beta = -0.182$, $p = 0.157$), and baseline NIHSS score ($\beta = -0.142$, $p = 0.167$) were not statistically significant. The adjusted R^2 of the model was 0.290.

To formally evaluate effect modification by infarct location, a combined linear regression model incorporating interaction terms between infarct location (anterior vs. posterior) and each key predictor was constructed using the full dataset after excluding patients with 'other' infarct locations. The model included interaction terms for fasting glucose, total CSVD burden score, baseline NIHSS score, diabetes mellitus, and END. None of the interaction terms

Table 2. Univariate linear regression analysis of factors associated with Δ NIHSS.

Variable	β (95% CI)	<i>p</i> -value
Fasting glucose, mmol/L	−0.339 (−0.459, −0.220)	<0.001
Diabetes mellitus (yes vs. no)	−0.338 (−0.458, −0.219)	<0.001
Hemoglobin A1c, %	−0.302 (−0.423, −0.181)	<0.001
Total CSVD burden score	−0.294 (−0.415, −0.173)	<0.001
Early neurological deterioration (yes vs. no)	−0.293 (−0.414, −0.172)	<0.001
Baseline NIHSS score	−0.146 (−0.271, −0.020)	0.023
Maximal infarct diameter, mm	0.119 (−0.007, 0.245)	0.065
Age, years	−0.088 (−0.214, 0.039)	0.172
Homocysteine, μ mol/L	0.086 (−0.041, 0.212)	0.183
Current smoking (yes vs. no)	−0.058 (−0.184, 0.069)	0.371
Diastolic blood pressure, mmHg	−0.056 (−0.182, 0.071)	0.388
Hypertension (yes vs. no)	−0.054 (−0.181, 0.073)	0.404
Early rehabilitation (yes vs. no)	0.050 (−0.077, 0.176)	0.440
Low-density lipoprotein cholesterol, mmol/L	0.048 (−0.078, 0.175)	0.454
C-reactive protein, mg/L	0.047 (−0.080, 0.174)	0.468
Prior stroke/TIA (yes vs. no)	−0.040 (−0.167, 0.087)	0.534
Albumin, g/L	−0.028 (−0.155, 0.099)	0.667
Hyperlipidemia (yes vs. no)	−0.027 (−0.154, 0.100)	0.676
Sex (Male vs. female)	0.015 (−0.112, 0.142)	0.817
Infarct location (posterior vs. anterior)	−0.031 (−0.300, 0.238)	0.822
Infarct location (other vs. anterior)	−0.035 (−0.470, 0.400)	0.875
Systolic blood pressure, mmHg	−0.010 (−0.137, 0.117)	0.881

Abbreviations: CI, confidence interval; CSVD, cerebral small vessel disease; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

Table 3. Multivariable linear regression model for Δ NIHSS.

Variable	β (95% CI)	<i>p</i> -value
Fasting glucose, mmol/L	−0.205 (−0.363, −0.047)	0.012
Diabetes mellitus (yes vs. no)	−0.180 (−0.339, −0.022)	0.026
Total CSVD burden score	−0.255 (−0.364, −0.146)	<0.001
Early neurological deterioration (yes vs. no)	−0.238 (−0.347, −0.128)	<0.001
Baseline NIHSS score	−0.158 (−0.265, −0.050)	0.004
Adjusted R^2	0.283	

Abbreviations: CI, confidence interval; CSVD, cerebral small vessel disease; NIHSS, National Institutes of Health Stroke Scale.

Table 4. Multivariable linear regression analyses stratified by infarct location.

Variable	Anterior circulation (n = 120)		Posterior circulation (n = 98)	
	β (95% CI)	<i>p</i> -value	β (95% CI)	<i>p</i> -value
Fasting glucose, mmol/L	−0.166 (−0.407, 0.075)	0.176	−0.220–0.4 (70, 0.029)	0.083
Diabetes mellitus (yes vs. no)	−0.272 (−0.508, −0.035)	0.025	−0.182 (−0.436, 0.071)	0.157
Total CSVD burden score	−0.234 (−0.382, −0.085)	0.002	−0.317 (−0.498, −0.136)	<0.001
Early neurological deterioration (yes vs. no)	−0.259 (−0.401, −0.118)	<0.001	−0.312 (−0.520, −0.105)	0.004
Baseline NIHSS score	−0.192 (−0.324, −0.060)	0.005	−0.142 (−0.344, 0.060)	0.167
Adjusted R^2	0.355		0.290	

Abbreviations: CI, confidence interval; CSVD, cerebral small vessel disease; NIHSS, National Institutes of Health Stroke Scale.

reached statistical significance (all $p > 0.05$; Table 5), indicating that infarct location did not significantly modify the

effects of these predictors on Δ NIHSS. Consequently, the observed differences in variable significance between the

Table 5. Interaction analyses between infarct location and key predictors.

Interaction term	β (95% CI)	<i>p</i> -value
Fasting glucose $\times$ infarct location	−0.006 (−0.260, 0.249)	0.964
Total CSVD burden score $\times$ infarct location	0.096 (−0.166, 0.358)	0.471
Baseline NIHSS score $\times$ infarct location	−0.132 (−0.409, 0.145)	0.348
Diabetes mellitus $\times$ infarct location	−0.026 (−0.281, 0.229)	0.841
Early neurological deterioration $\times$ infarct location	0.072 (−0.203, 0.346)	0.607

Note: Infarct location was coded with posterior circulation as the reference and anterior circulation as the comparison group. None of the interaction terms were statistically significant (all $p > 0.05$), indicating no evidence of effect modification.

Abbreviations: CI, confidence interval; CSVD, cerebral small vessel disease; NIHSS, National Institutes of Health Stroke Scale.

subgroup models may be attributable to differences in sample size and clinical characteristics rather than true effect heterogeneity.

4. Discussion

In this single-center retrospective study of 243 patients with PAD-related infarction, we systematically investigated factors associated with short-term neurological improvement (Δ NIHSS) within 14 days after admission. Multivariable stepwise regression identified fasting glucose, diabetes mellitus, total CSVD burden score, early neurological deterioration (END), and baseline NIHSS score as independent factors associated with Δ NIHSS (adjusted $R^2 = 0.283$). Subgroup analyses revealed that, in anterior circulation infarctions, diabetes mellitus, total CSVD burden, END, and baseline NIHSS score were independently associated with Δ NIHSS, while fasting glucose did not reach statistical significance. In posterior circulation infarctions, only total CSVD burden and END remained statistically significant. Interaction analyses revealed no significant modification of these associations by infarct location. Collectively, these findings provide new insights into the mechanisms and clinical management of short-term neurological recovery following PAD-related infarction.

Our study demonstrated that fasting glucose ($\beta = -0.205$, $p = 0.012$) and diabetes mellitus ($\beta = -0.180$, $p = 0.026$) were independently and negatively associated with Δ NIHSS, indicating that acute hyperglycemia and diabetes mellitus may adversely affect early neurological recovery in PAD patients. Although hemoglobin A1c (HbA1c) was significantly associated with Δ NIHSS in the univariate analysis, it was not retained in the final multivariable model, suggesting that acute glycemic status may be more closely related to short-term neurological improvement than chronic glycemic control in this cohort.

Previous studies have consistently demonstrated an association between hyperglycemia and unfavorable stroke outcomes. A meta-analysis by Capes et al. [12] demonstrated that admission hyperglycemia was associated with a 3.28-fold increase in the risk of in-hospital or 30-day mortality and a 1.41-fold increase in the risk of poor functional

recovery among non-diabetic patients with ischemic stroke. Within the PAD subtype, Kanazawa et al. [2] identified diabetes mellitus as an independent risk factor for END in patients with perforator artery infarction. The mechanisms linking hyperglycemia to poor neurological recovery are likely multifactorial. Acute hyperglycemia may exacerbate tissue acidosis, excitotoxicity, oxidative stress, and inflammatory responses within ischemic penumbra, thereby promoting neuronal injury and apoptosis [13].

From a clinical perspective, these findings suggest that management of PAD should not be limited to long-term glycemic control alone. Early careful monitoring of glucose levels, together with appropriate glycemic management during the acute phase, may be important for optimizing neurological recovery. The relatively low adjusted R^2 (0.283) indicates that a substantial proportion of the variability in Δ NIHSS remains unexplained. This finding suggests that additional unmeasured factors, such as dynamic inflammatory markers, cerebral collateral circulation status, and rehabilitation intensity, may also contribute to short-term neurological recovery.

A core finding of this study was that the total CSVD burden score was significantly and independently associated with Δ NIHSS across all models (overall: $\beta = -0.255$; anterior $\beta = -0.234$; posterior $\beta = -0.317$), highlighting its importance as an independent factor associated with short-term neurological improvement in patients with PAD. Among all retained variables, total CSVD burden score ($\beta = -0.255$) and END ($\beta = -0.238$) exhibited the largest effect sizes in the overall model, followed by fasting glucose ($\beta = -0.205$), diabetes mellitus ($\beta = -0.180$), and baseline NIHSS score ($\beta = -0.158$). A previous study has shown that a higher total CSVD burden score is also associated with global cognitive decline [14]. Huang et al. [7] reported that moderate-to-severe total CSVD burden was independently associated with reduced NIHSS improvement at 7 days among patients with acute ischemic stroke undergoing endovascular treatment.

Several mechanisms may explain the association between CSVD burden and impaired neurological recovery. CSVD-related blood-brain barrier leakage and chronic

cerebral hypoperfusion may impair collateral circulation and reduce compensatory capacity within the ischemic penumbra [15,16,17,18]. These findings underscore the potential value of routinely assessing overall CSVD burden in clinical practice to facilitate risk stratification and improve prediction of early recovery trajectories and inform interventions aimed at improving microvascular health (e.g., strict blood pressure control, antiplatelet therapy).

Although none of the interaction terms reached statistical significance, the relatively small sample size of the posterior circulation subgroup ($n = 98$) may have reduced the power to detect effect modification. Therefore, the absence of significant interactions should be interpreted with caution, and larger multicenter studies are warranted to confirm the homogeneity of effects across locations.

In our study, baseline NIHSS score was significantly and negatively associated with Δ NIHSS ($\beta = -0.158$, $p = 0.004$), indicating that greater neurological deficit severity at presentation was associated with less short-term neurological improvement. Saver et al. [19] reported that each 30-minute delay in stroke treatment reduced the probability of a favorable outcome by approximately 10%, with baseline NIHSS representing a key determinant of treatment benefit. Baseline neurological deficits may reflect infarct severity and the involvement of critical functional pathways. More severe deficits are often associated with larger functional impairment and reduced potential for neurological recovery.

In subgroup analyses, baseline NIHSS score remained an independent factor only in patients with anterior circulation infarction and not in those with posterior circulation infarction. This finding may be related to the design characteristics of the NIHSS. The scale emphasizes symptoms commonly observed in anterior circulation stroke, including aphasia, visual field deficits, and motor weakness, but is less sensitive to symptoms typical of posterior circulation stroke, such as vertigo, diplopia, and ataxia. Consequently, the NIHSS may underestimate the true neurological deficit in some cases of posterior circulation disease [20]. Demir Unal [9] similarly reported that the NIHSS is more effective and reliable for assessing anterior circulation strokes than posterior circulation strokes. However, because the interaction term between baseline NIHSS score and infarction location was not statistically significant ($p = 0.348$), the lack of statistical significance in the posterior circulation subgroup may be due to the limited sample size ($n = 98$) and reduced statistical power rather than a true biological difference in effect. Therefore, the prognostic relevance of baseline NIHSS score for short-term neurological recovery in the overall PAD population remains clinically relevant.

Early neurological deterioration (END) was also independently associated with Δ NIHSS in the overall model ($\beta = -0.238$, $p < 0.001$) and remained significant in both the anterior ($\beta = -0.259$, $p < 0.001$) and posterior ($\beta = -0.312$, $p = 0.004$) circulation subgroups. Mechanistically, END

in PAD is frequently driven by progressive infarct enlargement and hemodynamic compromise due to proximal perforator pathology, which may extend the ischemic penumbra and limit early neurorepair [2,3,5]. In addition, a higher total CSVD burden may reflect underlying microvascular pathology and impair post-stroke neurorepair, as suggested by the independent association between moderate-to-severe CSVD burden and reduced NIHSS improvement at 7 days in patients receiving endovascular treatment [7]. Clinically, these findings underscore the importance of early identification of patients at risk for END through enhanced neurological monitoring. Timely escalation of antithrombotic therapy may be warranted to halt neurological decline in these patients. However, it is important to note that the standardized coefficients of the binary predictors (diabetes and END) represent the effect of a change from 0 to 1 in standard deviations (SD), depending on the prevalence of these diseases, and are not directly equivalent to the effect of a change of 1 standard deviation (SD) in the continuous predictors. Therefore, the ordering of effect sizes in this study should be interpreted as descriptive rather than deterministic.

Although the variables retained in the subgroup models differed slightly between the anterior and posterior circulation groups, formal interaction analyses incorporating all five core predictors (fasting glucose, total CSVD burden, baseline NIHSS score, diabetes mellitus, and END) revealed no statistically significant interactions with infarct location (all $p > 0.05$). These findings suggest that the associations between the factors and Δ NIHSS do not differ substantially between anterior and posterior circulation infarction. This finding aligns with the findings of Fan et al. [21], who reported no significant difference in the prognostic performance of the ASTRAL score between anterior and posterior circulation stroke patients treated with thrombolysis.

The observed differences in retained variables between subgroup models likely stem from limited sample size and variations in the distribution of clinical characteristics. Furthermore, the slightly higher adjusted R^2 in the anterior circulation model (0.355) compared with the posterior circulation model (0.290) may, at least in part, reflect the greater sensitivity of the NIHSS to deficits commonly observed in anterior circulation stroke. Future studies with larger sample sizes and external validation are warranted to further explore potential differences between anterior and posterior circulation infarctions.

Our findings have several implications for the clinical management of patients with PAD. First, glycemic management warrants attention during both the acute and chronic phases of care. Close monitoring of blood glucose levels after admission may help prevent hyperglycemia-induced neuronal injury, while appropriate long-term glycemic control may contribute to overall cerebrovascular health. Second, given the association between total CSVD burden

and reduced neurological improvement, routine reporting of CSVD burden on admission imaging may help clinicians identify patients with lower recovery potential. Such information may support individualized rehabilitation planning and optimization of vascular risk factor management. Third, baseline NIHSS score remains a readily available and clinically useful tool for early risk stratification, especially in patients with anterior circulation infarction. Finally, although no substantial effect modification by infarct location was observed, clinical assessment may benefit from consideration of location-specific characteristics. Greater attention to baseline neurological deficit severity may be particularly relevant in anterior circulation infarctions, whereas assessment of CSVD burden appears important in both vascular territories and may be especially valuable in posterior circulation infarctions, where the NIHSS may underestimate neurological impairment. Collectively, these findings provide an evidence base for more individualized management strategies in PAD patients.

5. Limitation

This study has several limitations. First, the single-center retrospective design may have introduced selection and information biases, thereby limiting the generalizability of the findings. Second, the study evaluated only short-term neurological improvement (Δ NIHSS) at 14 days after admission. Furthermore, the NIHSS has inherent limitations, including nonlinearity, unequal item weighting, and lower sensitivity for posterior circulation deficits. Moreover, long-term functional outcomes, such as the 90-day mRS score, were not assessed. Third, several potentially important confounding factors were not included, including inflammatory markers (e.g., neutrophil-to-lymphocyte ratio and interleukin-6), platelet function indices, collateral circulation status, and detailed treatment-related variables (e.g., antiplatelet therapy, statin use, and rehabilitation intensity). Fourth, although the total CSVD burden score was evaluated, the independent contributions of its individual components (e.g., white matter hyperintensities and lacunes) were not examined. Fifth, branch atheromatous disease (BAD) and lacunar infarction were not analyzed separately, despite their potentially distinct pathophysiological mechanisms and prognostic profiles. Finally, the subgroup sample sizes, especially in the posterior circulation group ($n = 98$), were relatively small, which may have reduced statistical power and increased the risk of type II errors and model instability. Therefore, external validation in larger prospective multicenter cohorts is warranted.

6. Conclusion

In summary, among patients with PAD-related infarction, lower fasting glucose levels, absence of diabetes mellitus, lower total CSVD burden, absence of END, and milder baseline neurological deficits are independently associated with greater neurological improvement within 14 days af-

ter admission, with CSVD burden and END demonstrating the largest effect size among them. Although the spectrum of factors retained in subgroup models differed slightly between anterior and posterior circulation subgroups, interaction analyses revealed no statistically significant evidence that infarct location modifies the associations between these factors and Δ NIHSS. These findings may facilitate early identification of patients with varying recovery potential and provide evidence to support individualized glycemic management, and secondary prevention strategies. Future prospective multicenter studies are needed to validate these findings and further investigate the prognostic significance of individual CSVD components on PAD prognosis and potential therapeutic targets.

Key Points

- Among patients with perforating artery disease (PAD)-related infarction, lower fasting glucose, absence of diabetes mellitus, lower total cerebral small vessel disease (CSVD) burden, absence of early neurological deterioration (END), and milder baseline neurological deficits were independently associated with greater short-term neurological improvement (Δ NIHSS) within 14 days after admission.
- Total CSVD burden and END exhibited the largest effect sizes among the five identified factors, followed by fasting glucose, diabetes mellitus, and baseline NIHSS score.
- No statistically significant interaction was detected between infarct location and any of the five core factors (fasting glucose, diabetes mellitus, total CSVD burden, END, and baseline NIHSS score), suggesting no evidence of effect modification by infarct location.
- The final model explained a modest proportion of the variability in Δ NIHSS (adjusted $R^2 = 0.283$), indicating that additional unmeasured factors likely contribute to short-term neurological recovery.

Availability of Data and Materials

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

Author Contributions

YMG designed the research study. YMG and DDB performed the research. YMG and DDB analyzed the data. YMG drafted this article. Both authors contributed to the important editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study protocol was approved by the Institutional Review Board of Ningbo Zhenhai People's Hospital (Ap-

proval No. 2026-007). Due to the retrospective nature of the study and the anonymization of patient data, the requirement for individual informed consent was waived. This study was performed in accordance with the principles of the Declaration of Helsinki.

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Conflicts of Interest

The authors declare no conflicts of interest.

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