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Relative score of early neurological deterioration in perforator artery infarction: a retrospective study

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Abstract

Background and aims Compared to small vessel occlusion (SVO) patients, branch atheromatous disease (BAD) patients are more likely to develop early neurological deterioration (END). Stroke patients with END have a poor prognosis. Initial clinical features/radiological findings are often insufficient to distinguish between BAD and SVO; therefore, they may not detect END. In this retrospective study, we investigated relative factors for END in perforator artery infarction and created a scoring system for END in these patients.

Methods We extracted data from stroke patients with perforator artery infarction admitted to the Department of Neurology at Juntendo University between January 2016 and December 2022. We examined factors, such as the presence of SVO and BAD, leading to END. Variables with a P-value < 0.1 on univariate analysis were entered into binominal logistic regression analysis.

Results Of the 1,420 stroke patients admitted over a 7-year period, 201 with perforator infarction were included in this study. END was found in 27 of 201 patients (13.4%). Binominal logistic regression analysis of background factors less than $p < 0.1$ revealed that age > 69 ($P = 0.032$; odds ratio [OR], 3.941; 95% confidence interval [CI], 1.126–13.769), body mass index < 23.8 ($P = 0.041$; OR, 3.183; 95%CI, 1.049–9.654), and pretreatment with anti-platelets ($P = 0.003$; OR, 5.183; 95%CI, 1.783–15.071) were significant factors. Regarding anti-platelet therapy, END was observed in 34.4% of patients administered aspirin and 35.0% administered clopidogrel. Initial infarct lesion size over 15 mm on initial MRI had a P value of 0.076 in univariate analysis and an odds ratio of 1.330 (95% CI 0.471–3.755; $P = 0.590$) in binomial logistic regression analysis. The length of stay and modified Rankin Scale at discharge were significantly exacerbated in the END group. Creating a scoring system with 1 point for each relevant factor (pEND score), significant correlations were obtained with ROC curves, and over 2 points produced the highest sensitivity and specificity for detecting END.

Conclusion Patients with high pEND scores may require intensive care from early hospitalization. In addition, the occurrence of stroke during anti-platelet therapy suggests the need for alternative treatment.

Keywords Branch atheromatous disease, Perforator artery infarction, Early neurological deterioration, Relative factors, pEND score

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Background

In 1989, Caplan first used the term branch atheromatous disease (BAD) to describe occlusion or stenosis at the origin of the deep penetrating artery of the brain associated with microatheroma or junctional plaque, leading to internal capsule or pontine small infract [1]. Compared to small vessel occlusion (SVO) patients, BAD patients are more likely to develop early neurological deterioration (END). It has been reported that once END occurs, BAD patients have a poor prognosis [2]. Early intravenous thrombolysis for BAD patients does not prevent the development of END [3]; however, studies have reported that early, intensive anti-platelet or anti-coagulant therapy may reduce the risk of END and improve the clinical outcome of patients [4, 5]. Therefore, early diagnosis of BAD is very important. Although the rate of BAD is high in infarcts in the lenticulostriate artery and anterior pontine artery, predictive factors for END remain to be elucidated [6]. We previously proposed the WORSEN score as a predictive measure of END in patients with ischemic stroke, and reported striate-capsular infarction and pontine infarction as deterioration factors [7]. BAD patients often show clinical features, such as SVO at onset; therefore, it is difficult to diagnose BAD based on admission neurological examination alone [8]. BAD is usually defined as a lesion extending three or more consecutive slices or an infarct diameter ≥ 15 mm in diffusion-weighted imaging [6, 9]. However, there is a lack of consensus about whether a similar definition can be applied to infarction in the brainstem region, including the paramedian pontine artery territory [6, 9]. Initial radiological findings are often unable to reliably distinguish between BAD and SVO. Nevertheless, when BAD presents with progressive neurological symptoms, it is often accompanied by enlargement of the infarct lesion on acute-phase diffusion-weighted imaging, making it difficult to evaluate it by diagnostic imaging at the first visit [10]. In recent years, with the development of vessel wall imaging, the possibility of differentiating BAD and SVO in the lenticulostriate artery region has been reported [11]; however, it is not commonly used because of the type of magnetic resonance imaging and imaging conditions.

In this study, we focused on the pons, internal capsule, corona radiata, and thalamus, which are areas where SVO/BAD can occur, and defined them as perforator artery infarcts. As the definition of BAD is controversial, we focused on END in perforator artery infarctions in the present study. We investigated relative factors that cause END in perforator artery infarction using data obtained from emergency room and created a scoring system for END in cerebral perforator artery infarction.

Methods

Study design

We extracted the patients with perforator artery infarctions (infarct lesions in internal capsule, corona radiata, thalamus, and pons, and with no embolic sources) from stroke patients admitted to the Department of Neurology, Juntendo University between January 2016 and December 2022, and investigated the factors leading to END. END was defined as a deterioration of National Institutes of Health Stroke Scale (NIHSS) score of 4 or more within 1 week of onset. Patients were enrolled at the time of admission, and additional information was added as appropriate until discharge. Analyses were performed from January to March 2023.

Inclusion and exclusion criteria

Patients with cerebral infarction in the perforator artery region without 50% or more stenosis in the main artery and without high-risk embolic factors were registered in this study. BAD and SVO were determined based on the comprehensive judgment of the attending physician, including the course after hospitalization and detailed examination at hospital discharge/transfer. Exclusion criteria were: individuals who received hyperacute phase treatment, cases that were beyond 72 h post-onset, and cases where MRI imaging was not feasible.

Outcome measures

We analyzed perforator artery infarctions, including SVO and BAD, and investigated factors associated with END. If this leads to a deeper understanding of END, it may be possible to provide more intensive medical treatment if these factors are identified in the emergency department and prevent END.

Background data and risk factors

To assess factors leading to END, we obtained the following information from each patient's medical record: history of using medicines, such as anti-coagulant, anti-platelet, anti-hypertensive, diuretic, statin, and oral hypoglycemic agents; medical history, such as hypertension (HT; defined as systolic blood pressure [BP] > 140 mmHg, diastolic BP > 90 mmHg, or drug treatment for HT), diabetes (DM; defined as glycated hemoglobin level [HbA1c] of > 6.8%, or drug treatment for DM), dyslipidemia (DL; defined as low-density lipoprotein-cholesterol level of > 140 mg/dl, high-density lipoprotein-cholesterol level of < 40 mg/dl, triglyceride level of > 149 mg/dl, or drug treatment for DL), ischemic heart disease, atrial fibrillation (Af), cerebral infarction, and malignant tumors; smoking history; height; weight; body mass index (BMI); visit vital signs; and NIHSS score on admission and at exacerbation were recorded by a certified stroke-trained neurologist. Blood tests, brain computed tomography,

magnetic resonance imaging, and electrocardiography were performed. We diagnosed brain infarction by focal hyper-intensity that was judged not attributable to normal anisotropic diffusion or magnetic susceptibility artifact. Then, we extracted cases diagnosed as lacunar infarction according to the Trial of Org 10,172 in Acute Stroke Treatment classification [12] or BAD [1]. As previously reported, BAD was defined as lesions measuring 15 mm or larger [9].

Treatment was based on Japanese stroke guidelines. We administered dual anti-platelet therapy (typically aspirin 200 mg/day and clopidogrel 75 mg), including edaravone, argatroban, and fluid loading in the acute phase; however, treatment was decided based on the discretion of each attending physician.

Ethical consideration and statistical analysis

The protocol of this retrospective study was approved by the Human Ethics Review Committee of Juntendo University School of Medicine. The data were analyzed with SPSS 29.0 (SAS Institute Inc., Cary, NC). Data are expressed as mean±standard deviation values or mean (Interquartile Range) for continuous variables. All statistical analyses were performed using χ^2 test for categorical variables, Mann-Whitney U-test for continuous variables, and Kruskal-Wallis test for non-parametric analyses. Variables with a P value<0.1 in univariate analysis were entered into binomial logistic regression analysis using the forced entry method. P-values of <0.05 were considered significant.

Results

Of 1420 stroke patients registered in the 7-year period, a total of 201 patients (14.1%) diagnosed with perforator artery infarct were enrolled in this study (SVO, 105; BAD, 96; large artery sclerosis, 144; cardiogenic embolism, 362; other etiology, 415; transient ischemic attack, 74; intracranial hemorrhage, 207; and other diagnosis such as cerebral venous thrombosis, moyamoya disease, or angiitis, 17). Among the ischemic stroke patients, END was noted in 103 patients (total patient number [excluding transient ischemic attack], 1122; END+/-, 76/845; 8.25% in patients with large artery sclerosis, cardiogenic embolism, and other etiology). However, among the perforator artery infarction patients, END was noted in 27 patients (13.4%), significantly more than patients with large artery sclerosis, cardiogenic embolism, and other etiology (P=0.021). Among patients with a diagnosis of perforator artery infarct, none received hyperacute treatment. All patients were evaluated within 72 h from onset and underwent MRI. We typically diagnose without MRI for cases with undetermined etiology due to the inclusion of cardiogenic factors.

Patients were divided into a group with END and a group without END. Background factors and examination data of patients with neurological deterioration were analyzed (Tables 1 and 2). Univariate analysis revealed relationships for age, BMI, pretreatment with anti-platelets, calcium channel blocker, clopidogrel loading, infarct lesion size over 15 mm on initial MRI, and infarction of the corona radiata between the two groups (P-value<0.1). There were no significant differences in height, smoking history, HT, DM, DL, ischemic heart disease, Af, history of cerebral infarction, malignant tumor, onset to arrival duration, infarct lesion of internal capsule/pons/thalamus, vital signs at onset, and NIHSS score. Binominal logistic regression analysis was performed on factors associated with END (Table 3). Originally, age, BMI and lesion size values were intended to be directly used in the analysis; however, we had a limited number of cases. Age was 69 years old, and BMI was 23 when divided by average age and average BMI. A lesion size cut of 15 mm was used for BAD diagnosis criteria. Bodyweight, which is a component of BMI, was excluded. We found that age>69 (P=0.032; odds ratio [OR], 3.941; 95% confidence interval [CI], 1.126–13.769), body mass index<23.8 (P=0.041; OR, 3.183; 95%CI, 1.049–9.654), and pretreatment with anti-platelets (P=0.003; OR, 5.183; 95%CI, 1.783–15.071) were significantly related. Furthermore, END was observed in 34.4% of aspirin and 35.0% of clopidogrel anti-platelet therapy patients. As previously reported, in cases with END, the length of stay and modified Rankin Scale at discharge were significantly exacerbated, and nearly 90% of exacerbated cases were transferred to a rehabilitation hospital (END+: 24, 88.9%; END -: 45, 31.2%; P-value<0.001).

We constructed a scoring system. Age, BMI, and pretreatment with anti-platelets, which represented significant differences in binominal logistic regression analysis, were scored as 1 point each (pEND score). END was observed in 1 of 49 patients (2.0%) with a score of 0; 2 of 60 (3.3%) with a score of 1; 11 of 65 (16.9%) with a score of 2; and 13 of 27 patients (48.1%) with a score of 3. END occurred more frequently as score increased (Fig. 1A). When the cutoff point was set at a pEND score of 2 points, a sensitivity value of 0.889 and a specificity value of 0.689 for the detection of neurological deterioration were obtained (according to receiver operating characteristic [ROC] curve analysis; area under ROC curve: 0.811, Fig. 1B, power estimates were calculated based on α=0.05 and β=0.8, indicating that the pEND score analysis required at least 26 patients per group). END was found in 1 and 26 patients with final diagnoses of SVO and BAD, respectively (Fig. 1C and D). When a pEND score of 2 points was used for the final diagnosis of BAD patients, the sensitivity was 0.885 and the specificity was

Table 1 Data of patient background and pre-medication

END	+ (27)		- (174)		*P*-value
	N	%	*N*	%	
Sex (male)	15	55.6	101	58.0	0.807
Age	76.5 ± 11.7		68.2 ± 13.4		**0.003**
Age > 69 (mean age: 69)	23	85.2	89	51.1	**< 0.001**
Body height (cm)	161.6 ± 9.4		162.9 ± 9.2		0.473
Body weight (kg)	59.1 ± 13.0		64.1 ± 14.3		**0.093**
BMI (kg/m^2)	22.2 ± 3.6		23.9 ± 4.0		**0.039**
BMI (kg/m^2) < 23.8 (mean BMI: 23.8)	22	81.5	80	45.9	**< 0.001**
Smoking habit	4	14.8	43	24.7	0.333
HT	24	88.9	153	87.9	1.000
DM	11	40.7	69	39.7	0.915
DL	21	77.8	119	68.4	0.324
Ischemic heart disease	4	14.8	17	9.8	0.495
Af	2	7.4	13	7.5	1.000
History of stroke	6	22.2	22	12.6	0.181
Malignancy	1	3.7	6	3.4	1.000
Onset to arrival duration (hour)	12(12–48)		12(4.5–42)		0.368
Pre-medication					
Anti-coagulant	1	3.7	11	6.3	1.000
Anti-platelet	18	66.7	37	21.3	**< 0.001**
Calcium channel blocker	13	48.1	51	29.3	**0.051**
Angiotensin II receptor blocker	6	22.2	36	20.7	0.855
Angiotensin-converting-enzyme inhibitor	1	3.7	3	1.7	0.441
Diuretic	1	3.7	6	3.4	1.000
Statin	7	25.9	30	17.2	0.279
Dipeptidyl peptidase 4 inhibitor/Glucagon-like peptide-1	6	22.2	20	11.5	0.122
Radiological finding					
Lesion size on initial MRI	11.2 ± 6.4		14.4 ± 6.95		**0.009**
Lesion size over 15 mm on initial MRI	9	33.3	32	18.3	**0.076**
Infarct lesion; pons	7	25.9	55	31.6	0.552
Infarct lesion; internal capsule	4	14.8	38	21.8	0.611
Infarct lesion; corona radiata	15	55.5	67	38.5	**0.093**
Infarct lesion; thalamus	1	3.7	14	8.0	0.698
Treatment					
Clopidogrel loading	20	74.0	161	92.5	**0.003**
Outcome					
Hospital stay day	26(21–38)		15(12–21)		**< 0.001**
Modified Rankin Scale	2(1–4)		1(0–2)		**< 0.001**
Modified Rankin Scale ≤0–2	15	55.6	154	88.5	**< 0.001**
Transfer to rehabilitation hospital	24	88.9	45	31.2	**< 0.001**

Abbreviation: BMI, body mass index; HT, hypertension; DM, diabetes; DL, dyslipidemia; Af, atrial fibrillation; Mean age/BMI of this cohort was 69 and 23.8, respectively. Data are expressed as mean ± SD, except Hospital stay and modified ranking scale are expressed as median and interquartile range

0.514, according to ROC curve analysis (area under the ROC curve: 0.788).

Discussion

Of the 1,420 stroke patients enrolled over a 7-year period, there were 105 SVO patients and 96 BAD patients, totaling 201 perforator artery infarctions, which were included in the present study. Patients were divided into two groups (with and without END). Univariate analysis of patient data, including background, medication history, blood tests, and radiological images, revealed related factors (P-value < 0.1) of age, BMI, pretreatment with antiplatelets, calcium channel blocker use, clopidogrel loading, infarct lesion size over 15 mm on initial MRI, and infarction of the corona radiata. Binomial logistic regression analysis was performed on items with a P value < 0.1 in univariate analysis, and significant differences were found in age, BMI, and pretreatment with antiplatelets. For infarct lesion size over 15 mm on initial MRI, the P value was 0.076 in univariate analysis, and the

Table 2 Data of vital signs, symptoms, and laboratory test findings

END	+ (27)	- (174)	*P*-value
	N	*N*	
Heart rate (/min)	77.0 ± 10.6	77.9 ± 13.7	**0.834**
Systolic blood pressure (mmHg)	163.1 ± 27.1	161.7 ± 28.5	0.788
Diastolic blood pressure (mmHg)	90.3 ± 14.0	90.6 ± 19.6	0.905
NIHSS (on admission)	3(1–4)	2(1–4)	0.505
Laboratory data			
White blood cell (10^3 /μL)	6396.3 ± 1528.8	6981.0 ± 2318.3	0.210
Hemoglobin (g/dL)	13.5 ± 2.2	14.1 ± 1.7	0.435
Platelet (10^4/μL)	19.3 ± 5.7	22.9 ± 13.8	0.140
Uric acid (mg/dL)	5.23 ± 1.26	5.49 ± 1.55	0.293
Creatinine (mg/dL)	1.09 ± 1.48	1.18 ± 1.78	0.884
Estimated glomerular filtration rate (mL/min/1.73m^2)	67.9 ± 24.2	69.6 ± 24.9	0.649
High-density lipoprotein (mg/dL)	49.4 ± 13.0	52.3 ± 14.0	0.332
Low-density lipoprotein (mg/dL)	127.2 ± 43.0	128.5 ± 43.2	0.781
Triglyceride (mg/dL)	194.2 ± 253.2	148.8 ± 104.6	0.508
Blood sugar (mg/dL)	139.0 ± 84.3	132.6 ± 51.0	0.820
Hemoglobin A1c (%)	6.77 ± 2.03	6.52 ± 1.36	0.829
N-terminal pro-brain natriuretic peptide (pg/mL)	878.1 ± 2246.2	814.1 ± 2451.3	0.409
Troponin T (ng/mL)	0.03 ± 0.03	0.08 ± 0.51	0.356
High-sensitivity C-reactive protein (mg/dL)	0.22 ± 0.36	0.58 ± 1.48	0.214
Prothrombin time-international normalized ratio	1.05 ± 0.25	1.09 ± 0.73	0.994
D-dimer (μg/mL)	2.13 ± 1.42	2.34 ± 3.23	0.334
Eicosapentaenoic acid /Arachidonic acid	0.36 ± 0.25	0.37 ± 0.36	0.590

Abbreviation: NIHSS, National Institutes of Health Stroke Scale

Data are expressed as mean ± SD, except NIHSS (on admission), which is expressed as median and interquartile range

Table 3 Binomial logistic regression analysis

	Odds Ratio	95%CI	*P*-value
Age > 69	3.941	1.126–13.769	**0.032**
BMI < 23.8	3.183	1.049–9.654	**0.041**
Pretreatment with anti-platelets	5.183	1.783–15.071	**0.003**
Calcium channel blocker	0.998	0.359–2.772	0.997
Clopidogrel loading	0.653	0.170–2.509	0.535
Lesion size over 15 mm on initial MRI	1.330	0.471–3.755	0.590
Infract lesion; corona radiata	1.611	0.617–4.208	0.330

Body weight is excluded as it is a component of BMI. Mean age and BMI of this study group were 69 and 23.1, respectivly

OR was 1.330 (95% CI 0.471–3.755, P=0.590) in binomial logistic regression analysis, showing no significant difference.

Historical epidemiological data on BAD is scarce, and most studies were performed on Asian populations [9]. Previous studies reported associations with various factors, including infarct size, infarct site, mean platelet volume, and serum uric acid/creatinine ratio [13–15]. Regarding the age at which significant differences were observed, the findings of previous studies varied from no age difference between patients with and without END [13–15] to a higher mean age in the group without END [16]; however, all reports were limited to univariate analysis.

Age is the strongest unmodifiable risk factor for ischemic stroke, and the risk doubles every 10 years after the age of 55 [17], because the prevalence of certain stroke risk factors, including HT, DM, Af, and coronary and peripheral artery disease, increases steadily with age. In one cohort study, age was divided into quartiles according to the number of patients over 65 years old and they found significant differences in the incidences of Af and ischemic stroke, and the prevalence of dementia with increasing age [18]. Moreover, there was no significant difference in NIHSS at the onset of cerebral infarction, but there was a significant difference in modified Rankin Scale at discharge. These findings suggest that the prognosis of cerebral infarction worsens with age. Another review suggested that one of the main risk factors for carotid artery stenosis and carotid-related stroke is age [19], which was thought to be because of vascular aging. Vessel volume and diameter and intimal thickness

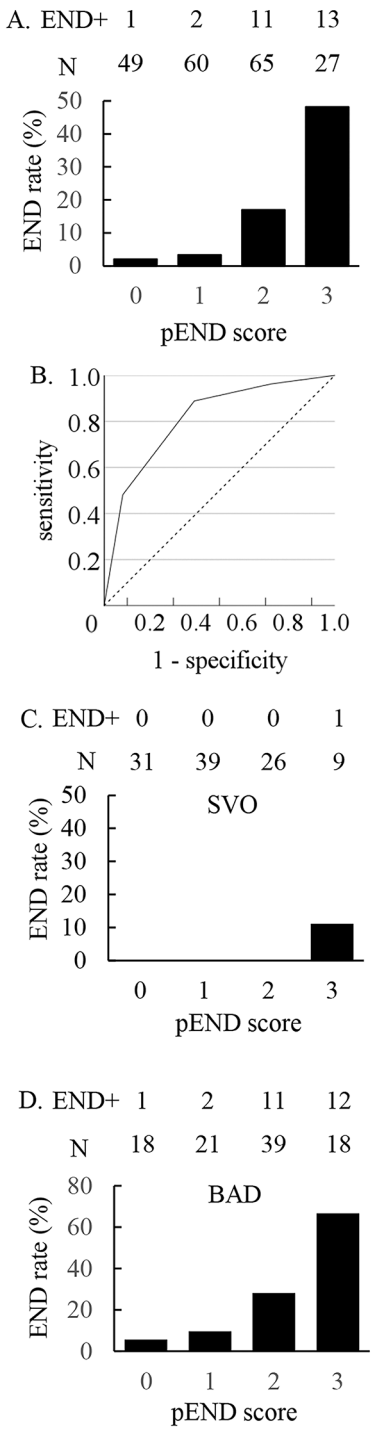

Fig. 1 **A**. Early neurological deteroration (END) rate in each pEND score. The frequency of END increased as pEND scores increased. **B**. Receiver operating characteristic (ROC) curve for early neurological deterioration in pEND score. Area under ROC curve (AUC): 0.811. **C**. END rate in each pEND score in SVO (cutoff at pEND score 2, sensitivity 1, specificity 0.673). **D**. END rate in each pEND score in BAD (cutoff at pEND score 2, sensitivity 0.885, specificity 0.514). END+: Early neurological deterioration occurred (patient number); N: Patient number in each pEND score

increase with age, primarily due to atherosclerotic changes in the vessel wall. At the cellular and extracellular level, elastin fibrils, smooth muscle cells, and total cellularity are decreased, whereas lipid, cholesterol, calcium phosphate deposition, and angiogenesis are increased. Causes of vascular aging at the molecular level include oxidative stress, chronic inflammatory responses, mitochondrial dysfunction, epigenetic alterations, and

dysregulation of noncoding RNA expression. Age-related loss of tissue healing and repair capacity makes plaque more fragile and the carotid artery more susceptible to ischemic stroke. Occlusion or stenosis at the origin of the deep penetrating arteries of the brain associated with microatheroma or junctional plaques is thought to be the cause of BAD [1]. Our findings support these previous studies that reported that age is a risk factor for BAD such as carotid artery stenosis.

Being underweight is a well-known risk factor for various chronic diseases, as it increases the risk of mortality, osteoporosis and fracture, and respiratory diseases, including asthma [20]. Several studies have reported a relationship between BMI and cerebral infarction. A previous cohort study reported that the incidence of stroke, myocardial infarction, and all-cause mortality increased in proportion to the severity of being underweight [20]. Sarcopenia is a syndrome associated with impaired muscle and metabolic function characterized by an age-related decline in skeletal muscle mass and low levels of muscle function [21]. Recent studies have reported that a decrease in skeletal muscle mass, such as sarcopenia, increases chronic inflammation and insulin resistance in vivo, which causes various metabolic diseases, including obesity, HT, DL, and DM [20, 21]; thus, sarcopenia causes atherosclerosis due to these metabolic abnormalities. In addition, it is thought that the decline in BMI with aging, nutritional status, and anemia affect the outcome of ischemic stroke [17, 22].

In this study, 34.4% (10/29) of aspirin-treated patients and 35.0% (7/20) of clopidogrel-treated patients developed cerebral infarction and END. These may be associated with aspirin resistance and clopidogrel resistance. Previous reports have also shown that aspirin resistance is associated with END [23]. Aspirin inhibits the conversion of arachidonic acid to prostaglandin H_2 by acetylating cyclooxygenase-1 [24], reduces the formation of thromboxane A_2, and inhibits platelet aggregation and thrombus formation [25]. However, aspirin-resistant patients do not experience a decrease in thromboxane A_2 and are at increased risk of vascular events. Aspirin resistance was prevalent in 28.9% of patients with cerebral infarction [26] and other studies reported that the prevalence of aspirin resistance varies between 5% and 60% due to differences in platelet function assays, and clinical and demographic factors [27]. Furthermore, clopidogrel resistance may be due to genetic polymorphisms, such as cytochrome P450 2C19(CYP2C19), which have low metabolic capacity of CYP2C19 such as CYP2C19*2 (G 681 A) and CYP2C19*3 (G 636 A) [28]. This poor metabolizer is commonly found in Japanese patients (*2 is found in 26.7% and *3 in 12.8% of the Japanese population) [29]. Although platelet-aggregation ability was not measured in the present study, our findings support the prevalence rates reported in previous studies. If BAD occurs while taking these anti-platelet drugs, it may be necessary to perform acute treatment while considering resistance. As an alternative therapy, ozagrel sodium [30], which inhibits the synthesis of thromboxane A_2, may be an option for aspirin-resistant patients, and prasugrel, which is not affected by CYP2C19, may be an option for clopidogrel-resistant patients. The standard treatment for BAD has not yet been established; therefore, further studies are necessary.

Combination therapy with argatroban, cilostazol, and edaravone achieved better outcomes than conventional treatment for BAD in the lenticulostriate artery and anterior pontine artery regions, and the addition of clopidogrel to these treatments has been reported to improve outcomes in the lenticulostriate artery region [31]. A previous study reported that cilostazol had beneficial vasodilatory and endothelial-protective effects [32], and it may be more effective in anterior pontine artery regions with a diameter of 200–300 μm than in lenticulostriate artery regions with a diameter of 700–800 μm. Early treatment may prevent END; however, no significant differences in infarct lesion size over 15 mm on initial MRI in either univariate or multivariate analysis were found in the present study. Thus, predicting END by classifying patients into BAD and SVO based on infarct diameter may not be feasible.

Our study has several limitations. First, we used a non-random treatment allocation procedure and retrospective design. Second, regarding antiplatelet treatment, drug resistance may be an influencing factor. However, we were unable to evaluate platelet aggregation function in the present study, so this remains to be elucidated. Third, the number of cases was small. Fourth, the Cox-Snell R^2 test was 0.175, and the Nagelkerke R^2 test was 0.320; thus, the results may not necessarily be replicated in other institutions. Fifth, the treatment for BAD has not been completely established. Further prospective randomized multicenter studies are needed to address these limitations.

Conclusions

BAD has a high possibility of developing END, improvement is difficult once deterioration occurs, and the prognosis is poor. In this study, we performed a retrospective, single-center study and identified age, BMI, and pretreatment with anti-platelets as relative factors for END in perforator artery infarction. Although the potential for neurological deterioration in BAD, depending on the location of the infarcted lesion, remains controversial [33, 34], our findings suggest identifying neurological deterioration based on background data, including imaging available in the Emergency Department. For treatment with consideration of resistance to antiplatelet therapy,

ozagrel, prasugrel, cilostazol, and clopidogrel may be useful for the treatment of BAD. When we encounter a perforating branch infarction and it is associated with any of the deterioration factors, we should consider aggravation and give the patient early and focused treatment. Our findings suggest that this will help improve the prognosis of perforator artery infarct.

Abbreviations

BAD	Branch atheromatous disease
SVO	Small vessel occlusion
END	Early neurological deterioration
NIHSS	National Institutes of Health Stroke Scale
HT	Hypertension
DM	Diabetes
DL	Dyslipidemia
Af	Atrial fibrillation
BMI	Body mass index
CYP2C19	Cytochrome P450 2C19

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Author contributions
Conceptualization, KK, NM; Methodology, NM, KH; Investigation, KK, NM, KH, CK; Formal analysis, KK, NM.; Resources, NM, KH, CK; Writing—original draft, KK, NM; Writing—Review and editing, all authors; Supervision, NH.

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Data availability
The datasets analyzed in the present study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The protocol of this retrospective study was approved by the Human Ethics Review Committee of Juntendo University School of Medicine. The patients provided written informed consent to participate in this study. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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