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Correlation between blood pressure variability and deep cerebral microbleeds in patients with acute ischemic stroke

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Abstract

Introduction: *To observe the 24-h ambulatory blood pressure characteristics of patients with acute ischemic stroke and explore the correlation between blood pressure variability and strictly deep cerebral microbleeds (CMBs).*

Material and methods: *A convenient sampling method was used to enrol 131 patients with acute ischemic stroke in the Department of Neurology between April 2021 and May 2022. Hospitalised patients with acute ischemic stroke were assessed retrospectively; their ambulatory blood pressure was monitored continuously for 24 h, and the relevant parameters were recorded. Magnetic susceptibility-weighted imaging was used to divide the CMBs into a strictly deep CMB group (n = 24) and a non-CMB group (n = 107) according to the location of the CMBs. A logistic regression analysis was performed to determine the independent correlation between the 24-h ambulatory blood pressure parameters and strictly deep CMBs. The receiver operating characteristic (ROC) was further used to analyse the predictive value of the ambulatory blood pressure parameters for strictly deep CMBs in patients with acute ischemic stroke.*

Results: *The results showed that the night systolic blood pressure standard deviation and the night diastolic blood pressure standard deviation (NDBP-SD) in the strictly deep CMB group were higher than those in the non-CMB group ($p < 0.05$). The multiple logistic regression analysis indicated that the NDBP-SD (odds ratio [OR] = 1.205, 95% confidence interval [CI]: 1.011-1.436, p = 0.038) was an independent risk factor for strictly deep CMBs in patients. The ROC curve analysis revealed that the area under the curve value of the NDBP-SD was 0.682, and the intercept was 7.81. When NDBP-SD is ≥ 7.81, the occurrence of strictly deep CMBs is closely related (OR = 3.872, 95% CI: 1.347-11.125, p = 0.012).*

Conclusions: *The NDBP-SD is an independent risk factor for strictly deep CMBs in patients with acute ischemic stroke. When NDBP-SD is > 7.81, it may promote the production of strictly deep CMBs.*

Key words: *acute ischemic stroke, deep brain microbleeds, blood pressure variability.*

Introduction

Cerebral microbleeds (CMBs) are subclinical lesions of the brain parenchyma characterised by microbleeds and belong to the category of cerebral small vessel disease (CSVD) [14]. The pathogenesis of CMBs is still unclear. At present, it is mainly considered to be related to amyloid vascular degeneration and hypertensive vascular damage. Amyloid vascular degeneration mainly involves the deposition of amyloid protein on the vascular wall; this is more common in the intracranial cortex and pia mater blood vessels, which can easily lead to cerebral cortex and cerebral lobe CMBs. Hypertensive arterial disease mainly causes vascular arteriosclerosis, wall hyaline degeneration, abnormal lipid

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deposition, fibrinoid necrosis, etc. It primarily affects the intracranial deep perforating artery, with the resulting CMB lesions located mostly in the deep brain tissue and subtentorial parts [16]. In addition, CMBs may be associated with advanced age, long-term smoking history, poor blood glucose control, inappropriate anticoagulation and abnormal antiplatelet/lipid metabolism. Many studies have demonstrated CMBs to be associated with ischemic or haemorrhagic stroke recurrence, vascular dementia and stroke-related mortality [2]. Furthermore, CMBs are considered to be a marker of poor prognosis in acute ischemic stroke [23].

Hypertension is an extremely important risk factor for cerebrovascular disease that can be manipulated [26]. The main mechanism causes vascular arteriosclerosis, wall hyaline degeneration, abnormal lipid deposition, fibrinoid necrosis, etc., mainly affecting the deep intracranial perforating arteries [3]. A study by Henskens *et al*. found that CMBs are more likely to occur in people with no obvious history of cerebrovascular disease but with a clear diagnosis of hypertension and in patients with high baseline blood pressure levels [15]. However, blood pressure in the human body is not static; it is affected by a variety of factors in internal and external environments, so occasional in-clinic blood pressure measurements will lead to misdiagnosis and missed diagnosis [21]. Ambulatory blood pressure monitoring can provide objective blood pressure information within a certain period and reflect rhythmic changes and variability in blood pressure.

Blood pressure variability (BPV) refers to the fluctuation in blood pressure over a certain period of time, which can predict the degree of target organ damage [24]. Blood pressure variability is of great significance for predicting the risk of cardiovascular and cerebrovascular diseases and evaluating the prognosis of the disease [19]. Previous studies have shown that abnormal 24-h BPV increases the risk of cerebrovascular disease [28]. Compared with traditional blood pressure monitoring, BPV can be more individualised; it can offer a more comprehensive diagnosis and assessment of blood pressure levels and effectively predict corresponding target organ damage earlier. As the diagnosis and treatment of hypertension are increasingly dependent on ambulatory blood pressure monitoring, the regulation of blood pressure rhythm has become one of the important measures of blood pressure control.

However, there are few reports on the correlation between 24-h ambulatory BPV and the location of CMBs, and there is no report on the relationship between circadian BPV and CMBs. Therefore, this study used a retrospective case series method to explore the correlation between deep CMBs and 24-h ambulatory BPV in patients with acute ischemic stroke to provide a reference for evaluating the condition and formulating reasonable clinical treatment plans.

Material and methods

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Zhuji Affiliated Hospital of Shaoxing University. Written informed consent was obtained from all participants in this study.

Research subjects

A convenient sampling method was used to enrol 131 patients with acute ischemic stroke in the Department of Neurology from April 2021 to May 2022. According to CMB location, the CMBs were divided into a strictly deep CMB group (n = 24) and a non-CMB group (n = 107). Strictly deep CMBs are defined as involving only deep microbleeds. The deep cerebrum includes the basal ganglia, thalamus, internal capsule, external capsule and corpus callosum as well as deep and paraventricular white matter.

The inclusion criteria were as follows: 1) diagnosis of acute ischemic stroke or transient ischemic attack within 2 weeks after onset per the 'China Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke 2018' [5] and 2) patients able to cooperate with the completion of post-admission-related haematological examinations, brain computed tomography (CT), magnetic resonance imaging (MRI) (MRI + magnetic resonance angiography [MRA] + diffusion-weighted imaging [DWI] + susceptibility-weighted imaging [SWI]) and 24-h ambulatory blood pressure monitoring. The exclusion criteria were as follows: 1) secondary hypertension, 2) malignant hypertension requiring intravenous antihypertensive drugs (blood pressure persistently higher than 220/100 mmHg), 3) patients with clinically severe stroke (as defined by the 2021 European Stroke Organisation Thrombolysis Guidelines), a National Institutes of Health Stroke Scale score of > 25 points and imaging features of severe stroke (brain CT or MRI results showed a cerebral infarction area greater than one-third of the middle cerebral artery blood supply area) [1], 4) history of severe brain trauma, cerebral haemorrhage, subarachnoid haemorrhage, intravenous thrombolysis, severe metabolic disease, blood system disease and severe liver and kidney insufficiency, 5) mixed positive CMBs and cortical positive CMBs and 6) MRI examination could not be performed due to the presence of pacemakers or metal materials in the body.

Data collection

Clinical data, including demographics, vascular risk factors and laboratory test results, were collected. Specifically, these included the following: 1) demographic information (age and gender), 2) hypertension, diabetes and hyperlipidaemia and 3) platelet–lymphocyte ratio (PLR), neutrophil–lymphocyte ratio (NLR), lymphocyte–monocyte ratio (LMR), urine microalbumin–creatinine ratio (ACR), cystatin C, homocysteine (Hcy) and serum amyloid A.

Neuroimaging data collection and evaluation

Brain scans were performed within 24 h of admission using an uMR 560 1.5-T superconducting magnetic resonance system (China United Imaging), which included T1- and T2-weighted imaging, DWI, fluid-attenuated inversion recovery, SWI and other sequences. Within 2 weeks of onset, 1.5-T MRI was used to complete the head MRI + MRA + DWI + SWI. The CMB data included the following diagnostic criteria for CMB [10]: 1) hypointense loss on SWI, 2) round without surrounding oedema, 3) diameter of 2-10 mm, 4) lesion surrounded by more than half of the brain parenchyma and 5) other cases with similar imaging findings (diffuse axonal injury, calcification, cavernous haemangioma, small blood vessel flow shadows, etc.) caused by traumatic brain injury were excluded. The CMB assessment team used the Microbleed Anatomical Rating Scale [12] under blinded conditions to assess the presence of deep CMBs (with and only below the deep CMBs) and cases with a negative CMB number.

The deep brain includes the basal ganglia, thalamus, internal capsule, external capsule, corpus callosum and deep and paraventricular white matter. The diagnosis of CMB was performed by two senior neurologists who did not have contact with the patients or their clinical data.

Ambulatory blood pressure monitoring

To avoid the influence of an increase in blood pressure response after acute ischemic stroke, all patients underwent 24-h ambulatory blood pressure monitoring 3 days after admission. Using a non-invasive, portable ambulatory blood pressure tester (MC-6800 monitor, Shenzhen Mindray Biomedical Electronics Co., Ltd., China), ambulatory blood pressure was monitored continuously for 24 h. The measurement interval is set to be once every 20 minutes in the morning (05:00~06:00). Measure every 20 minutes during the day (06:01-22:00). Measure every 40 minutes at night (22:01 to 04:59 the next day) [17]. Blood pressure was measured in the non-paralyzed upper limbs. The subjects continued to take their original antihypertensive drugs, and normal activities were not restricted, although strenuous activities were avoided. When the cuff was inflated to measure blood pressure, the patient avoided moving the upper extremity being measured. The effective value of 24-h monitoring was greater than 80%; if the effective value was less than 80%, it was treated as invalid data, and the parameters and data related to ambulatory blood pressure were recorded and accurately calculated in detail, as follows: 24-h systolic blood pressure (24-h SBP), 24-h diastolic blood pressure (24-h DBP), day SBP (DSBP), day DBP (DDBP), night SBP (NSBP), night DBP (NDBP), 24-h day SBP standard deviation (SD) (24-h SBP-SD), 24-h DBP SD (24-h DBP-SD), day SBP SD (DSBP-SD), day DBP SD (DDBP-SD), night SBP SD (NSBP-SD) and night DPB SD (NDBP-SD).

Statistical analysis

This study used SPSS 25.0 software for statistical processing. Enumeration data were expressed as frequencies and percentages, and Pearson's test and continuous-corrected Chi-squared tests were used for comparisons between groups. The measurement data were first analysed by S-W test for normality; those with a normal distribution were expressed as mean ± standard deviation (x ± S), and comparisons between groups were performed using Student's *t* tests. If the data were not normally distributed, they were expressed as median and interquartile ranges, and comparisons between groups were performed using Mann-Whitney *U* tests. Using the presence or absence of deep CMBs as the dependent variable, the independent variables were screened according to the test level ($p < 0.1$) and clinical significance in a univariate regression analysis, and a multivariate logistic regression model was established to determine the independent risk factors for deep CMBs. A value of $p < 0.05$ was considered statistically significant. The receiver operating characteristic (ROC) curve was used to analyse the predictive value of ambulatory blood pressure parameters for the occurrence of deep CMBs in patients with acute ischemic stroke.

Results

The results of CMB detection in the research subjects

All 199 consecutive patients with acute ischemic stroke in the included group routinely underwent head CT and head MRI after admission. A total of 92 patients were CMB positive, with an incidence of 46.23%, and 107 patients were CMB negative. Among them, 24 pa-

tients with strictly deep CMBs (with and only deep CMBs), 23 patients with strictly cortical positive CMBs (with and only cortical CMBs) and 45 patients with mixed positive CMBs (deep + cortical, deep + subcortical, cortical + subcortical) were detected. Finally, 131 patients with strictly cortical and mixed positive CMBs were included in the statistical analysis.

Comparison of baseline data between the strictly deep CMB and non-CMB groups

A total of 131 patients with acute ischemic stroke were included in this study, including 84 males (64.12%) and 47 females (35.88%), with an average age of 70 (61-75) years. In the strictly deep CMB (n = 24) and non-CMB (n = 107) groups, there were no significant differences in age, gender, hypertension, diabetes, hyperlipidaemia, hyperacidaemia, cystatin C, serum amyloid A, PLR, NLR, LMR and urinary ACR ($p > 0.05$) between the two groups, and the patients in both groups were comparable (Table I).

Statistical analysis of ambulatory blood pressure parameters between the strictly deep CMB and non-CMB groups

The patients' 24-h ambulatory blood pressure monitoring results were recorded, and the related parameter statistics were evaluated. The univariate analysis showed that 24-h SBP, 24-h DBP, 24-h SBP-SD, 24-h DBP-SD, DSBP, DDBP, DSBP-SD, DDBP-SD, NSBP and NDBP were not statistically significant in the strictly deep CMB group. The NSBP-SD (t = -3.227, p = 0.002) and NDBP-SD (z = -2.446, p = 0.014) values in the strictly deep CMB group were higher than those in the non-CMB group, and the difference between the two groups was statistically significant ($p < 0.05$) (Table II).

Logistic regression analysis of factors related to strictly deep CMBs in patients with acute ischemic stroke

The baseline data and ambulatory blood pressure-related parameters were screened according to the test level ($p < 0.1$) and clinical significance in the univariate regression analysis, and a further multivariate logistic regression analysis was performed. The presence or absence of strictly deep CMBs was used as the dependent variable, while age, gender, diabetes, hypertension, hyperlipidaemia, PLR, NLR, LMR, cystatin C, ACR, serum amyloid A and Hcy were independent variables. The results showed that the NDBP-SD (odds ratio [OR] = 1.205, 95% confidence interval [CI]: 1.011-1.436, p = 0.038) had a significant independent correlation with deep CMBs (Table III).

ROC curve of NDBP-SD as an independent risk factor for strictly deep CMBs in patients with acute ischemic stroke

The results of the ROC curve analysis revealed that the area under the curve (AUC) of NDBP-SD was 0.682, the SE value was 0.057, the cut-off value was 7.81, the specificity was 50.5%, the sensitivity was 79.2% and the 95% CI was 0.571-0.794 (Fig. 1).

Table I. Comparison of baseline data between strictly deep cerebral microbleed (CMB) group and non-CMB group

Variable	Strictly deep CMB group (n = 24)	Non-CMB group (n = 107)	$t/Z/\chi^2$	P
Age (year), mean ±SD	70.0 (60.8-77.5)	70.0 (61.0-75.0)	–0.423	0.672
Male, n (%)	18 (75.0)	66 (61.7)	1.511	0.219
Diabetes, n (%)	6 (25.0)	32 (29.9)	0.229	0.632
Hypertension, n (%)	21 (87.5)	87 (81.3)	0.180	0.672
Hyperlipidemia, n (%)	11 (45.8)	42 (39.3)	0.352	0.553
Platelet to lymphocyte ratio (PLR)	132.6 (110.1~181.9)	155.6 (118.2~201.3)	–1.214	0.225
Neutrophil to lymphocyte ratio (NLR)	2.6 (2.2~3.3)	3.1 (2.3~4.3)	–1.371	0.170
Lymphocyte to monocyte ratio (LMR)	3.7 ±0.9	3.6 ±1.4	–0.673	0.504
Cystatin C (mg/l)	0.9 (0.74~1.04)	0.9 (0.7~1.04)	–0.182	0.856
Urinary microalbumin creatinine ratio (ACR)	0.3 (0.2~1.2)	0.6 (0.2~1.5)	–0.827	0.408
Serum amyloid A (mg/l)	6.0 (0.8~13.0)	8.0 (3.0~21.4)	–1.221	0.222
Homocysteine (mol/l)	15.0 (12.5~17.7)	13.8 (10.6~18.0)	–0.937	0.349

Table II. Comparison of ambulatory blood pressure parameters between strictly deep cerebral microbleed (CMB) group and non-CMB group

Variable	Strictly deep CMB group (n = 24)	Non-CMB group (n = 107)	t/Z	P
24h SBP	141.1 ±13.3	138.4 ±15.3	–0.801	0.424
24h DBP	80.0 ±10.4	78.3 ±9.5	–0.786	0.433
DSBP	142.1 ±12.9	139.3 ±15.1	–0.844	0.400
DDBP	81.0 ±10.8	78.9 ±9.4	–0.958	0.340
NSBP	138.0 ±16.7	135.0 ±19.2	–0.696	0.488
NDBP	78.0 ±11.2	75.2 ±11.5	–1.095	0.275
24h SBP-SD	15.2 ±4.2	13.7 ±3.7	–1.699	0.092
DSBP-SD	14.6 ±4.5	13.3 ±3.7	–1.453	0.149
NDBP-SD	10.4 ±3.6	8.0 ±3.2	–3.227	0.002*
24h DBP-SD	11.0 (9.4~13.6)	9.9 (8.6~12.5)	–1.735	0.083
DDBP-SD	11.2 (8.6~13.3)	10.0 (8.1~12.5)	–1.321	0.187
NSBP-SD	11.2 (8.7~17.4)	9.0 (6.9~14.2)	–2.446	0.014*

*$p < 0.05$

Table III. Logistic regression analysis of related factors of deep cerebral microbleeds (CMBs) in patients with acute ischemic stroke

Variable	Univariate logistic regression analysis		Multivariate logistic regression analysis	
	OR value (95% CI)	P	OR value (95% CI)	P
NSBP-SD	1.090 (1.010~1.770)	0.027	1.016 (0.916~1.128)	0.758
NDBP-SD	1.231 (1.074~1.410)	0.003	1.205 (1.011~1.436)	0.038
Age	1.006 (0.968~1.046)	0.747	1.007 (0.966~1.050)	0.735
Hypertension	1.598 (0.434~5.893)	0.481	1.293 (0.339~4.936)	0.706

According to the cut-off value, the NDBP-SD was further changed into a binary variable for a univariate regression analysis

According to the cut-off value of 7.81, the NDBP-SD was further changed into a binary variable for univariate regression analysis. The results showed that the NDBP-SD (OR = 3.872, 95% CI: 1.347-11.125, p = 0.012) was correlated with strictly deep CMBs. When NDBP-SD ≥ 7.81, the occurrence of deep CMBs was 3.872 times that of NDBP-SD < 7.81 (Table IV).

Discussion

Cerebral microbleeds are caused mainly by the leakage of arterioles, venules and capillaries, and their main components are hemosiderin and macrophages that phagocytose hemosiderin [4]. According to previous related studies, the incidence of CMBs in patients with ischemic stroke ranges from 35% to 71% [13]. In the present study, the incidence of CMBs was 46.23%,

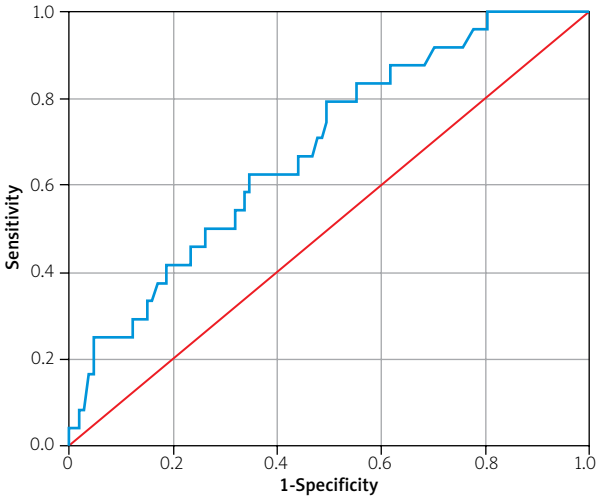

Fig. 1. Night diastolic blood pressure-standard deviation (NDBP-SD) is the ROC curve of independent risk factors for deep cerebral microbleeds (CMBs) in patients with acute ischemic stroke.

Table IV. Night diastolic blood pressure-standard deviation (NDBP-SD) was further changed into a dichotomous variable for univariate regression analysis

Variable	OR value (95% CI)	*P*
NSBP-SD	3.872 (1.347~11.125)	0.012

which was basically consistent with the results of previous related studies.

It has been shown that age and hypertension are independent risk factors for CMBs, and the prevalence of CMBs increases with age, with prevalence rates of 11%, 22% and 39% in the 60-69, 70-79 and 80 years and older age groups, respectively [11]. The incidence of CMBs in patients with hypertension is significantly higher than that in the general population, and the number of CMBs is proportional to the level of blood pressure control [7]. In addition, the risk factors associated with CMBs include a history of diabetes, abnormal lipid metabolism, abnormal renal function and inappropriate anticoagulation/antiplatelet therapy [8,27]. However, in this study, the univariate analysis of the baseline data of the enrolled patients showed that there was no statistical significance in age, hypertension, diabetes history, abnormal renal function and abnormal blood lipid metabolism between the strictly deep CMB group and the non-CMB group. This is different from the results of some previous studies. Considering the small sample size of this study and the inclusion of patients with acute ischemic stroke, such patients are often accompanied by risk factors for cerebrovascular disease, such as hypertension, diabetes and abnormal blood lipid metabolism, resulting in no statistical difference between the two groups of samples.

In this study, the proportion of patients with hypertension in the strictly deep CMB group was 87.5%, and the proportion in the non-CMB group was 81.3%, indicating that the detection rate of CMBs in patients with acute ischemic stroke and hypertension was higher. The NLR – a systemic inflammatory indicator – is associated with the occurrence, development, prognosis and mortality of cardiovascular and cerebrovascular diseases [20]. However, Chung *et al*. found that NLR has nothing to do with the progression of CSVD [6]. In the present study, there were no significant differences in systemic inflammatory indicators (such as NLR) and vascular inflammatory indicators (such as Hcy) between the strictly deep CMB group and the non-CMB group. Considering the small number of samples included in this study, the sample size should be expanded to further explore the relationship between the two.

A cross-sectional study of 178 patients with acute ischemic stroke by Liang *et al*. showed that the coefficient of variation of 24-h SBP was an independent risk factor for CMBs [17]. Similarly, studies have shown that in elderly patients with hypertension and underlying vascular endothelial dysfunction, the 24-h blood pressure variation coefficient and 24-h blood pressure standard deviation were significantly increased. This indicates that hypertension and increased BPV are closely related to vascular endothelial dysfunction, and this correlation may indicate that higher BPV may lead to more severe vascular dysfunction, resulting in the generation of CMB lesions [22]. Corresponding studies have also revealed the correlation between BPV and the location of CMBs.

A 1-year follow-up study of 720 patients with ischemic stroke by Liu et al. showed that systolic BPV and diastolic BPV were independently associated with strictly deep CMBs, while diastolic BPV was independently associated with infratentorial CMBs, but the inter-office average during follow-up. Blood pressure is an indicator that is influenced by numerous factors, and it involves the possibility of a missed diagnosis or misdiagnosis of a transient increase or decrease in blood pressure [18]. In the present study, the univariate analysis of ambulatory blood pressure parameters showed that there were statistically significant differences in NSBP-SD and NDBP-SD between the two groups. The mean values of NSBP-SD and NDBP-SD in the strictly deep CMB group were higher than those in the non-CMB group. After a further multivariate regression analysis, NDBP-SD was independently correlated with the occurrence of strictly deep CMBs, indicating that NDBP-SD was an independent risk factor for the occurrence of strictly deep CMBs.

Compared with previous research, the present study focused on the analysis of BPV while refining the diurnal BPV. Studies have shown that nocturnal diastolic BPV is associated with stroke recurrence in patients with ischemic stroke and small artery occlusion [25]. We extended the existing study on the relationship between BPV and CMBs and evaluated the model of NDBP-SD composition to predict strictly deep CMBs using the ROC curve. The AUC of the model was 0.682, and the NDBP-SD cut-off value was 7.81, which shows that the model has better predictive value. A further binary univariate regression analysis of NDBP-SD showed when NDBP-SD $\geq$ 7.81, the occurrence of deep CMBs was 3.872 times that of NDBP-SD $<$ 7.81, further suggesting that NDBP-SD $\geq$ 7.81 might promote the generation of deep CMBs. The results of this study suggest that the parameters related to mean blood pressure and the variability of daytime blood pressure are not statistically significant, which is inconsistent with the results of previous research, considering that this is related to the purpose of reducing daytime blood

pressure in patients with acute ischemic stroke after admission.

After focusing on intensive daytime blood pressure management, this study believes that the treatment of hypertension should be aimed at reducing mean blood pressure and BPV while focusing on daytime blood pressure management, with particular emphasis on night-time diastolic BPV.

Although 24-h ambulatory blood pressure monitoring can more objectively reflect blood pressure levels and their variability than incidental blood pressure measurement in the office, there is still some contingency. In addition, this study was a single-centre study, its sample size was small, and the data were not representative. The results of this research are based on the overall analysis of patients with acute ischemic stroke and do not make specific divisions in terms of aetiology and mechanism. The distribution of and risk factors for CMBs may vary according to different stroke subtypes, which may have implications for influencing the results of this research. Therefore, long-term follow-up studies with large-sized samples are required in the future to further explore the correlation between ambulatory blood pressure and CMBs and to explore whether the occurrence and progression of CMBs can be prevented when the average blood pressure and BPV are controlled.

Conclusions

The standard deviation of nocturnal diastolic blood pressure in patients with acute ischemic stroke is an independent risk factor for deep CMBs. A night-time diastolic standard deviation greater than 7.81 may promote the generation of strictly deep CMBs. Therefore, the monitoring of and intervention in 24-h ambulatory blood pressure levels and NDBP-SD may be an important therapeutic method for regulating deep CMBs.

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Disclosure

The authors report no conflict of interest.

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