



# Association Between the Circadian Rhythm of Arterial Blood Pressure and White Matter Lesions in Hospitalized Hypertensive Patients: A Cross-Sectional Study

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**Background:** White matter lesions (WMLs) are associated with an increased risk of stroke, cognitive impairment, and vascular dementia. Hypertension stands as the most significant modifiable independent risk factor contributing to WMLs. However, little is known about the relationship between WMLs and altered circadian rhythms of blood pressure (BP) in patients with essential hypertension.

**Methods:** This cross-sectional observational study enrolled patients diagnosed with essential hypertension. Participants were stratified into mild, moderate, and severe WMLs subgroups based on Fazekas scale assessments, with a control group of individuals without WMLs. All participants underwent 24-hour ambulatory BP monitoring and were classified according to circadian rhythm patterns: dipper, non-dipper, and antidiipper. Comparative analyses were performed on demographic characteristics, ambulatory BP profiles, and circadian rhythm patterns across groups. Univariate analysis and multivariate logistic regression were employed to identify independent risk factors for WMLs.

**Results:** 33 in the control group and 112 in the WMLs group were included. There were significant differences in age, history of diabetes mellitus and cardiovascular disease ( $p < 0.05$ ). Compared with the control group, mean 24h systolic BP (SBP), mean daytime SBP (DSBP), and mean nocturnal SBP (NSBP) were greater in the WMLs group, and 24hSBPSD, DSBPSD, DDBPSD, and NSBPSD were greater in the WMLs group ( $p < 0.05$ ). The circadian rhythms were significantly different between the WMLs group and the control group ( $p < 0.05$ ). Age, non-dipper, and antidiipper pattern were found to be independent risk factors for WMLs. Multivariate logistic regression revealed that age (OR 1.128 CI 1.082–1.175,  $p < 0.001$ ) and the non-dipper pattern (OR 4.855 CI 1.062–22.184,  $p = 0.042$ ) were independent risk factors for WMLs.

**Conclusion:** Age and non-dipper and antidiipper patterns are associated with an increased risk of WMLs. Non-dipper BP is an independent risk factor for WMLs. Middle-aged and elderly people with primary hypertension with non-dipper BP need to manage and control nocturnal BP.

**Keywords:** white matter lesions, ambulatory blood pressure monitoring, blood pressure variability, circadian rhythm of blood pressure, blood pressure at night

## Introduction

White matter lesions (WMLs) are a manifestation of cerebral small vessel disease. WMLs are prevalent among middle-aged and elderly people, and their prevalence increases with age, affecting approximately 5% of people aged 50 years to almost 100% of people older than 90 years.<sup>1</sup> WMLs are associated with an increased risk of stroke, cognitive impairment, and vascular dementia and play a role in the development of late-onset depression,<sup>2–4</sup> and even studies

have shown that WMLs increase the risk of cerebral hemorrhage in patients receiving intravenous thrombolysis.<sup>5,6</sup> Therefore, it has become particularly important to study the risk factors for WMLs and to control their development.

Advanced age, hypertension, obstructive sleep apnea syndrome, diabetes mellitus, and elevated serum homocysteine levels are risk factors for elevated WMLs, with hypertension being the most important modifiable independent risk factor.<sup>7–11</sup> Measurements based on mean blood pressure (BP) on admission are commonly used to define hypertension. However, such a definition often does not reliably reflect a patient's true BP and ignores fluctuations in BP levels. To date, fluctuations in the circadian rhythm of BP have been largely ignored in clinical practice.<sup>12–15</sup> Previous studies have shown that alterations in the circadian rhythm of blood pressure are associated with cardiovascular mortality, cardiovascular events, Alzheimer's disease, and stroke in hypertensive patients.<sup>13–15</sup> Alterations in circadian rhythms of BP are more predictive of future cardiovascular mortality and morbidity than traditional clinical or diurnal BP. The brain, as a high blood flow organ, is vulnerable to elevated BP and rapid changes. BP variability damages the brain, and also affects kidney and vascular endothelial dysfunction to varying degrees.

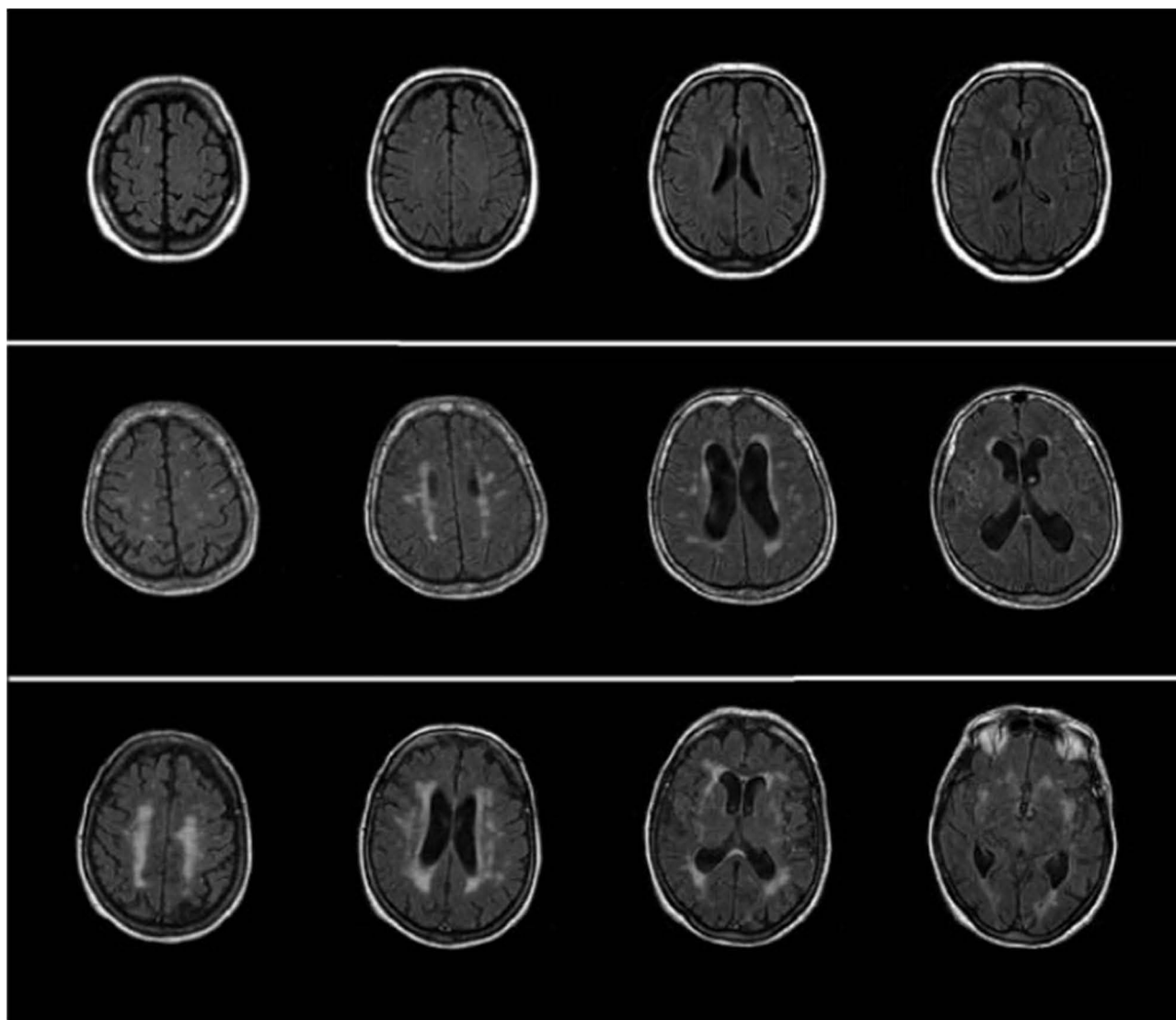
Although the relationship between hypertension and WMLs is well established, the relationship between WMLs and circadian fluctuations in arterial BP remains unclear. In studies on the effects of nocturnal BP fluctuations on WMLs, the effects of non-dipper BP and antidipper BP agents on WMLs remain controversial. Therefore, this study was designed to improve our understanding of the relationship between the circadian rhythm of arterial BP and WMLs in hypertensive patients. This provides guidance for BP control in patients with WMLs combined with essential hypertension and mitigates the development of WMLs in such patients.

## Patients and Methods

This retrospective cross-sectional observational study was derived from data from the Second Affiliated Hospital of Nanchang University, China. The hospital is a medical center in Jiangxi Province that provides medical services to 50 million people. Patients who were hospitalized in the department of neurology and diagnosed with essential hypertension between January 1, 2021, and June 30, 2023, were included as candidates. The study was approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University and was conducted in full accordance with the principles of the Declaration of Helsinki with the informed consent of the patients.

We included patients aged 40–85 years who were diagnosed with primary hypertension. The diagnosis of essential hypertension strictly adhered to the criteria outlined in the 2022 Chinese clinical practice guideline for hypertension. Both newly diagnosed cases through standardized guideline-based assessment and patients with previously documented hypertension diagnoses were included in this study. Of course, patients with diabetes and prior cardiovascular disease were included (based on the patient's self-report or medical records). Stringent exclusion criteria comprised: (1) patients with secondary hypertension confirmed through etiological evaluation; (2) individuals exhibiting uncontrolled BP (systolic BP  $\geq 140$  mmHg and/or diastolic BP  $\geq 90$  mmHg on repeated measurements, or exhibiting excessive BP variability with daytime systolic BP fluctuations  $\geq 30$  mmHg); (3) cases with incomplete clinical datasets or critical data deficiencies precluding comprehensive analysis. Because of the retrospective nature of this study, all parameters were collected on a complete medical records system. The data collected included demographic characteristics (age, sex, BMI), personal and family history (history of diabetes and cardiovascular disease), lifestyle (history of smoking and alcohol consumption, etc.), and a series of ancillary tests (glycosylated hemoglobin, total cholesterol, triglycerides, LDL, homocysteine, blood uric acid, and C-reactive protein). In the control group, the absence of WMLs was needed.

All enrolled patients included 3.0 T (GE HealthCare, Chicago, IL, USA) cranial magnetic resonance imaging (MRI) with T1-weighted imaging, T2-weighted imaging, and fluid-attenuated inversion recovery (FLAIR) sequences. WMLs on T2-weighted and FLAIR sequences were assessed using the modified Fazekas visual rating scale, which grades severity from 0 to 3: The absence of any lesions in the paraventricular region was indicated as "0"; cap-shaped or pencil-like thin layer lesions were represented by a "1"; smooth halo lesions were rated as "2"; and irregular high signal extending into deep white matter was scored as "3". A deep white matter score of 0 indicated the absence of disease; a score of 1 point indicated punctate disease; 2 points indicated merging lesions; and 3 points indicated a large area of fusion. The total score range is 0 to 6, divided into paraventricular and deep regions, each region having a maximum score of 3. Grade 0, no lesion; grade 1, speckled high signal; grade 2, patchy high signal (partial aggregation of speckles); and grade 3, patchy high signal (extensive fusion of lesions). Grades 1–3 correspond to mild (the total score is 1–2), moderate (the total score is 3–4) and severe (the total score is 5–6) WMLs respectively (Figure 1).



**Figure 1** The first line of imaging pictures with a score of 0 or 1, the second line has a score of 2 and the third line is 3.

WMLs assessments were conducted independently by two board-certified neuroradiologists who were blinded to the clinical data. Discordant interpretations underwent adjudication by a third senior neuroradiologist ( $\geq 15$  years' experience), with final determinations reached through consensus-based diagnosis following structured deliberation.

A 24-hour ambulatory BP monitor (Model EB12, G3401-00157) that had been validated in an independent trial of accuracy clinics. Before performing ambulatory BP monitoring (ABPM), it is recommended to first measure the BP of both arms in the clinic or review prior BP measurements from both arms. If the difference between the two arms is  $\geq 10$  mmHg, ABPM should be conducted on the arm with the higher BP. If the difference is  $< 10$  mmHg, it is suggested to select the non-dominant arm for ABPM in order to minimize the impact of arm movement on BP measurements. Patients routinely took their medications and performed normal daily activities and were informed that the measuring arm needed to remain stationary during automated ambulatory BP measurements. ABPM should be strictly conducted according to the 2022 Chinese ambulatory blood pressure monitoring guidelines. A diary card should be used to record daily activities on the day of BP monitoring, including wake-up time, sleep time, lunchtime, meal times, physical activities, and medication details. This will facilitate the preparation of the subsequent ABPM assessment report. We conduct ABPM on weekdays to provide BP data that more closely reflects daily work and life conditions. BP was measured every 30 minutes during the day (6:00–22:00) and every 1 hour at night (22:00–6:00). A percentage of valid data  $\geq 70\%$  was considered valid; otherwise, the

data were remonitored. Elevated ambulatory BP was defined as follows: elevated 24-hour BP as the mean 24-hour systolic BP  $\geq 130$  mmHg and/or mean 24-hour diastolic BP  $\geq 80$  mmHg; elevated daytime BP, ie, mean daytime systolic BP  $\geq 135$  mmHg and/or mean daytime diastolic BP  $\geq 85$  mmHg; and elevated nocturnal BP as the mean nocturnal systolic BP  $\geq 120$  mmHg and/or mean diastolic BP  $\geq 70$  mmHg at night.

The following ambulatory BP parameters were recorded: mean 24-hour systolic BP (24hSBP), mean 24-hour diastolic BP (24hDBP), mean daytime systolic BP (DSBP), mean daytime diastolic BP (DDBP), mean nocturnal systolic BP (NSBP), mean nocturnal diastolic BP (NDBP), standard deviation (SD) of the 24-hour ambulatory BP, and the BP circadian rhythm (according to the formula (average daytime pressure - average nighttime pressure)/average daytime pressure\*100%. Depending on the change in BP levels during the circadian rhythm, there are three dynamic blood pressure patterns: 1. Dipper BP (Normal NSBP reduction is a 10%-20% decrease compared to DSBP). 2. Non-dipper BP (A slight or no decrease in NSBP compared to DSBP is defined as a reduction of less than 10%). 3. Antidipper BP (NSBP may even increase compared to DSBP).

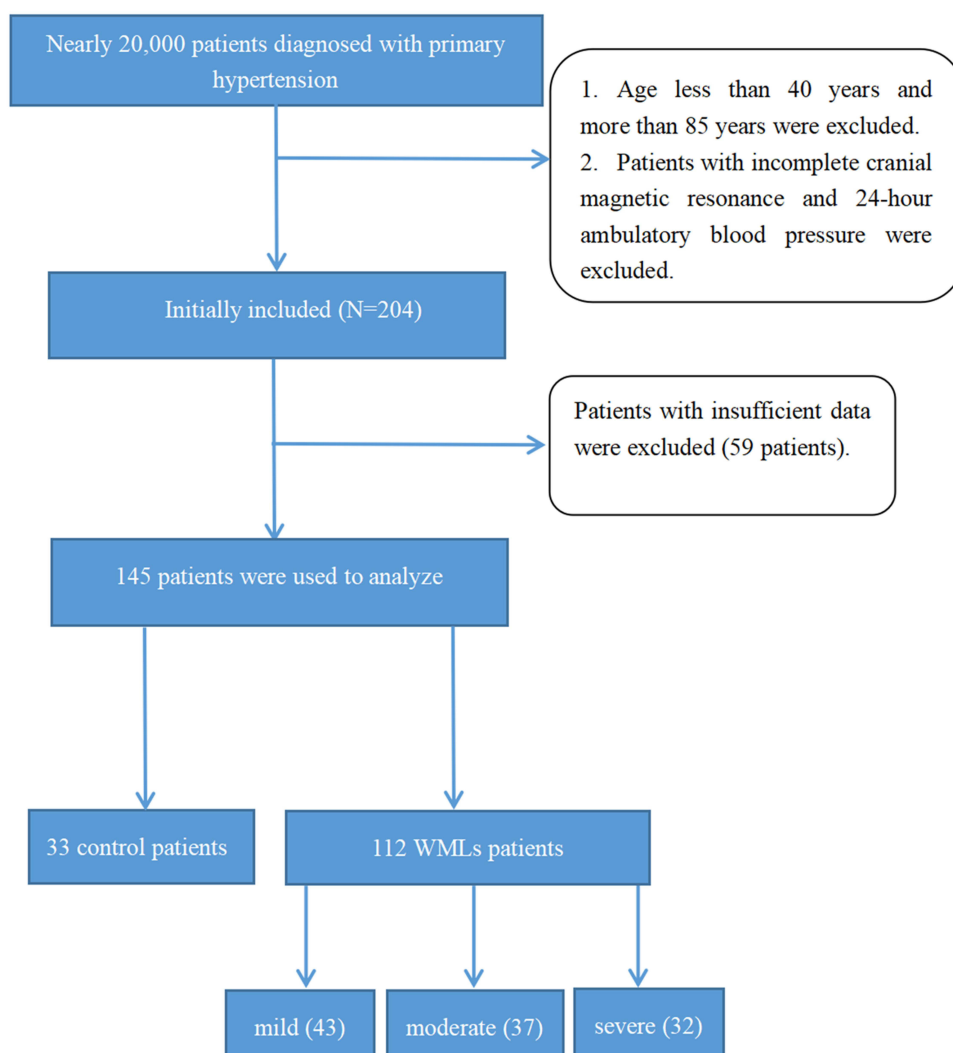
## Statistical Analysis

The Shapiro–Wilk tests were used to assess whether the data obeyed a normal distribution, the results for normally distributed continuous variables are given as the mean and standard deviation (SD), and the results that did not fit the normal distribution are given as the median and interquartile range. For categorical variables, frequencies and proportions are given. To detect differences between continuous variables in two groups, the independent samples *t* test was used for normally distributed variables, and the Mann–Whitney *U*-test was used for variables that did not conform to a normal distribution. For comparisons of multiple groups of data, statistical significance was analyzed using one-way ANOVA and post hoc tests were used to determine differences between groups based on adjusted standardized residuals. The required sample size is based on prior studies indicating that the incidence of WMLs in hypertensive patients reaches 80%.<sup>1</sup> The significance level is set at  $\alpha = 0.05$  (two-tailed), and the allowable margin of error is 20%. The calculated sample size is approximately 62 participants. Statistically significant variables in the cross-group analysis were included in the regression analysis. Multivariate logistic regression analysis was used to assess the relationship between circadian variation in BP and WMLs. All tests were performed using IBM SPSS Statistics v.25.0 software (SPSS, Chicago, IL, USA). *P* value  $<0.05$  was considered significant.

## Results

Of the 112 patients enrolled, 43 were in the mild WMLs group, 37 were in the moderate WMLs group, and 32 were in the severe WMLs group, of whom 50 (44.64%) were male. There were 33 patients in the control group, and 14 (42.4%) were male (Figure 2). There was no statistically significant difference in sex between the control and WMLs groups. Age, history of diabetes mellitus and history of cardiovascular disease were significantly greater in the WMLs group than in the control group. The mean age of the patients in the control group was significantly lower than that of the patients in the WMLs group, and between-group comparisons revealed that the mean age of the patients in the control group was significantly lower than that of the patients in the mild, moderate, and severe groups. The mean age of patients in the mild WMLs group was significantly younger than that of patients in the moderate or severe group. A history of diabetes mellitus was significantly lower in the control group than in the WMLs group, and between-group comparisons revealed that it was significantly lower in the control group than in the severe WMLs group and was not significantly different in any of the other groups. A history of cardiovascular disease was significantly lower in the control group than in the WMLs group, but there were no significant differences between the groups. Smoking history, BMI, total cholesterol, triglycerides, low-density lipoprotein, uric acid, homocysteine, C-reactive protein, and glycosylated hemoglobin were not significantly different between the control group and the WMLs group. The specific data are shown in Table 1.

The 24hSBP was significantly greater in the WMLs group than in the control group. A comparison between groups revealed that severe group were significantly more than moderate group, mild group and control group, and there were significantly more moderate group than control group. Compared with that in the control group, the DSBP in the WMLs group was significantly greater. Comparisons between groups revealed that there were significantly more severe patients in the severe group than in the mild group, and there were significantly more severe patients in the severe group than in



**Figure 2** Flowchart of patients included in the study.

the control group, while no significant differences were detected between the other groups. NSBP was significantly greater in the WMLs group than in the control group. The 24hSBPSD was significantly greater in the WMLs group than in the control group. A comparison between groups revealed that the severe group had significantly more severe disease than did the control group. DSBPSD was significantly greater in the WMLs group than in the control group. A comparison between the groups revealed that there were significantly more patients in the severe group than in the control group. DDBPSD was significantly greater in the WMLs group than in the control group. When WMLs was

**Table 1** Baseline Clinical and Clinical Characteristics

Variable	Control (n=33)	Mild WMLs (n=43)	Moderate WMLs (n=37)	Severe WMLs (n=32)	P
Mean age (SD), years	53.94±8.49	60.77±8.12	66.38±7.74	70.16±8.21	<0.001
Gender (%), male	14 (42.4)	20 (46.50)	16 (43.20)	14 (43.8)	0.822
History of diabetes	1 (3)	9 (20.9)	8 (21.6)	11 (34.4)	0.006
History of cardiovascular disease	4 (12.1)	12 (27.9)	15 (40.5)	22 (68.8)	0.001

(Continued)

**Table 1** (Continued).

Variable	Control (n=33)	Mild WMLs (n=43)	Moderate WMLs (n=37)	Severe WMLs (n=32)	P
History of smoking	5 (15.2)	9 (20.9)	9 (24.3)	7 (21.9)	0.372
BMI (Kg/m <sup>2</sup> )	24.27±3.34	24.01±3.08	24.18±2.80	25.18±1.45	0.970
CHOL (mmol/L)	4.83 (4.20, 5.46)	4.61 (4.08, 5.18)	4.55 (3.53, 5.61)	4.54 (3.95, 5.15)	0.184
TG (mmol/L)	1.24 (0.90, 1.83)	1.59 (1.25, 2.17)	1.49 (1.05, 1.74)	1.26 (0.81, 1.53)	0.512
LDLC (mmol/L)	2.62±0.73	2.54±0.73	2.40±0.88	2.51±0.88	0.399
UA (mmol/L)	306.7 (269.80, 375.45)	285.80 (242.70, 349.70)	238.60(257.90, 406.06)	300.10 (240.15, 354.38)	0.671
HCY (mmol/L)	12.65±3.62	13.48±3.79	12.86±3.59	12.31±2.92	0.680
CRP (mmol/L)	2.64 (1.29, 8.20)	1.82 (0.78, 5.66)	1.43 (0.86, 5.40)	2.22 (1.13, 7.11)	0.319
HbA1c (%)	5.69±0.78	6.02±1.24	5.81±0.92	5.87±0.82	0.252

**Note:** Bold value indicates statistical significance at  $p < 0.05$ .

**Abbreviations:** SD, standard deviation; BMI, body mass index; CHOL, cholesterol; TG, triglyceride; LDLC, low-density lipoprotein cholesterol; UA, uric acid; HCY, homocysteine; CRP, C-reactive protein; HbA1c, glycated hemoglobin; WMLs, white matter lesions.

divided into three groups, there was no significant difference between the groups. NSBPSD was significantly greater in the WMLs group than in the control group. When WMLs was divided into three groups, there was no significant difference between the groups. ABPM revealed 33 patients with dipper BP, 73 patients with non-dipper BP and 39 patients with antidipper BP. There was a significant difference between the WMLs group and the control group under the different BP patterns. The details can be found in [Table 2](#).

**Table 2** 24-Hour Ambulatory Blood Pressure Parameters in the WMLs Group and the Control Group

Variable	Control (n=33)	Mild WMLs (n=43)	Moderate WMLs (n=37)	Severe WMLs (n=32)	P
Ambulatory BP (mmHg)					
24hSBP	118.45±13.50e	123.88±13.29	127.97±13.30	137.25±15.77	<b>&lt;0.001</b>
24hDBP	73.85±10.11	72.65±9.65	73.41±9.51	75.75±10.35	0.973
DSBP	120.64±14.32	125.67±13.44	129.05±13.47	137.97±16.74	<b>0.001</b>
DDBP	76.18±10.56	74.40±9.83	74.81±9.87	77.41±11.05	0.699
NSBP	112.36±13.03e	119.23±14.83	125.54±15.61	135.28±15.22	<b>&lt;0.001</b>
NDBP	67.55±9.40	67.53±10.02	69.92±10.30	71.47±9.77	0.336
Standard deviation of ambulatory BP (mmHg)					
24hSBPSD	11.98±2.86c	12.56±3.10	13.61±2.71	14.50±4.08	<b>0.023</b>
24hDBPSD	9.65±2.30	9.88±2.04	10.42±2.91	10.92±3.37	0.186
DSBPSD	11.34±2.97e	12.35±3.87	13.45±2.92	14.34±4.36	<b>0.008</b>
DDBPSD	8.98±2.51	9.48±2.59	10.46±3.00	10.99±4.01	<b>0.041</b>
NSBPSD	9.38±3.08	9.47±2.93	10.72±3.74	11.90±4.77	<b>0.036</b>
NDBPSD	7.10±3.03	7.28±2.84	8.05±4.69	7.57±2.78	0.444
BP patterns					
Dipper	14 (42.40)	8 (18.60)	8 (21.60)	3 (9.40)	<b>0.007</b>
Non-dipper	14 (42.40)	27 (62.80)	15 (40.50)	17 (53.10)	
Antidipper	5 (15.20)	8 (18.60)	14 (37.80)	12 (37.50)	

**Note:** Bold value indicates statistical significance at  $p < 0.05$ .

**Abbreviations:** 24hSBP, mean 24-hour systolic blood pressure; 24hDBP, mean 24-hour diastolic blood pressure; DSBP, mean daytime systolic blood pressure; DDBP, mean daytime diastolic blood pressure; NSBP, mean nocturnal systolic blood pressure; NDBP, mean nocturnal diastolic blood pressure; SD, standard deviation; WMLs, white matter lesions.



the severity of WMLs in patients. Therefore, middle-aged and elderly people with primary hypertension with non-dipper BP patterns may need to manage and control nocturnal BP to mitigate the risk of developing WMLs.

Hypertension has been shown to be an independent risk factor for WMLs, and hypertension has been consistently associated with WMLs load measured cross-sectionally and with WMLs progression measured longitudinally.<sup>16–19</sup> By monitoring 24-hour ambulatory BP, we found that 24-hour systolic BP, daytime systolic BP, and nocturnal systolic BP were all risk factors for WMLs. A meta-analysis showed that elevated systolic BP was significantly associated with increased severity of WMLs, and for every 1 mmHg increase in systolic BP, WMLs increased by 0.01 cm<sup>3</sup>.<sup>20</sup> On the one hand, simple systolic hypertension is mainly observed in elderly individuals, who are more likely to develop WMLs, and the greater the systolic BP is, the more severe the WMLs are, which is in agreement with our results. On the other hand, the blood supply to the WMLs mainly comes from small perforating arteries, and its biological characteristics determine that the WMLs is sensitive to ischemia. When systolic BP increases, the cardiac afterload increases, the per-beat output decreases, and the blood supply to the brain decreases, causing WMLs. The relationship between diastolic BP and WMLs is currently controversial. One large cohort study revealed that WMLs were strongly associated with both systolic and diastolic BP, with WMLs associated with elevated diastolic BP before age 50 years and with elevated systolic BP after age 50 years.<sup>21</sup> Another prospective cohort study based on Three-City (3C)-Dijon MRI revealed a strong correlation between WMLs and diastolic BP.<sup>22</sup> However, some studies have also shown that diastolic BP is not associated with WMLs.<sup>23</sup> In our study, we also did not find that diastolic BP was associated with WMLs. First, because of the average age of our enrolled patients, elderly individuals accounted for 57.24% of our enrolled patients, and the distribution of elderly individuals may be more conducive to determining the relationship between systolic BP and WMLs. Therefore, further studies on the relationship between diastolic BP and WMLs are warranted.

BP variability (BPV) is the result of the interaction of hemodynamic, neurological, humoral, behavioral, and environmental factors.<sup>24</sup> A growing body of evidence emphasizes the importance of BPV as a risk factor for cardiovascular disease, cerebrovascular disease, and mortality at independent BP levels.<sup>25</sup> The SD of 24-hour ambulatory BP is the most commonly used indicator of BPV. However, the relationship between BPV and WMLs remains highly controversial. Zhou et al concluded that long-term or short-term BP SDs are not associated with measured WMLs loads.<sup>26</sup> Similarly, others reported no association between 24-hour BP SD and the presence of WMLs.<sup>27</sup> Our study revealed that higher systolic BP variability and diastolic BP variability increased the risk of WMLs and their subtypes in a middle-aged and elderly population with comorbid essential hypertension. Although there was a statistically significant difference between diastolic BP variability and WMLs, the clinical significance of this finding is unclear. However, the correlation between BPV and WMLs was no longer significant according to univariate and multivariate logistic regression analyses, which may be related to sample size and inclusion criteria. Consistent with our findings, it has recently been shown that elevated systolic SD is associated with increased WMLs lesion volume and is most pronounced in hypertensive patients.<sup>28</sup> Additional evidence comes from a study of WMLs in demented patients with postural hypotension and possible carotid sinus sensitivity. Patients with the greatest decrease in systolic BP had increased severity of WMLs detected by MRI. Our findings support that a reduction in systolic BPV may be a future goal in the prevention of WMLs.<sup>29</sup>

A normal circadian rhythm of BP is highly beneficial for adapting to bodily activities and protecting the structure and function of vital organs. When the circadian rhythm of BP weakens or disappears, even when the average BP levels during the day and night are similar, the risk of target organ damage and cardiovascular events significantly increases. Individuals with normal BP but an abnormal circadian rhythm of BP, characterized by a non-dipper pattern, have the same risk of cardiovascular and cerebrovascular mortality as hypertensive patients with a dipper circadian pattern. Hypertensive patients with antidipper BP patterns are more likely to experience damage to target organs such as the heart and brain.<sup>13</sup> The pathophysiologic mechanisms underlying the non-dipper and antidipper BP patterns are not well understood. It has been proposed that non-dipper and antidipper BP patterns lead to higher 24-hour mean BP levels, which results in accelerated atherosclerotic disease, leading to chronic ischemia and thus WMLs.<sup>30,31</sup> Furthermore, studies have shown that the vessels associated with WMLs are small deep perforating arteries without collateral circulation, which are most susceptible to ischemic damage. A weakened circadian rhythm of BP, with sustained elevated nocturnal BP, places these vessels under increased load during the night, exacerbating endothelial dysfunction, activating the endogenous coagulation system.<sup>8</sup> This ultimately leads to ischemic occlusion or sclerosis and rupture of small vessels, resulting in WMLs, lacunar infarctions, or

microbleeds in the brain. This mechanism partly explains how non-dipper and antidipper BP patterns contribute to the development of WMLs. Our findings provide further evidence that non-dipper and antidipper BP patterns, compared with dipper BP patterns, were found to be independent risk factors for WMLs in binary logistic regression analyses. A decrease in systolic BP at night protects the cardiovascular system, whereas for non-dipper and dipper BP patterns, systolic BP at night is relatively high for a long period of time, which leads to a decrease in vascular elasticity and an increase in pulsatility. These patients also exhibit more WMLs than dipper patients; however, whether other mechanisms are involved in this process remains to be elucidated. A prospective study revealed that in the general elderly population, abnormal patterns of systolic BP, including both non-dipper and antidipper BP patterns, independently accelerated the progression of WMLs.<sup>32</sup> This is consistent with our findings. A large community-based cohort study on 24-hour ambulatory BP monitoring revealed a 2-fold increase in WMLs volume in patients with essential hypertension with an antidipper BP pattern compared with patients with a dipper or non-dipper BP pattern.<sup>33</sup> Another prospective cohort study from Korea reached similar conclusions.<sup>30</sup> The underlying mechanism between the antidipper BP pattern and WMLs is currently unclear. Most studies have shown that the antidipper BP pattern is more likely to cause WMLs than the non-dipper because the antidipper pattern suggests increased sympathetic excitability, resulting in greater nocturnal BP, more severe atherosclerosis, and more pronounced target organ damage.<sup>34,35</sup> We found that only the non-dipper BP pattern was an independent risk factor for the severity of WMLs. The reason for this may be related to the fact that the proportion of non-dipper BP patterns in the WMLs severity subgroups was greater than that of the antidipper BP patterns.

Several studies have confirmed that age is the most important risk factor for WMLs. It is believed that with increasing age, atherosclerosis occurs in intracranial blood vessels, with thickening of the walls of small arteries, narrowing of the lumen, and occlusion, which causes hypoperfusion of the brain, leading to ischemia of brain tissue, demyelination of nerve cells, and decreased white matter integrity.<sup>36–38</sup> It is unclear at what age WMLs begin to develop, and precise data on the extent of disease that can be considered “normal” at a given age do not exist. Most studies suggest that at least some WMLs develop after the ages of 50 to 65 years, and there is no doubt that WMLs are common in elderly individuals, with Shinkawa reporting a 1.1-fold increase in the risk of WMLs with increasing age.<sup>11,39–41</sup> Our study is in line with the evidence from other scholars, but age is also an unavoidable risk factor.

Abnormal nocturnal BP patterns not only cause direct damage to target organs but also serve as an independent risk factor for the development of WMLs. Therefore, this study believes that it is necessary to control nocturnal BP. In addition to treating the primary causes of nocturnal BP (diabetes, kidney disease, cardiovascular disease, etc.), it is also necessary to rationally use long-acting anti-hypertensive drugs or take anti-hypertensive drugs in batches in the morning and evening according to the situation of long-term BP monitoring. Various models are currently being explored. For example, studies on the relationship between dynamic BP changes and aerobic exercise in elderly hypertensive patients have confirmed that moderate aerobic exercise not only reduces BP but also helps regulate the circadian rhythm of BP. In summary, multimodal and personalized treatment strategies are gradually being adopted. Our study also has some limitations: 1. This is a cross-sectional study, and the causal relationship between BP variability and WMLs is not clear. 2. In addition, retrospective studies have inherent drawbacks, for example, different use of anti-hypertensive drugs may confuse the results. 3. This study is a single-center study with a relatively small sample size, and the inclusion of patients over the age of 45 limits the generalizability of the results. Future research should further explore the role of circadian BP patterns in the development of WMLs, with multi-center, large-sample longitudinal studies and interventional trials to provide valuable insights into this field.

## Conclusion

In this cross-sectional study based on a general population of middle-aged and elderly individuals with essential hypertension, we concluded that age and non-dipper and antidipper BP patterns were associated with an increased risk of WMLs, independent of traditional risk factors. In contrast, the non-dipper BP pattern was an independent risk factor for WMLs severity. Therefore, we suggest that middle-aged and elderly people with primary hypertension with non-dipper BP patterns may need to manage and control nocturnal BP to mitigate the risk of developing WMLs and thus prevent a range of adverse effects associated with WMLs. Future research should further explore the role of circadian BP patterns in the development of WMLs and conduct longitudinal studies and interventional trials to provide valuable insights into this field.

## Data Sharing Statement

All relevant data are described within the paper. Deidentified data can be requested. The data can be requested by all interested researchers, who can be contacted via the corresponding author.

## Ethics Approval

The research was approved by the ethics committee of the Second Affiliated Hospital of Nanchang University.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare no conflicts of interest in this work.

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