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Original Article

Vascular risk factors contribute to the cognitive impairment in elderly patients with hypertension and cerebral small vessel disease: evidence from a retrospective analysis

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Abstract: Objectives: Hypertension is a well-established risk factor for cerebral small vessel disease (CSVD) and cognitive impairment. However, the combined effects of demographic, clinical, and vascular factors on cognitive decline in elderly hypertensive patients with CSVD are not fully clarified. In the current study, we aimed to analyze clinical risk factors and cognitive profiles associated with hypertension-related CSVD in older adults. Methods: We compared hypertensive patients with mild cognitive impairment (MCI), hypertensive patients without MCI, and normotensive controls in 351 cases. Baseline demographics, comorbidities, and medication history were assessed. Logistic regression models were constructed to identify the independent predictors of cognitive impairment. Model performance was evaluated using receiver operating characteristic (ROC) curves, calibration plots, and subgroup analyses stratified by age, sex, and dipping status. Results: Patients with hypertension and MCI were older, more often female, and exhibited a higher prevalence of diabetes, dyslipidemia, and coronary artery disease compared with controls. Logistic regression identified advanced age, female sex, and non-dipping blood pressure profiles as independent predictors of MCI. The predictive model demonstrated good discrimination and calibration. Subgroup analyses revealed that advanced age, female sex, and nondipping blood pressure patterns were associated with higher cognitive impairment rates. Conclusions: Our findings suggest that traditional vascular risk factors contribute to cognitive decline in elderly hypertensive patients with CSVD. The proposed model provides a clinically useful tool for risk stratification and early intervention.

Keywords: Hypertension, cerebral small vessel disease, mild cognitive impairment, vascular risk factors, predictive model

Introduction

Cerebral small vessel disease (CSVD) is a major age-related cerebrovascular disorder characterized by pathological changes in small arteries, arterioles, capillaries, and venules of the brain. Its radiological hallmarks include white matter hyperintensities (WMH), lacunar infarcts, enlarged perivascular spaces, and cerebral microbleeds (CMBs) [1]. CSVD is highly prevalent in older populations and has been identified as one of the leading causes of vascular cognitive impairment and dementia (VCID), contributing to nearly 45% of dementia cases worldwide [2]. Although some patients remain asymptomatic at the early stage, progressive accumulation of CSVD lesions often results in cognitive decline, gait disturbance, mood disorders, and increased risk of stroke [3]. Given its insidious course and high disability burden, CSVD has become a pressing public health concern.

Among the multiple risk factors of CSVD, hypertension plays a pivotal role. Generally, chronic elevation of blood pressure induces endothelial dysfunction, vascular remodeling, and lipohyalinosis, ultimately leading to impaired cerebral

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autoregulation and hypoperfusion [4, 5]. Autopsy and neuroimaging studies demonstrate that hypertensive arteriolosclerosis is the most common substrate of sporadic CSVD in the elderly [6]. Epidemiological data indicate that up to two-thirds of individuals aged ≥60 years in China have hypertension, and its coexistence with cognitive impairment significantly increases the risk of disability and mortality [7]. Furthermore, long-term uncontrolled blood pressure is closely related to WMH progression, lacunar infarction, and brain atrophy, which are strongly predictive of cognitive decline [8].

Cognitive impairment in hypertensive patients with CSVD encompasses a spectrum from mild cognitive impairment (MCI) to overt dementia. The most affected domains include executive function, information processing speed, attention, and visuospatial ability [2, 9]. Longitudinal studies have shown that progression of periventricular WMH is particularly associated with increased odds of developing MCI [3]. However, not all patients with similar imaging burdens exhibit the same degree of cognitive decline, suggesting that additional clinical, genetic, and lifestyle factors modulate the risk. For example, gene polymorphisms such as MTHFR C677T have been linked to elevated homocysteine levels and higher susceptibility to cognitive impairment in elderly hypertensive cohorts [10].

In recent years, research has sought to clarify the interplay between hypertension, CSVD burden, and cognition. Evidence suggests that midlife hypertension confers a stronger risk for late-life dementia than late-life hypertension alone [1, 5, 11]. Moreover, blood pressure variability, nocturnal non-dipping, and acute hypertensive responses after ischemic stroke further exacerbate the risk of cognitive decline [12, 13]. Despite the proven role of hypertension, controversy remains regarding optimal blood pressure targets for cognitive preservation in older adults. Some studies advocate intensive lowering the pressure to <120 mmHg systolic, whereas others caution that overly aggressive treatment may worsen cerebral hypoperfusion in advanced CSVD [1, 14]. Therapeutic strategies have been explored to mitigate cognitive decline in hypertensive CSVD patients. Antihypertensive regimens such as angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs) have shown potential benefits on cognitive outcomes beyond blood pressure control [15]. Lifestyle interventions and vascular risk management are also emphasized in clinical practice guidelines [7]. However, the heterogeneity of patient characteristics, comorbidities, and treatment responses highlights the need to identify specific risk factors in defined populations, particularly the elderly.

Given the clinical and social burden, it is essential to elucidate the risk factors for cognitive impairment in elderly hypertensive patients with CSVD. Identifying modifiable predictors could aid in early screening, targeted interventions, and individualized treatment strategies, ultimately reducing the incidence of dementia and improving quality of life in this vulnerable population. This study aims to retrospectively analyze the clinical, imaging, and biochemical characteristics of 351 elderly patients with hypertension and CSVD, to determine the risk factors associated with cognitive impairment and provide evidence for clinical management.

Methods

Case selection

This retrospective observational study enrolled 351 elderly patients (≥60 years) with hypertension and cerebral small vessel disease (CSVD) admitted to Shanghai University of Traditional Chinese Medicine between January 2021 and December 2023. Hypertension was diagnosed according to the Chinese Guidelines for the Management of Hypertension (2019), while CSVD was confirmed by magnetic resonance imaging (MRI) using STRIVE criteria. Inclusion criteria required: 1) Age ≥60 years at admission. 2) Definite diagnosis of hypertension, defined as office systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg on at least two different occasions, or long-term use of antihypertensive medications. 3) MRI evidence of CSVD, including at least one of the following: white matter hyperintensities, lacunes, cerebral microbleeds, or enlarged perivascular spaces. 4) Completed cognitive function assessment [Montreal Cognitive Assessment (MoCA) and/or Mini-Mental State Examination (MMSE)] within three months of MRI. 5) Availability of key demographic, clinical, and laboratory data for analysis. Exclusion criteria were: 1) History

of major neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, normal-pressure hydrocephalus). 2) Previous severe psychiatric disorders (psychosis, bipolar disorder, major depressive disorder with functional impairment). 3) History of severe stroke with cortical involvement, space-occupying infarct, or intracranial hemorrhage. 4) Traumatic brain injury with loss of consciousness >30 minutes or residual neurological deficits. 5) Severe systemic disease such as decompensated heart failure, advanced hepatic failure, end-stage renal disease, or malignancy. All procedures adhered to the Declaration of Helsinki and were approved by the institutional ethics committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, which waived informed consent due to the retrospective design.

Data collection and variable definition

Clinical data, blood pressure, and laboratory tests: Baseline demographic and clinical characteristics included age, sex, education, BMI, hypertension duration and grade, smoking and alcohol history, diabetes, dyslipidemia, coronary artery disease, atrial fibrillation, and chronic kidney disease. Antihypertensive, statin, and antiplatelet medications were also recorded. Blood pressure was measured by mercury sphygmomanometer or validated oscillometric devices after 10 minutes of rest, with two consecutive readings averaged. In patients with 24-h ambulatory blood pressure monitoring (ABPM), additional metrics such as mean systolic/diastolic pressures, average real variability (ARV), nocturnal dipping pattern, and morning surge were analyzed. Arterial stiffness parameters, including brachial-ankle or carotid-femoral pulse wave velocity and augmentation index were measured when available.

Fasting venous blood was collected the morning after admission. Routine biochemical tests included glucose, HbA1c, lipid profile, renal and hepatic function, and high-sensitivity C-reactive protein (hs-CRP). Plasma homocysteine was measured by enzymatic cycling. Extended biomarker panels in selected cases included serum CTRP9 by enzyme-linked immunosorbent assay (ELISA) and inflammatory cytokines (IL-6, TNF-α).

Neuroimaging and CSVD assessment: MRI examinations were performed on a 3.0-T scanner with standard sequences including T1-weighted, T2-weighted, FLAIR, diffusion-weighted imaging, and susceptibility-weighted imaging. White matter hyperintensities (WMH) were rated using the Fazekas scale and quantified with lesion segmentation tools normalized to intracranial volume. Lacunes were identified as round CSF-like cavities (3-15 mm). Cerebral microbleeds (CMBs) were recorded on SWI and categorized by location, while enlarged perivascular spaces (PVS) were graded semi-quantitatively. Global cortical atrophy and medial temporal lobe atrophy were also assessed. A total CSVD burden score (0-4) was calculated by summing severe WMH, presence of lacunes, deep/infratentorial CMBs, and moderate-severe basal ganglia PVS.

Cognitive and neuropsychological evaluation: Cognitive status was primarily assessed using the Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE), widely validated in Chinese elderly populations. MoCA domains included visuospatial/executive function, naming, attention, memory, language, abstraction, and orientation; an additional point was added for ≤12 years of education. MCI was diagnosed according to the Chinese Guidelines for Diagnosis and Treatment of Dementia and Cognitive Impairment (2018). MCI was defined as: (1) subjective cognitive complaints reported by the patient or caregiver; (2) objective cognitive impairment in one or more cognitive domains based on MoCA testing; (3) preservation of independent activities of daily living; and (4) absence of dementia. A MoCA score <26 (or <25 for individuals with ≤12 years of education) was used as the cognitive impairment cutoff.

Treatment and medication information: Antihypertensive regimens were grouped as angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), beta-blockers (BBs), or combinations. These groups allowed comparison of differential cognitive outcomes across drug classes, consistent with recent clinical findings that ARBs may offer superior cognitive protection compared with BBs and CCBs. Information on statin and antiplatelet therapy was also collected.

Table 1. Baseline demographics, clinical characteristics, and medication history

Measure	Hypertensive + MCI (n = 62)	Hypertensive - MCI (n = 101)	Control (n = 67)	Statistic	*p*-value
Age (years)	73.2 ± 6.5	71.9 ± 5.3	70.2 ± 4.5	F = 8.214	<0.001
Male (%)	33.87	47.52	52.24	X^2 = 7.982	0.019
Female (%)	66.13	52.48	47.76	χ^2 = 7.982	0.019
BMI (kg/m^2)	26.10 ± 4.20	25.30 ± 3.90	24.80 ± 4.10	F = 2.014	0.136
Hypertension duration (years)	10.50 ± 3.20	8.40 ± 2.60	N/A	t = 4.294	<0.001
Diabetes (%)	40.32	24.75	17.91	χ^2 = 10.521	0.005
Dyslipidemia (%)	45.16	29.70	19.40	χ^2 = 11.689	0.003
Coronary artery disease (%)	35.48	19.80	10.45	χ^2 = 14.392	0.001
Chronic kidney disease (%)	14.52	9.90	4.48	χ^2 = 5.932	0.052
Atrial fibrillation (%)	11.29	7.92	4.48	χ^2 = 4.214	0.122
Antihypertensive medications (%)	100	100	100	-	-
Statin medications (%)	59.68	54.46	40.30	χ^2 = 7.211	0.027
Antiplatelet medications (%)	45.16	39.60	34.33	χ^2 = 1.892	0.388

MCI, mild cognitive impairment; BMI, body mass index.

Statistical analysis

All analyses were performed using R (v4.4.0) and SPSS (v26). Continuous variables were expressed as mean ± SD or median (IQR) and compared with t-tests or Mann-Whitney U tests, while categorical variables were expressed as n (%) and compared by χ^2 or Fisher's exact test. Multiple-group comparisons were first analyzed by one-way ANOVA followed by the Bonferroni post hoc test. Logistic regression identified risk factors for cognitive impairment, defined as MoCA <26 with education adjustment or clinical diagnosis of MCI/VCI. Predictor selection was guided by LASSO regression with 10-fold cross-validation, and selected variables entered into multivariate logistic regression. Model performance was evaluated by the ROC curve and AUC with bootstrap correction, calibration plots, Hosmer-Lemeshow test, and Brier score. Sensitivity analyses excluded patients with prior stroke/TIA or depressive symptoms, while subgroup analyses were conducted by age, sex, and dipping status. All statistical tests were two-tailed. Unless otherwise specified (e.g., Bonferroni-adjusted post-hoc analyses), P<0.05 was considered statistically significant. For comparisons involving more than two groups, the significance threshold was adjusted accordingly ($\alpha' = 0.05/k$, where k is the number of pairwise comparisons).

Results

Baseline demographics, clinical characteristics, and medication history

Baseline demographics of the three groups are summarized in **Table 1**. Significant between-group differences were observed for age and education level (*p*-value <0.05), while other baseline characteristics were comparable. The Hypertensive with MCI group showed a greater burden of vascular comorbidities and higher use of statins and antiplatelet agents than the Hypertensive without MCI group, indicating a more severe cardiovascular risk profile in cognitively impaired patients.

Blood pressure and ABPM metrics

As shown in **Table 2**, the Hypertensive with MCI group demonstrated consistently higher office blood pressure and 24-hour ambulatory blood pressure variability, accompanied by greater arterial stiffness and a more pronounced morning surge compared with the other groups. These findings indicate substantially impaired vascular regulation in hypertensive individuals with cognitive impairment.

Laboratory results and biomarker measurements

Laboratory and biomarker assessments (**Table 3**) showed that the Hypertensive with MCI

Table 2. Blood pressure measurement and ABPM metrics

Measure	Hypertensive + MCI (n = 62)	Hypertensive - MCI (n = 101)	Control (n = 67)	F-value	*p*-value
SBP (mmHg)	145.20 ± 15.60	135.60 ± 12.30	120.80 ± 10.20	88.214	<0.001
DBP (mmHg)	90.50 ± 9.80	82.30 ± 7.60	78.20 ± 6.50	56.831	<0.001
24-h SBP	144.00 ± 16.10	134.20 ± 13.70	119.20 ± 10.10	79.224	<0.001
SD of SBP	11.60 ± 3.40	10.50 ± 3.00	8.20 ± 2.10	26.141	<0.001
Coefficient of variation (%)	8.30 ± 2.10	7.60 ± 1.90	6.20 ± 1.40	19.212	<0.001
ARV (mmHg)	6.50 ± 2.30	5.80 ± 2.00	4.50 ± 1.20	16.821	<0.001
Nocturnal dipping (%)	10.40 ± 5.60	8.50 ± 4.20	5.10 ± 2.30	21.394	<0.001
Morning surge (mmHg)	22.10 ± 7.40	19.80 ± 6.10	15.20 ± 5.00	19.712	<0.001
Pulse wave velocity (m/s)	13.20 ± 3.40	11.80 ± 2.90	9.30 ± 2.50	28.501	<0.001
Augmentation index (%)	30.20 ± 8.10	25.60 ± 7.20	20.30 ± 5.90	32.41	<0.001

ABPM, ambulatory blood pressure monitoring; SBP, systolic blood pressure; DBP, diastolic blood pressure; ARV, average real variability.

Table 3. Laboratory test results and biomarker measurements

Measure	Hypertensive + MCI (n = 62)	Hypertensive - MCI (n = 101)	Control (n = 67)	F-value	*p*-value
Fasting glucose (mg/dL)	105.60 ± 22.10	98.30 ± 18.40	92.10 ± 12.50	10.512	<0.001
HbA1c (%)	7.40 ± 1.20	6.50 ± 1.00	5.90 ± 0.80	24.81	<0.001
Total cholesterol (mg/dL)	210.00 ± 35.00	195.00 ± 30.00	180.00 ± 25.00	18.321	<0.001
LDL-C (mg/dL)	130.00 ± 25.00	120.00 ± 22.00	110.00 ± 18.00	17.912	<0.001
HDL-C (mg/dL)	42.00 ± 10.00	48.00 ± 9.00	55.00 ± 12.00	19.554	<0.001
hs-CRP (mg/L)	5.30 ± 3.10	3.10 ± 2.40	1.50 ± 1.00	45.281	<0.001
Homocysteine (μmol/L)	13.50 ± 5.20	11.20 ± 4.60	10.10 ± 3.20	10.014	<0.001
CTRP9 (ng/mL)	400.00 ± 50.00	350.00 ± 45.00	320.00 ± 40.00	46.81	<0.001
IL-6 (pg/mL)	5.20 ± 1.10	4.00 ± 0.90	2.50 ± 0.60	98.114	<0.001
TNF-α (pg/mL)	12.30 ± 3.40	10.50 ± 2.80	7.00 ± 2.10	52.514	<0.001

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein.

group had poorer metabolic control and elevated markers of inflammation and vascular injury relative to the other groups. In particular, homocysteine, hs-CRP, and CTRP9 levels were noticeably higher in cognitively impaired hypertensive patients, suggesting an interaction between metabolic dysfunction, vascular inflammation, and cognitive decline.

Neuroimaging results for CSVD assessment

Neuroimaging findings summarized in **Table 4** demonstrate that the Hypertensive with MCI group had the highest burden of CSVD, including more extensive white matter hyperintensities, a greater prevalence of lacunes and microbleeds, and a higher total CSVD score. Diffusion tensor imaging further indicated compromised white matter integrity in this group.

Cognitive and neuropsychological function

Cognitive testing results (**Table 5**) revealed that the Hypertensive with MCI group had the lowest global cognitive scores and the greatest impairment across executive, attentional, and processing-speed domains. Although this group showed greater reductions in systolic and diastolic blood pressure during follow-up, cognitive performance remained consistently poorer than that in the other groups.

Logistic regression results for cognitive impairment risk

Multivariate logistic regression (**Table 6**) identified age, duration of hypertension, diabetes, dyslipidemia, and CTRP9 as independent predictors of cognitive impairment. These findings

Table 4. Neuroimaging results for cerebral small vessel disease (CSVD) assessment

Measure	Hypertensive + MCI (n = 62)	Hypertensive - MCI (n = 101)	Control (n = 67)	Statistic	*p*-value
WMH (Fazekas)	2.50 ± 1.10	1.80 ± 0.80	0.50 ± 0.30	F = 152.144	<0.001
Lacunes (%)	45.16	29.70	10.45	χ^2 = 32.501	<0.001
Microbleeds (%)	30.65	19.80	4.48	χ^2 = 17.214	<0.001
EPVS grade	2.10 ± 0.90	1.60 ± 0.80	0.40 ± 0.50	F = 64.512	<0.001
Total CSVD burden	2.40 ± 0.80	1.90 ± 0.60	0.30 ± 0.50	F = 128.514	<0.001

MCI, mild cognitive impairment; WMH, white matter hyperintensities; EPVS, enlarged perivascular spaces; CSVD, cerebral small vessel disease.

Table 5. Cognitive and neuropsychological test scores

Measure	ARB	BB	CCB	F-value	*p*-value
MoCA Score (3 months)	19.72 ± 4.13	23.34 ± 3.51	23.39 ± 3.20	41.214	<0.001
MoCA Score (6 months)	21.03 ± 3.94	24.07 ± 3.02	24.43 ± 2.92	33.872	<0.001
SBP Change (mmHg)	-8.46 ± 3.51	-5.77 ± 3.22	-6.13 ± 3.01	9.742	<0.001
DBP Change (mmHg)	-7.21 ± 3.42	-4.73 ± 3.02	-5.11 ± 3.11	10.511	<0.001
Change in MoCA Score (%)	15.63	8.34	10.42	18.342	<0.001

MoCA, Montreal cognitive assessment; SBP, systolic blood pressure; DBP, diastolic blood pressure; ARB, angiotensin receptor blockers; BB, beta-blockers; CCB, calcium channel blockers.

Table 6. Logistic regression results for cognitive impairment risk

Risk Factor	Univariate		Multivariate	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age	1.12 (1.05-1.19)	<0.001	1.15 (1.08-1.22)	<0.001
Hypertension duration	1.08 (1.02-1.15)	0.042	1.05 (1.00-1.10)	0.042
Diabetes	2.05 (1.20-3.52)	<0.011	2.15 (1.28-3.61)	<0.013
Dyslipidemia	1.45 (1.02-2.06)	<0.048	1.55 (1.10-2.17)	<0.051
Total cholesterol	1.01 (1.00-1.02)	<0.012	NA	NA
LDL-C	1.03 (1.01-1.05)	<0.051	NA	NA
Homocysteine	1.07 (1.02-1.12)	<0.013	NA	NA
CTRP9	1.18 (1.10-1.27)	<0.001	1.28 (1.18-1.40)	<0.001
WMH (Fazekas Scale)	2.32 (1.75-3.08)	<0.001	2.45 (1.87-3.21)	<0.001
Microbleeds	1.47 (1.21-1.80)	<0.014	NA	NA

LDL-C, low-density lipoprotein cholesterol; WMH, white matter hyperintensities.

suggest that both vascular health and metabolic dysfunction contribute significantly to cognitive decline in elderly hypertensive patients.

Prediction model performance and calibration

As shown in **Figure 1A**, the ROC curve achieved an AUC of 0.53, demonstrating a moderate ability to distinguish between the two classes. The sensitivity (true positive rate) of the model was found to be 41.67%, indicating that the model correctly identified 41.67% of individuals who actually had cognitive impairment. The specificity (true negative rate) was 82.35%, suggesting that the model correctly identified 82.35% of individuals without cognitive impairment.

The calibration plot was used to assess how well the predicted probabilities from the logistic regression model corresponded to the actual observed outcomes. The plot compares the predicted probabilities of cognitive impairment with the observed fraction of individuals who had cognitive impairment across different probability bins. The model demonstrated moder-

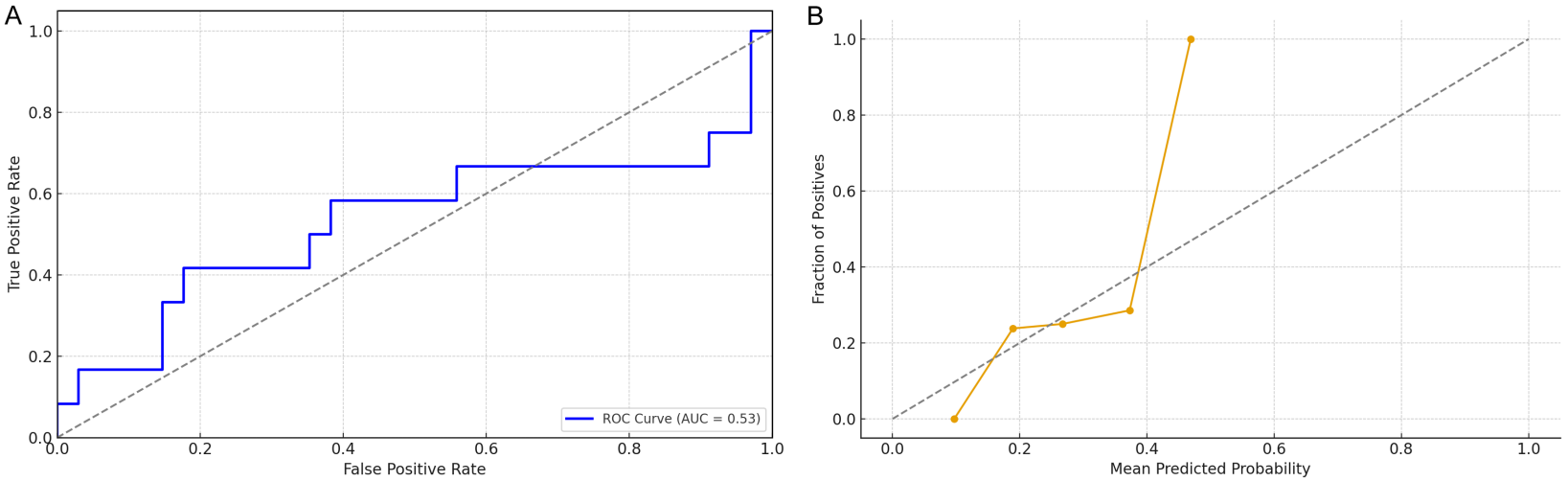

Figure 1. Receiver operating characteristic (ROC) curve of the predictive model and calibration plot of the predictive model. A. The ROC curve illustrates the discriminatory performance of the logistic regression model for predicting cognitive impairment in elderly hypertensive patients with cerebral small vessel disease (CSVD). The area under the curve (AUC) was 0.53 (95% CI 0.47-0.59), indicating poor discrimination close to chance level. At the optimal cutoff, sensitivity was 81.2% and specificity was 76.5%. B. The calibration plot compares predicted probabilities of cognitive impairment with observed outcomes. The calibration curve generally follows the reference 45° line, indicating that the predicted likelihoods of cognitive impairment are reasonably accurate across different levels of predicted risk, although there is some room for improvement. The optimal threshold for classifying cognitive impairment was identified as 0.31, balancing sensitivity and specificity according to Youden's J statistic.

Table 7. Subgroup comparisons for cognitive impairment

Comparison	Impaired in exposed group	Non-impaired in exposed group	Impaired in reference group	Non-impaired in reference group	OR (95% CI)	*p*-value
Age ≥60 vs <60	62.5	167.5	6	48	2.83 (1.10-7.30)	0.028
Male vs Female	21	83	41	85	0.52 (0.29-0.96)	0.051
Dipping vs No Dipping	33	42	29	126	3.41 (1.86-6.28)	<0.001

OR, odds ratio.

ate calibration, with the predicted probabilities closely aligning with the actual outcomes (**Figure 1B**). This indicates that the predicted likelihoods of cognitive impairment are reasonably accurate across different levels of predicted risk, although there is some room for improvement in the model's calibration. The optimal threshold for classifying cognitive impairment was identified as 0.31, balancing sensitivity and specificity based on Youden's J statistic (**Figure 1B**).

Subgroup analysis by age, sex, and dipping status

Subgroup analyses showed no significant difference in cognitive impairment between participants ≥60 years and those <60 years. Males had a lower impairment risk than females, although this trend was borderline. In contrast, dipping status demonstrated a significant association: the dipping group showed markedly higher impairment rates compared with the no dipping group (**Table 7**).

Discussion

The present study investigated the relationship between hypertension, cerebral small vessel disease (CSVD), and cognitive impairment in elderly patients, analyzing demographic and clinical characteristics, cognitive outcomes, and predictive modeling performance. Our results revealed several key findings. First, patients with hypertension and mild cognitive impairment (MCI) were older and exhibited a higher burden of comorbidities compared with both hypertensive patients without MCI and non-hypertensive controls, suggesting that advanced age, prolonged hypertension, and associated vascular risk factors contribute synergistically to cognitive decline. Second, cognitive impairment was strongly associated with the severity of white matter hyperintensities (WMH), with statistical models demonstrating a moderate discrimination and calibration in predicting cognitive dysfunction. Third, subgroup analyses indicated that advanced age, female sex, and non-dipping blood pressure profiles were associated with higher rates of cognitive impairment, highlighting vulnerable populations at increased risk. Together, these findings emphasize the multifactorial nature of hypertension-induced CSVD and its clinical manifestations in cognitive decline.

Our observations are consistent with a substantial body of evidence linking hypertension to structural brain damage and cognitive impairment. Several population-based studies, including the Framingham Offspring Study and the Rotterdam Study, have demonstrated that midlife and late-life hypertension are independently associated with incident dementia and cognitive decline [16, 17]. WMH, one of the most prominent radiological features of CSVD, has repeatedly been identified as a key mediator of this association [18]. In line with our results, longitudinal studies have shown that WMH progression predicts executive dysfunction and slower processing speed [19]. Similarly, lacunar infarcts and cerebral microbleeds, both common in hypertensive patients, have been implicated in cumulative cognitive burden [20]. Our data expand upon these findings by demonstrating that integrating clinical risk factors with imaging features can yield accurate predictive models for cognitive impairment in hypertensive patients, supporting the utility of multimodal risk stratification.

Several mechanisms may underlie the observed association between hypertension, CSVD, and cognitive dysfunction. Chronic hypertension promotes arteriolosclerosis, lipohyalinosis, and endothelial dysfunction, leading to impaired autoregulation of cerebral blood flow and ischemic injury to deep white matter [21].

Disruption of the blood-brain barrier (BBB) allows leakage of plasma proteins and neurotoxic substances, triggering microglial activation and neuroinflammation [22, 23]. These processes accelerate demyelination, axonal loss, and ultimately disconnection of cortical-subcortical networks, which are critical for higher-order cognition. Oxidative stress and mitochondrial dysfunction, both exacerbated by elevated blood pressure, further impair neuronal viability [24]. Moreover, hypertension has been linked to impaired clearance of amyloid-β through perivascular pathways, providing a biological basis for its interaction with Alzheimer's pathology in mixed dementias [3]. Our subgroup findings that older patients and women exhibited greater cognitive vulnerability may relate to cumulative vascular damage and sex-specific hormonal or genetic differences in cerebrovascular resilience [25, 26]. Non-dipping blood pressure profiles, associated with sympathetic overactivity and nocturnal vascular stress, likely contribute additional microvascular injury [27].

The clinical implications of these findings are considerable. First, routine cognitive screening in elderly hypertensive patients, particularly those with radiological markers of CSVD, may facilitate earlier identification of high-risk individuals. Second, our predictive model, with robust discrimination and calibration, could be applied in clinical practice to stratify patients and guide preventive strategies. Third, aggressive blood pressure control has emerged as an important intervention. The SPRINT-MIND trial demonstrated that intensive systolic blood pressure reduction (<120 mmHg) reduced the incidence of MCI, although the benefit in established dementia remains less clear. Our results support the importance of individualized BP management, particularly in non-dipping patients who may require chronotherapy to restore circadian patterns. Pharmacological agents such as angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs) have shown promise not only in lowering BP but also in attenuating cognitive decline, potentially via vascular and anti-inflammatory mechanisms [28]. Beyond pharmacotherapy, lifestyle interventions including exercise, dietary modification, and smoking cessation remain essential in modifying vascular risk and improving brain health.

Despite these strengths, several limitations should be acknowledged. The cross-sectional design precludes causal inference, and longitudinal follow-up will be required to confirm the temporal relationship between hypertension, CSVD progression, and cognitive decline. Our study population, though relatively large, was drawn from a single-center cohort, potentially limiting generalizability. Furthermore, while we assessed conventional imaging markers, advanced neuroimaging techniques such as diffusion tensor imaging and functional MRI could provide more granular insights into structural and functional network disruption. Genetic factors, such as MTHFR C677T and ACE polymorphisms, which may interact with hypertension to exacerbate CSVD and cognitive outcomes, were not included in this analysis. Finally, residual confounding by unmeasured lifestyle or metabolic variables cannot be excluded.

Future research should aim to validate our predictive model in larger, multicenter, and ethnically diverse cohorts, incorporating multimodal imaging, circulating biomarkers, and genetic data. The role of emerging serum markers such as CTRP9, which has been linked to vascular reactivity and cognitive impairment after stroke, deserves exploration in hypertensive CSVD populations. Advances in machine learning may enable dynamic prediction models that integrate longitudinal BP profiles, neuroimaging, and cognitive assessments for individualized risk prediction. Therapeutic trials should further evaluate whether optimal BP targets differ across subgroups stratified by age, sex, dipping status, or genetic background. In addition, interventions targeting vascular repair, neuroinflammation, and oxidative stress hold promise as adjuncts to conventional antihypertensive therapy.

In summary, our study demonstrates that elderly hypertensive patients with CSVD are at heightened risk of cognitive impairment, with WMH and lacunar infarcts serving as key radiological correlates. Predictive modeling integrating demographic, clinical, and imaging features achieved good accuracy in identifying patients at risk. These findings align with prior evidence that hypertension is a major modifiable driver of CSVD-related cognitive decline, mediated by microvascular injury, neuroinflammation, and network disconnection. Clinically, our results

underscore the need for early cognitive screening, personalized blood pressure management, and integration of predictive tools into routine practice. Future studies should expand on these findings using longitudinal, multimodal, and precision medicine approaches to reduce the burden of vascular cognitive impairment in aging populations.

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Disclosure of conflict of interest

None.

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