Article

The Impact of Combined Application of Donepezil and Nimodipine on Patients with Comorbid Cerebral Small Vessel Disease and Cognitive Dysfunction: Efficacy and Influence on Nutritional Status

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Abstract

Background and objective: Cerebral small vessel disease (CSVD) often coexists with cognitive dysfunction in patients, leading to significant challenges in treatment and management. This study aimed to examine the efficacy of combined application of donepezil and nimodipine on patients with comorbid CSVD and cognitive dysfunction and the effects on patients' albumin and prealbumin levels.

Methods: The records of 112 patients with comorbid CSVD and cognitive dysfunction treated at the People's Hospital of Suzhou New District from January 2019 to December 2022 were analysed retrospectively. A total of 50 patients receiving donepezil were allocated to the control group, and 62 patients receiving both nimodipine and donepezil to the study group. Outcomes compared between the two groups included serum homocysteine (Hcy), high sensitivity C-reactive protein (hs-CRP), albumin, and prealbumin before and after therapy, efficacy, and adverse reactions. Additionally, logistic regression was performed to analyze the risk factors impacting patient prognosis.

Results: Prior to therapy, the two groups did not differ significantly in Hcy and hs-CRP levels ($p > 0.05$), whereas after therapy, the levels in both groups dropped significantly ($p < 0.01$), with more obvious lower levels in the study group ($p < 0.05$). After treatment, the study group presented significantly higher albumin and prealbumin levels than the control group ($p < 0.001$). An obvious higher overall response rate was observed in the study group compared to the control group ($p = 0.012$). No significant intergroup discrepancy was found regarding the total incidence of adverse reactions ($p = 0.752$). Univariate analysis identified age, course of disease, heart rate (HR), Montreal Cognitive Assessment (MoCA) score, diastolic blood pressure (DBP), systolic blood pressure (SBP), drinking history, as well as medication regimen as risk factors impacting patient prognosis. Multivariate logistic regression analysis identified SBP, DBP, and medication regimen as the independent risk factors.

Conclusion: Combined application of donepezil and nimodipine can effectively treat patients with comorbid CSVD and cognitive dysfunction. It can significantly lower the Hcy and hs-CRP levels and improve the nutritional status without increasing the frequency of adverse reactions. In addition, for CSVD patients with cognitive dysfunction, age, course of disease, MoCA score, HR, SBP, DBP, drinking history, and medication regimen are risk factors impacting patient prognosis, while SBP, DBP, and medication regimen are independent risk factors.

Keywords

donepezil; nimodipine; cerebral small vessel disease; cognitive dysfunction; nutritional status

Introduction

Epidemiological data regarding cerebral small vessel disease (CSVD), a frequently diagnosed cerebrovascular disease, and cognitive impairment indicate that the condition is more common in older adults, with the incidence increasing with age [1]. Patients with the disease may have

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cerebral microhemorrhage, white matter lesions, and lacunar cerebral infarction, which triggers various clinical manifestations such as cognitive dysfunction [2,3]. Currently, the treatment methods for CSVD and associated cognitive impairment primarily focus on managing the underlying causes and symptoms. This includes controlling risk factors such as blood pressure, blood glucose, and lipid levels, along with quitting smoking and implementing lifestyle changes [3].

For patients with both CSVD and cognitive dysfunction, cholinesterase inhibitors, such as galanthamine and donepezil, are usually prescribed in western medicine [4–6]. Donepezil, a cholinesterase inhibitor, can inhibit cholinesterase activity to exert a neuroprotective effect [7]. With advances in clinical research, drugs such as nimodipine have also been found to have a positive effect on patients with comorbid CSVD and cognitive dysfunction [8]. Nimodipine, a calcium channel blocker, reduces the risk of cerebral vasospasm and protects brain cells from damage by dilating cerebral blood vessels, accelerating cerebral blood flow and improving blood supply [9]. Currently, there are many studies on the combined use of nimodipine in the treatment of CSVD. For example, Zhang *et al*. [10] revealed that the combined use of rosuvastatin and nimodipine is safe and effective in the treatment of mild cognitive dysfunction in patients with CSVD. The combined use of donepezil and nimodipine may potentially manage cognitive impairment and CSVD by increasing acetylcholine concentration and improving cerebral blood flow [11]. However, the combined use of donepezil and nimodipine in the treatment of comorbid CSVD and cognitive dysfunction has not been extensively studied.

This study examined the efficacy of donepezil combined with nimodipine in patients with comorbid CSVD and cognitive dysfunction to offer guidance on follow-up therapy.

Materials and Methods

Sample Information

The records of 160 CSVD patients with cognitive dysfunction treated in the People's Hospital of Suzhou New District from January 2019 to December 2022 were analysed retrospectively.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: patients met the diagnostic criteria of CSVD as described in *Expert Consensus on Diagnosis and Treatment of Cerebral Small Vessel Disease* and were diagnosed as CSVD by imaging [12]; patients achieved a Montreal Cognitive Assessment (MoCA) score less than 26 points [13]; patients cooperated with treatment, and patients had detailed clinical records.

The exclusion criteria were as follows: patients suffered from malignancy, comorbid severe organ dysfunction, or cognitive dysfunction caused by other factors; patients suffered from Parkinson's disease or Alzheimer's disease; patients had an addiction to drugs or alcohol; patients were allergic to the drugs used in the current research.

Sample Screening

A total of 160 patients were screened according to the above criteria, and 112 patients met the requirements of this study. A total of 50 patients receiving donepezil were allocated to the control group, and 62 patients receiving both nimodipine and donepezil to the study group.

Treatment Means

Each patient in the control group was given donepezil hydrochloride tablets (Chongqing Zein Biotechnology Co., Ltd., State Food and Drug Administration (SFDA) approval number: H20010723; specification: 5 mg), 10 mg orally each time, once a day, for 12 weeks as a course of treatment. In addition to the treatment described for the control group, patients in the study group were given nimodipine tablets (Harbin Pharm. Group Sanjing Pharmaceutical Co., Ltd., Harbin, China, SFDA approval number: H23021402; specification: 20 mg) 20 mg orally each time, three times a day, for 12 weeks as a course of treatment. Both groups received continuous treatment for one complete course.

Outcome Measures

The primary outcome measures were as follows: (1) The serum homocysteine (Hcy) and high sensitivity C-reactive protein (hs-CRP) levels in the two groups were analyzed and compared pre-therapy and post-treatment. Fasting venous blood (3 mL) was taken from every patient in the morning on the day of pre-therapy and after 1 course of treatment, followed by 10-min centrifugation with a low-speed centrifuge (3000 r/min). Next, Hcy and hs-CRP were measured by a Roche COBAS c702 biochemical analyzer. (2) Comparative analysis was performed on albumin and prealbumin levels pre-therapy and post-treatment in the two groups. The albumin and prealbumin levels in the fasting venous blood of the patients were measured using the bio-

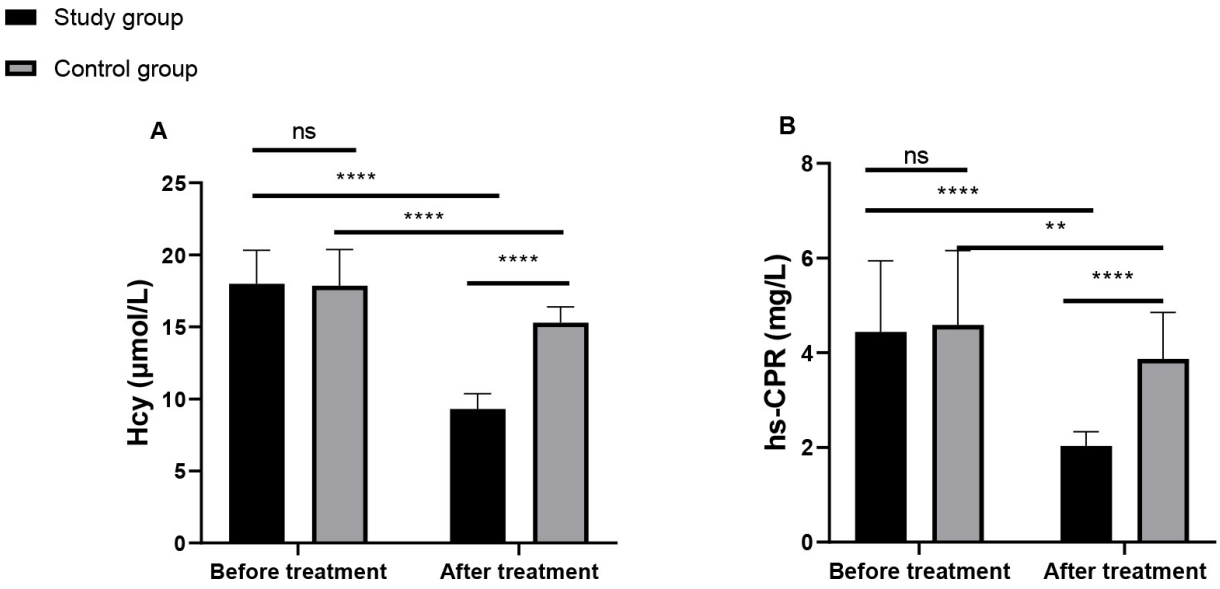

Fig. 1. Comparison of Hcy and hs-CRP levels between the two groups before and after treatment. (A) Comparison of Hcy levels between the two groups before and after treatment ($^{ns}p > 0.05$, $^{****}p < 0.0001$). (B) Comparison of hs-CRP levels between the two groups before and after treatment ($^{ns}p > 0.05$, $^{**}p < 0.01$, $^{****}p < 0.0001$). Notes: For the study group: n = 62; For the control group: n = 50. Hcy, homocysteine; hs-CRP, high sensitivity C-reactive protein; ns, non-significant.

chemical analyzer. (3) The efficacy of the two groups was analyzed and compared in the light of the following criteria: the cognitive function of patients was evaluated by MoCA score, with 26 being the lowest boundary for dividing dementia, and a higher score after treatment indicating better efficacy [14]. MoCA score improvement rate = (MoCA score after therapy – MoCA score before therapy)/MoCA score before treatment × 100%. Markedly effective: the MoCA score improvement rate is higher than 20%; Effective: the MoCA score improvement rate is 12%–19%; ineffective: the MoCA score improvement rate is less than 12%. Overall response rate = markedly effective rate + effective rate.

The secondary outcome measures were as follows: (1) The incidence of adverse reactions, including blood pressure decrease, flushed complexion, and feeling of fullness in the head in the two groups was evaluated. (2) Logistic regression was conducted to analyze risk factors impacting the patient prognosis.

Statistical Analyses

This study adopted SPSS v22.0 (SPSS Inc., Chicago, IL, USA) for statistical analyses of data, and GraphPad 8 software package (GraphPad Software Inc., San Diego, CA, USA) for data visualization into corresponding figures. The normality test was conducted on measurement data, and those with normal distribution were described by the mean ± SD. Their inter-group and intro-group comparisons were performed using the independent-samples *T* test and paired *t* test, respectively. Counting data were described by percentage (%), analyzed via the chi-square test, and presented by χ^2. Logistic regression analysis was performed for analysing the independent risk factors of patient prognosis. $p < 0.05$ was considered a significant difference.

Results

Baseline Data of Patients

No obvious discrepancy was observed between the control and study groups regarding age, sex, body mass index (BMI), course of disease, MoCA score, smoking history, drinking history and place of residence ($p > 0.05$, Table 1).

Inter-Group Comparison of Hcy and hs-CRP Levels

Pre-therapy, the two groups showed no significant discrepancy in Hcy and hs-CRP levels ($p > 0.05$), whereas post-therapy, the levels in both groups decreased significantly ($p < 0.001$), with more obvious decreases in the study group ($p < 0.001$, Fig. 1).

Table 1. Baseline data.

Factor	Study group (n = 62)	Control group (n = 50)	χ^2	*p*
Age				
≥45 years old	26	26	1.127	0.288
<45 years old	36	24		
Sex				
Male	40	31	0.076	0.784
Female	22	19		
BMI				
≥23 kg/m^2	28	29	1.826	0.177
<23 kg/m^2	34	21		
Course of disease				
≥5 years	39	24	2.498	0.114
<5 years	23	26		
MoCA score				
≥20 points	30	29	1.026	0.311
<20 points	32	21		
Smoking history				
Yes	35	30	0.143	0.705
No	27	20		
Drinking history				
Yes	27	21	0.027	0.869
No	35	29		
Place of residence				
Rural area	48	35	0.794	0.373
Urban area	14	15		

BMI, Body mass index; MoCA, Montreal Cognitive Assessment.

Table 2. Comparison of efficacy between the two groups [n (%)].

Group	Markedly effective	Effective	Ineffective	Overall response
Study group (n = 62)	27 (43.55)	29 (46.77)	6 (9.68)	56 (90.32)
Control group (n = 50)	15 (30.00)	21 (42.00)	14 (28.00)	36 (72.00)
χ^2	2.168	0.255	6.335	6.335
p	0.141	0.613	0.012	0.012

Comparison of Albumin and Prealbumin Levels in the Two Patient Groups

Analysis and comparison of albumin and prealbumin levels revealed no significant inter-group differences before treatment ($p > 0.05$). Post-treatment, both groups showed a significant increase in albumin and prealbumin levels ($p < 0.001$), with more obvious increases in the study group ($p < 0.001$, Fig. 2).

Comparison of Efficacy between the Two Groups

Statistical analysis of efficacy revealed a significantly higher overall response rate in the study group compared to the control group ($p = 0.012$, Table 2).

Comparison of Adverse Reactions between the Two Groups

The study group showed no significant difference from the control group in the total incidence of adverse reactions ($p = 0.752$, Table 3).

Analysis of Related Factors Affecting Prognosis

Patients who achieved a markedly effective or effective treatment outcome were considered to have a favorable prognosis and were allocated to the good prognosis group (n = 92). Patients who had an ineffective treatment outcome were considered to have an unfavourable prognosis and were allocated to the poor prognosis group (n = 20). The inter-group discrepancy of clinical data was compared,

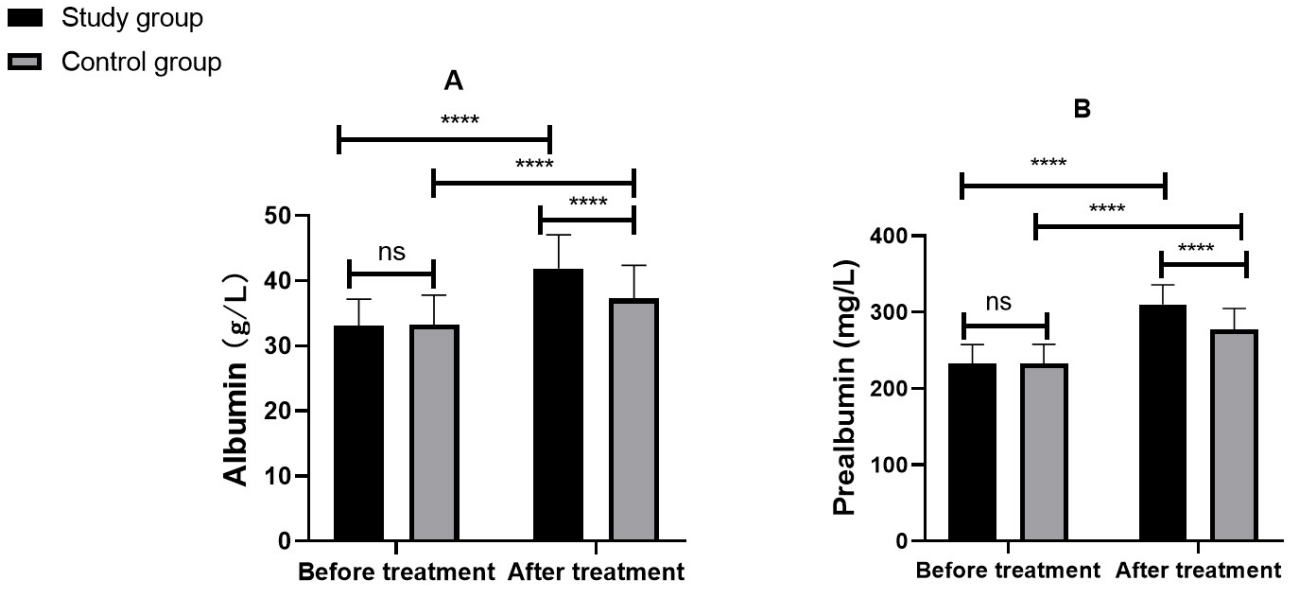

Fig. 2. Comparison of albumin and prealbumin levels before and after treatment in the two groups. (A) Comparison of albumin levels before and after treatment in the two groups ($^{ns}p > 0.05$, $^{****}p < 0.0001$). (B) Comparison of prealbumin levels before and after treatment in the two groups ($^{ns}p > 0.05$, $^{****}p < 0.0001$). Notes: For the study group: n = 62; For the control group: n = 50.

Table 3. Incidence of adverse reactions in the two groups [n (%)].

Group	Blood pressure decrease	Facial flushing	Feeling of fullness in the head	Total adverse reactions
Study group (n = 62)	2 (3.23)	1 (1.61)	1 (1.61)	4 (6.45)
Control group (n = 50)	1 (2.00)	2 (4.00)	1 (2.00)	4 (8.00)
χ^2				0.003
p				0.958

Note: The chi-square test was conducted with Yates correction for continuity.

and univariate analysis was performed. Age, course of disease, MoCA score, heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), drinking history, as well as medication regimen, were identified as risk factors affecting patient prognosis (Table 4). Notably, different indexes were assigned (Table 5), followed by multivariate analysis. Logistic regression analysis identified SBP, DBP, and medication regimen as independent risk factors affecting patient prognosis (Table 6).

Discussion

With the rapid progression of aging populations in China, there is a growing number of patients affected by CSVD [15]. CSVD is defined as intracranial hemorrhagic damage or cerebral ischemia caused by intracranial arterioles and arterioles [16]. Its early symptoms are not obvious, but as the disease progresses, cognitive impairment is aggravated. Without timely and effective treatment, it seriously compromises the health and quality of life of patients and causes stress to families and societies [17–19]. Nimodipine, a frequently used drug for CSVD, can effectively suppress the influx of calcium ions into vascular smooth muscle cells, thereby relaxing blood vessels and replenishing the local blood supply of brain tissue in time to alleviate the injury of small cerebral vessels [8,20]. Donepezil can effectively increase cerebral blood flow, activate N receptors, and reduce the toxic effects of free radicals and glutamate on brain nerves, thus protecting brain cells and promoting the recovery of tissue function [21]. This study explored the efficacy of combined application of donepezil and nimodipine on patients with comorbid CSVD and cognitive dysfunction.

High plasma Hcy levels may be a risk factor for cognitive decline and neurodegenerative diseases [22]. High Hcy levels can trigger vascular endothelial injury and arteriosclerosis, which disrupts the blood supply to the brain and triggers cognitive decline [23]. Hs-CRP is also a crucial risk factor for cognitive dysfunction in CSVD patients. It plays a crucial role in several cognitive functions, in-

Table 4. Univariate analysis.

Factor	Good prognosis group (n = 92)	Poor prognosis group (n = 20)	χ^2	*p* value
Age				
≥45 years old	47	5	4.4951	0.0340
<45 years old	45	15		
Sex				
Male	60	11	0.7390	0.3900
Female	32	9		
BMI				
≥23 kg/m^2	50	7	2.4611	0.1167
<23 kg/m^2	42	13		
Course of disease				
≥5 years	46	17	8.1781	0.0042
<5 years	46	3		
MoCA score				
≥20 points	53	6	5.0231	0.0250
<20 points	39	14		
Heart rate				
50–80 beats/min	70	8	10.121	0.0015
Others	22	12		
Systolic blood pressure				
90–120 mmHg	69	7	12.051	0.0005
Others	23	13		
Diastolic blood pressure				
60–80 mmHg	68	9	6.3921	0.0115
Others	24	11		
Smoking history				
Yes	50	15	2.8771	0.0898
No	42	5		
Drinking history				
Yes	35	13	4.8751	0.0273
No	57	7		
Place of residence				
Rural area	70	13	1.0521	0.3050
Urban area	22	7		
Medication regimen				
Donepezil+Nimodipine	56	6	6.3351	0.0118
Nimodipine	36	14		

BMI, Body mass index; MoCA, Montreal Cognitive Assessment.

cluding abstract ability, visual space ability, computational power, and executive function [24]. Thus, it is important to observe the changes in Hcy and hs-CRP levels when assessing cognitive dysfunction in CSVD patients. In this study, before therapy, the two groups did not differ significantly regarding Hcy and hs-CRP levels, while after therapy, both levels decreased significantly, with more obvious lower levels in the study group. This finding shows that nimodipine combined with donepezil can inhibit Hcy and hs-CRP levels and alleviate the cognitive dysfunction of patients. In addition, this study revealed significantly higher albumin and prealbumin levels in the study group than the control group post-treatment, and showed a significantly higher overall response rate in the study group, but found no notable inter-group difference in the total incidence of adverse reactions. The results imply that nimodipine plus donepezil deliver substantial efficacy on CSVD complicated by cognitive dysfunction, without increasing the frequency of adverse reactions. The combination of nimodipine and donepezil has shown significant therapeutic efficacy in the treatment of CSVD complicated by cognitive dysfunction. This is because this combined treatment ap-

Table 5. Assignment.

Factors	Assignment
Age	<45 years old = 0, ≥45 years old = 1
Course of disease	<5 = 0, ≥5 = 1
MoCA score	≥20 points = 0, <20 points = 1
Heart rate	50–80 beats/min = 0, others = 1
Systolic blood pressure	90–120 mmHg = 0, others = 1
Diastolic blood pressure	60–80 mmHg = 0, others = 1
Drinking history	No = 0, Yes = 1
Medication regimen	Donepezil+Nimodipine = 0, Nimodipine = 1
Prognosis	Good prognosis = 0, poor prognosis = 1

MoCA, Montreal Cognitive Assessment.

Table 6. Multivariate logistic regression analysis.

Factor	B	S.E.	Wals	df	Sig.	Exp (B)	95% C.I. for Exp (B).	
							Lower limit	Upper limit
Age	–0.986	0.574	2.951	1	0.086	0.373	0.121	1.149
Course of disease	–0.850	0.596	2.037	1	0.153	0.427	0.133	1.373
MoCA score	0.077	0.591	0.017	1	0.896	1.080	0.339	3.439
Heart rate	–0.855	0.641	1.781	1	0.182	0.425	0.121	1.493
Systolic blood pressure	–2.930	1.105	7.038	1	0.008	0.053	0.006	0.465
Diastolic blood pressure	–2.784	1.079	6.661	1	0.010	0.062	0.007	0.512
Drinking history	0.139	0.576	0.058	1	0.809	1.150	0.372	3.555
Medication regimen	1.627	0.579	7.895	1	0.005	5.086	1.635	15.818

MoCA, Montreal Cognitive Assessment.

proach not only improves the underlying pathological processes of the disease but also positively impacts the nutritional status of patients. Nimodipine and donepezil work by improving cerebral blood flow, ensuring an adequate supply of oxygen and nutrients to brain cells, and benefiting their normal functioning. Similar to the results of our study, Yang *et al*. [11] revealed that combined application of donepezil and nimodipine can effectively treat vascular dementia and improve Mini-Mental State Examination (MMSE) and Activities of Daily Living (ADL) scores. Lastly, this study analyzed factors for patient prognosis, and found age, course of disease, MoCA score, HR, SBP, DBP, drinking history, and medication regimen were risk factors. Logistic regression analysis identified SBP, DBP, and medication regimen as independent risk factors for patient prognosis. Too high or too low blood pressure may affect the metabolism and circulatory kinetics of nimodipine, thereby affecting its efficacy [9]. Therefore, the stability of SBP and DBP, along with their regulation, plays an important role in the efficacy of donepezil combined with nimodipine in treating CSVD complicated by cognitive dysfunction [7].

The study has certain limitations. Firstly, this study is subject to potential biases due to its limited sample size, which may impact the conclusions drawn. Additionally, the dosage of both drugs was not specifically investigated, highlighting the need for further research to determine the optimal dosage. Therefore, it is crucial to conduct future studies that encompass a more comprehensive analysis of the application of donepezil combined with nimodipine in the treatment of CSVD complicated by cognitive dysfunction.

Conclusion

Combined application of donepezil and nimodipine can effectively treat patients with comorbid CSVD and cognitive dysfunction. It can significantly lower the Hcy and hs-CRP levels and improve the nutritional status without increasing the frequency of adverse reactions. In addition, age, course of disease, MoCA score, HR, SBP, DBP, drinking history, and medication regimen are risk factors for the prognosis of CSVD patients with cognitive impairment, and SBP, DBP, and medication regimen are independent risk factors.

Abbreviations

CSVD, cerebral small vessel disease; Hcy, homocysteine; hs-CRP, high sensitivity C-reactive protein; MoCA, Montreal Cognitive Assessment; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Author Contributions

LS, LM and LR designed the research study. LS and LM performed the research. LS and LR analyzed the data. All authors contributed to the drafting or important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was carried out under approval from the Medical Ethics Committee of the People's Hospital of Suzhou New District (ethical approval number: 03174LL) and it met all tenets of the Declaration of Helsinki. This retrospective study was granted an informed consent waiver by the ethics committee, as the study involves minimal risk and it is difficult to obtain informed consent from the participants. The data used in the research have been de-identified and cannot be traced back to individuals.

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Conflict of Interest

The authors declare no conflict of interest.

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