Diagnostic Values of Serum Levels of Homocysteine and Uric Acid for Predicting Vascular Mild Cognitive Impairment in Patients with Cerebral Small Vessel Disease

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Background: This study aimed to investigate the diagnostic values of serum levels of Hcy and UA for predicting vascular mild cognitive impairment (VMCI) in patients with cerebral small vessel disease (SVD).

Material/Method: We selected 172 cerebral SVD patients and divided them into a VMCI group and a non-VMCI group. Eighty-six healthy individuals without nervous system diseases were selected as the control group. Enzymatic cycling method was performed to detect serum Hcy and UA levels. Serum levels of folic acid (FOA) and vitamin B12 (VitB12) were detected by chemiluminescence immunoassay. Montreal cognitive assessment (MoCA) was applied to evaluate the cognitive function. The ROC curve was used to evaluate the diagnostic values of serum Hcy and UA levels for predicting VMCI. Logistic regression analysis was used to determine the possible risk factors.

Results: Compared with the non-VMCI and control groups, serum FOA and VitB12 levels were lower and serum Hcy and UA levels were higher in the VMCI group. AUC values of serum Hcy and UA levels were 0.703 and 0.829, respectively. Serum Hcy and UA levels were negatively correlated with serum FOA and VitB12 levels, total MoCA score, and subscores on visuospatial ability and executive function, on language ability and on delayed recall, and they were positively correlated with serum cholesterol (CH) level. Serum Hcy and UA levels were indicated as risk factors for VMCI in cerebral SVD patients.

Conclusions: These results suggest that serum Hcy and UA levels may serve as predictive factors for VMCI in cerebral SVD patients.

MeSH Keywords: **Aminohippuric Acids • Blood Vessels • Homocysteine**

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Background

Small vessel disease (SVD) encompasses a group of pathological processes that affect the small vessels of the brain, including small arteries, arterioles, and venules [1]. SVD is common in people over 70 years old, and most cases of amnestic mild cognitive impairment (MCI) are caused by Alzheimer disease pathology, while non-amnestic MCI is usually related to Lewy body pathology [2–4]. Cerebral SVD is mainly manifested by static focal cerebrovascular diseases, such as static focal lacunar infarction, cerebral microbleeds, some micro-leukoaraiosis, and progressive cognitive dysfunction [5]. It is initiated by elevated blood-brain barrier permeability, leading to enlarged Virchow Robin (perivascular) spaces, symptomatic lacunar infarction, white matter lesions, and microbleeds [6]. Cognitive impairment in SVD is characterized by prominent impairment of executive function and processing speed, along with relative preservation of episodic memory [1,7]. Vascular mild cognitive impairment (VMCI) is an abnormal condition caused by vascular diseases, and the patients are often identified with cognitive deficits that are not severe enough to fit the criteria for dementia [8]. In the early stage, most VMCI patients have no obvious clinical symptoms [9]; therefore, it is urgent to find new reliable molecular markers able to predict cognitive impairments in SVD patients.

Homocysteine (Hcy), a non-essential amino acid containing sulfur, is produced by the metabolism of methionine [10]. Feng et al. demonstrated that Hcy level is closely associated with SVD, especially leukoaraiosis (LA) and silent brain infarctions (SBI), and it was considered as an independent risk factor for SVD [11]. Hcy is also considered to be a risk factor for cardiovascular diseases in clinical practice [12]. Uric acid (UA) is a natural water-soluble antioxidant in the human body, which also has a pro-oxidant effect [13]. Previous studies have demonstrated that serum UA levels are independently and inversely associated with mild cognitive dysfunction, and UA might play a protective role in aging-associated decline in cognitive function [14–16]. In addition, hyperuricemia has been reported to be an important factor for cardiovascular and cerebrovascular diseases in elderly people, so an early UA test is beneficial for detecting and preventing cardiovascular diseases [17]. Serum UA level may also have an effect on the vascular system via various pathways; therefore, it might be associated with the occurrence and development of SVD [18]. However, few specific studies have explored the associations of serum Hcy and UA levels with VMCI in patients with cerebral SVD. This study proposed a hypothesis that serum Hcy and UA levels are related to VMCI in patients with cerebral SVD. For this reason, we aimed to investigate the possible diagnostic values of serum Hcy and UA levels in predicting VMCI in cerebral SVD patients, so as to provide valid predictors for VMCI in patients with cerebral SVD.

Material and Methods

Ethical statement

This study was performed with the approval of the Ethics Committee of the First Affiliated Hospital of Anhui Medical University and the Ethics Committee of Lu'an Municipal Hospital. Informed consents were collected from all patients in this research.

Study subjects

Between June 2013 and July 2015, a total of 172 patients with cerebral SVD were collected from the Department of Neurology in the First Affiliated Hospital of Anhui Medical University and the Department of Neurology in Lu'an Municipal Hospital. Inclusion criteria were: 1) Patients met the diagnostic criteria for cerebral SVD [19], and suffered from transient ischemic attacks; 2) Patients were diagnosed with leukoaraiosis, lacunar infarction or cerebral microbleeds (CMBs) after receiving head magnetic resonance imaging (MRI) and carotid ultrasonography; 3) Patients were diagnosed with lesions less than 15 mm in size under the cerebral cortex, without watershed or subcortical infarction, or without intracranial and extracranial carotid stenosis; and 4) Patients were diagnosed with single or multiple lacunar infarction in the basal ganglia and under the cerebral cortex, or with periventricular ischemic white matter damage by computerized tomography (CT) and MRI [7,20]. Patients were 40–85 years old, with at least 5 years of education. According to the diagnostic criteria for vascular mild cognitive impairment (VMCI) and the Montreal cognitive assessment (MoCA) scale [21,22], all patients were divided into the VMCI group (MoCA score <26) and non-VMCI group (MoCA score ≥26); patients in the VMCI group were those with cerebral SVD who had abnormal cognitive function, while patients in the non-VMCI group were those with cerebral SVD who had normal cognitive function. There were 92 patients in the VMCI group, including 51 males and 41 females, with a mean age of 64.95±6.21 years old, and 80 patients in the non-VMCI group, including 47 males and 33 females with a mean age of 63.75±6.06 years old. Exclusion criteria were: 1) Dementia patients who were diagnosed with cognitive impairment that met the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [23]; 2) Patients who had been treated with nootropic drugs or vitamin preparations before diagnosis; 3) Patients who were diagnosed with severe liver, heart, kidney, thyroid, or hematopoietic system diseases; 4) Patients with communication barriers that can influence the evaluation of cognitive function; 5) Patients with white matter lesions that might be caused by tumor, inflammation, poisoning, or other pathological conditions; 6) Patients with cognitive impairments possibly caused by other brain disorders, such as normal-pressure hydrocephalus or Parkinson's disease (PD).

The control group consisted of 86 healthy individuals without nervous system disease who were randomly selected from the general population based on physical examination, including 49 males and 37 females, with a mean age of 62.88±5.90 years old.

Data collection

The baseline characteristics of all patients were recorded in detail at their first admissions, including age, sex, body mass index (BMI), education history, drinking history, smoking history, and past medical history (e.g., diabetes, hypertension, and coronary heart disease [CHD]). Routine physical examination, neurological physical examination, cranial MRI and brain CT, and carotid ultrasonography were performed for all patients. On the next morning, fasting venous blood samples were collected from patients to detect the levels of homocysteine (Hcy), uric acid (UA), vitamin B12, folic acid (FOA), serum cholesterol (CH), low-density lipoprotein cholesterol (LDL-CH), high-density lipoprotein cholesterol (HDL-CH), triglyceride (TG), and hypersensitive C-reactive protein (hs-CRP), followed by carotid ultrasound, electrocardiography (ECG), cardiac ultrasound, and other examinations. Another cranial MRI and head CT test were performed to exclude non-SVD patients. MoCA was performed 2 weeks after the onset of SVD to avoid bias caused by a short-term impact on cognitive function following an acute stroke.

Enzymatic cycling method and chemiluminescence immunoassay

Venous blood samples (10 ml) were taken from fasting patients and were centrifuged for 1 min at 1500 rpm, followed by collection of serum for the evaluation of Hcy, UA, FOA, and VitB12. Hcy reagent (Beijing Strong Biotechnologies, Inc., Beijing, China), and UA reagent (Pointe Biotech [Nanjing] Co., Ltd., Jiangsu, China) were used to detect the levels of Hcy and UA using an enzymatic cycling method with a Hitachi 7600-020 automatic biochemical analyzer (Hitachi, Tokyo, Japan). Chemiluminescence immunoassay was applied to detect the levels of FOA, VitB12, and other indicators with an E170 immunoassay analyzer (Hoffmann-La Roche Ltd., Basel, Switzerland).

Montreal cognitive assessment (MoCA)

MoCA was performed in conformity with the Montreal cognitive assessment scale (Beijing Version) and the standards recommended by Nasreddine et al. [24]. The total possible score is 30 points: 2 points for an object naming task, 5 points for visuospatial ability and executive function (alternation task adapted from the trail-making B task, cube-copying task, and clock-drawing task), 2 points for abstract thinking, 4 points for language ability (sentence repetition task and verbal fluency task), 6 points for attention and calculation ability (digits

forward and backward task, sustained attention task, and serial subtraction task), 6 points for orientation in time and space, and 5 points for delayed recall (short-term memory recall task). The MoCA examination was finished within 10–15 min. One extra point is given to patients with ≥12 years of education. The highest possible score is 30 points. Patients with MoCA score <26 points were considered to have cognitive dysfunction, while patients with MoCA score ≥26 points were considered to have normal cognitive function.

Statistical analysis

SPSS 19.0 statistical software (SPSS Inc., Chicago, IL) was used for data analysis. Measurement data are represented as mean ± standard deviation (SD). The t test was used for comparisons of measurement data between 2 groups. The chi-square test was used for the comparison of enumeration data between 2 groups. One-way analysis of variance (ANOVA) was used for comparisons among multiple groups. Pearson's correlation coefficient analysis was performed to analyze the correlation between variables. A receiver operating characteristic (ROC) curve was used to evaluate the diagnostic values of serum Hcy and UA levels for predicting VMCI in patients with cerebral SVD. Logistic regression analysis was applied to determine possible risk factors for VMCI in patients with cerebral SVD. $P<0.05$ was considered to be statistically significant.

Results

Comparisons of baseline characteristics of study subjects among the VMCI, non-VMCI, and control groups

The baseline characteristics of study subjects in the VMCI, non-VMCI, and control groups showed that there was no distinctive difference in sex, age, BMI, education year, hypertension history, diabetes history, hyperlipidemia history, CHD history, smoking history, and drinking history among the 3 groups (all $P>0.05$). No significant difference was observed among the 3 groups in terms of blood glucose, CH, TG, HDL-CH, LDL-CH, and hs-CRP levels (all $P>0.05$). However, serum FOA and VitB12 levels in the non-VMCI and VMCI groups were lower than those in the control group, and serum FOA and VitB12 levels in the VMCI group were lower than those in the non-VMCI group (all $P<0.05$) (Table 1).

Comparisons of serum Hcy and UA levels among the VMCI, non-VMCI, and control groups

Compared with the control group, serum Hcy and UA levels in the VMCI and non-VMCI groups were significantly increased (all $P<0.05$). Serum Hcy and UA levels were higher in the VMCI group than those in the non-VMCI group (both $P<0.05$) (Figure 1).

Table 1. Comparison of baseline characteristics of study subjects among the VMCI group, non-VMCI group, and control group.

Characteristic	Control group (n=86)	Non-VMCI group (n=80)	VMCI group (n=92)	P
Sex (male/female)	49/37	47/33	51/41	0.192
Age (years)	62.88±5.90	63.75±6.06	64.95±6.21	0.075
BMI (kg/m²)	21.86±2.37	22.41±1.72	22.49±1.62	0.066
Education year (years)	7.80±1.85	7.41±1.99	7.20±1.53	0.080
Hypertension history, n (%)	62 (72.09)	59 (73.75)	69 (75.00)	0.194
Diabetes history, n (%)	23 (26.74)	23 (28.75)	22 (23.91)	0.769
Hyperlipidemia history, n (%)	30 (34.88)	26 (32.50)	33 (35.87)	0.894
CHD history, n (%)	25 (29.07)	21 (26.25)	26 (28.26)	0.173
Smoking history, n (%)	25 (29.07)	23 (28.75)	24 (26.09)	0.888
Drinking history, n (%)	16 (18.61)	15 (18.75)	18 (19.57)	0.985
Blood glucose (mmol/L)	4.76±0.68	4.67±0.52	4.87±0.48	0.357
Cholesterol (mmol/L)	5.34±1.08	5.29±1.41	5.36±1.31	0.985
Triglyceride (mmol/L)	1.41±0.27	1.36±0.33	1.38±0.31	0.565
HDL-CH (mmol/L)	1.26±0.11	1.29±0.28	1.32±0.13	0.099
LDL-CH (mmol/L)	2.64±0.43	2.71±0.80	2.78±0.86	0.436
Folic acid (ng/ml)	18.73±2.91	16.31±3.26*	11.34±2.47*#	<0.001
Vitamin B12 (Pg/ml)	698.70±167.59	576.80±126.36*	370.42±104.51*#	<0.001
hs-CRP (mg/L)	4.29±2.24	4.20±2.00	3.95±1.85	0.512

VMCI – vascular mild cognitive impairment; CHD – coronary heart disease; BMI – body mass index; HDL-CH – high-density lipoprotein cholesterol; LDL-CH – low-density lipoprotein cholesterol; hs-CRP – high-sensitivity C-reactive protein; * $P<0.05$ compared with the control group; # $P<0.05$ compared with the non-VMCI group.
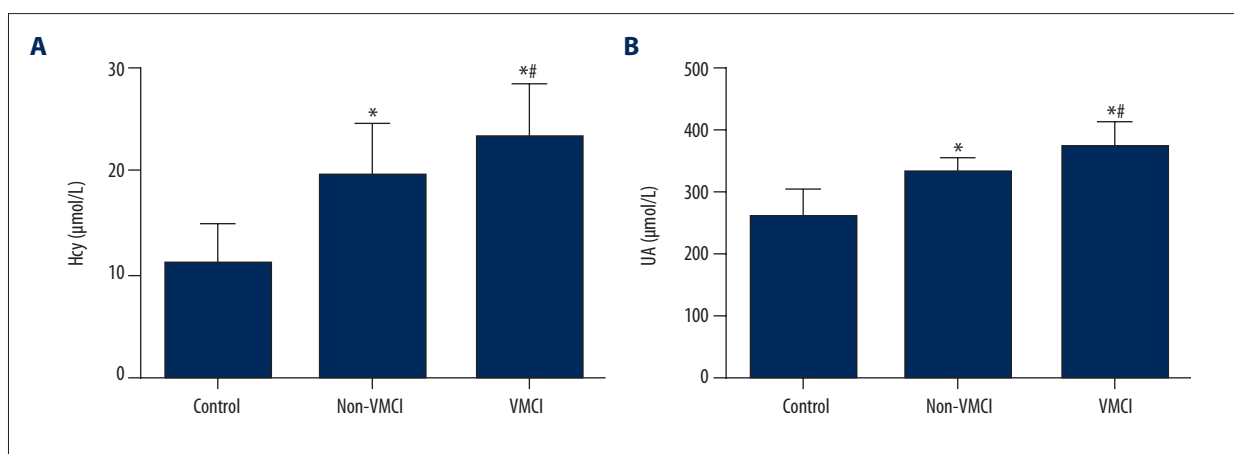

Figure 1. Comparisons of serum Hcy and UA levels among the VMCI group, non-VMCI group, and control group. (**A**) Comparison of serum Hcy level among the VMCI group, non-VMCI group, and control group; (**B**) Comparison of serum UA level among the VMCI group, non-VMCI group, and control group; Homocysteine (Hcy); Uric acid (UA); Vascular mild cognitive impairment (VMCI); * $P<0.05$ compared with the control group; # $P<0.05$ compared with the non-VMCI group.
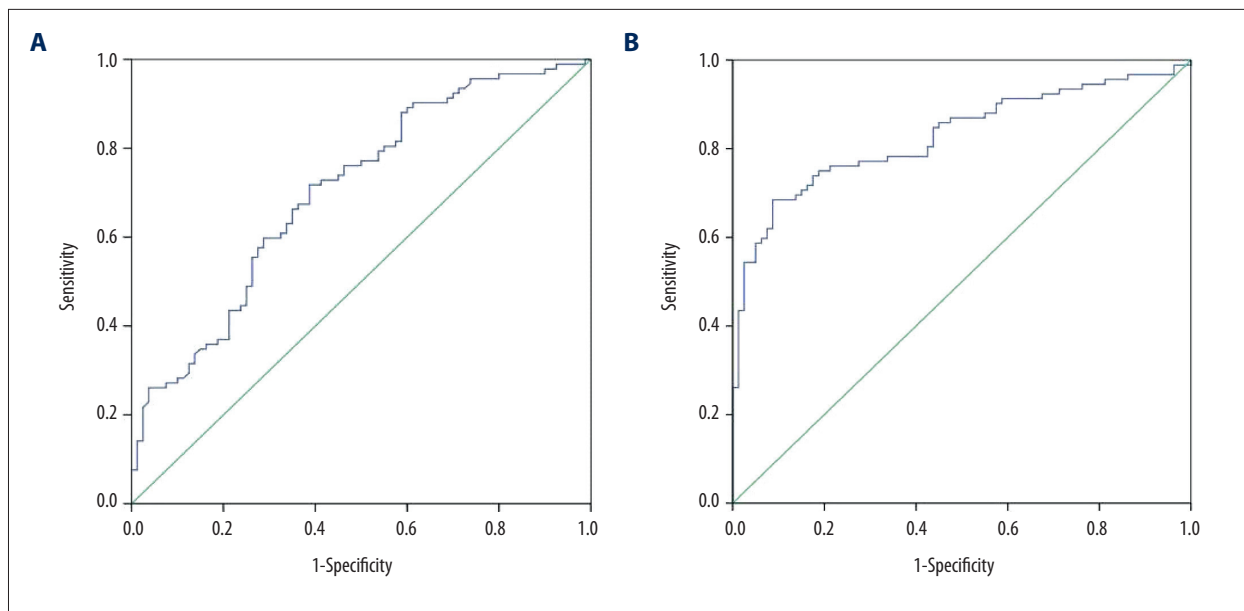
Figure 2. ROC curves of serum Hcy and UA levels predicting the occurrence of VMCI in patients with cerebral SVD. (**A**) ROC curve of serum Hcy level predicting the occurrence of VMCI in patients with cerebral SVD; (**B**) ROC curve of serum UA level predicting the occurrence of VMCI in patients with cerebral SVD; ROC – receiver operating characteristic curve; Hcy – homocysteine; UA – uric acid; VMCI – vascular mild cognitive impairment; SVD – small vessel disease.

Diagnostic values of serum Hcy and UA levels for predicting VMCI in patients with cerebral SVD

Diagnostic values of serum Hcy and UA levels for predicting the occurrence of VMCI in cerebral SVD patients were assessed by use of the ROC curves. The results showed that the area under the curve (AUC) of serum Hcy level was 0.703 (95%CI: 0.626–0.781). With an optimal cutoff value of 20.69 μmol/L, the sensitivity and specificity of serum Hcy levels in predicting VMCI in patients with cerebral SVD were 71.70% and 61.20%, respectively. The AUC of serum UA level was 0.829 (95%CI: 0.767–0.891). With an optimal cutoff value of 353.96 μmol/L, the sensitivity and specificity of serum UA levels in predicting VMCI in patients with cerebral SVD were 68.50% and 91.20%, respectively. All these data indicated the diagnostic values of serum Hcy and UA levels for predicting VMCI in patients with cerebral SVD (Figure 2).

Correlations of serum Hcy and UA levels with baseline characteristics of VMCI patients with cerebral SVD

According to the optimal cutoff value of serum Hcy level (20.69 μmol/L) in the ROC curve, VMCI patients with cerebral SVD were divided into a low-Hcy group (serum Hcy level <20.69 μmol/L) and a high-Hcy group (serum Hcy level ≥20.69 μmol/L). Similarly, according to the optimal cutoff value of serum UA level (353.96 μmol/L) in the ROC curve, VMCI patients with cerebral SVD were divided into a low-UA group (serum UA level <353.96 μmol/L) and a high-UA group (serum UA level

≥353.96 μmol/L). As shown in Table 2, there was no obvious difference in sex, age, BMI, education year, hypertension history, diabetes history, hyperlipidemia history, CHD history, smoking history, drinking history, blood glucose, TG, HDL-CH, LDL-CH, and hs-CRP between the low-Hcy and high-Hcy groups, as well as between the low-UA and high-UA groups (all *P*>0.05). The high-Hcy and high-UA groups had higher CH levels than the low-Hcy and low UA groups (both *P*<0.001). However, serum levels of FOA and VitB12 in the high-Hcy and high-UA groups were distinctly lower than those in the low-Hcy and low UA groups (all *P*<0.05). Pearson's correlation coefficient analysis suggested that serum Hcy and UA levels were negatively associated with FOA and VitB12 levels, and were positively correlated with CH levels (all *P*<0.05) (Table 3).

Correlations of serum Hcy and UA levels with MoCA total scores and subscores of VMCI patients with cerebral SVD

Pearson correlation coefficient analysis was applied to evaluate the correlations of serum Hcy and UA levels with MoCA total scores and subscores of VMCI patients with cerebral SVD. The results showed that serum Hcy and UA levels were negatively correlated with MoCA total score, subscores on visuospatial ability and executive function, on language ability, and on delayed recall (all *P*<0.05). Moreover, serum Hcy level was negatively correlated with scores on attention and calculation ability (both *P*<0.05). Serum Hcy and UA levels exhibited no significant correlations with subscores on object naming, on abstract thinking, and on orientation (all *P*>0.05) (Table 4).

Table 2. Correlations of serum Hcy and UA levels with baseline characteristics of VMCI patients with cerebral SVD.

Characteristic	Low-Hcy group (n=26)	High-Hcy group (n=66)	P	Low-UA group (n=29)	High-UA group (n=63)	P
Sex (male/female)	14/12	37/29	0.847	13/16	38/25	0.165
Age (years)	65.08±7.36	64.89±5.76	0.896	65.83±7.16	64.54±5.74	0.358
BMI (kg/m^2)	22.52±1.90	22.48±1.51	0.916	22.71±1.85	22.39±1.51	0.382
Education year (years)	7.35±1.72	7.14±1.46	0.557	7.52±1.70	7.05±1.43	0.171
Hypertension history, n (%)	21 (80.77)	48 (72.73)	0.423	21 (72.41)	48 (76.19)	0.698
Diabetes history, n (%)	8 (30.77)	14 (21.21)	0.333	6 (20.69)	14 (22.22)	0.869
Hyperlipidemia history, n (%)	9 (34.62)	24 (36.36)	0.875	8 (27.59)	25 (39.68)	0.261
CHD history, n (%)	9 (34.62)	17 (25.76)	0.396	7(24.141)	19 (30.16)	0.551
Smoking history, n (%)	6 (23.08)	18 (27.27)	0.680	6 (20.69)	18 (28.57)	0.424
Drinking history, n (%)	6 (23.08)	12 (18.18)	0.594	5 (17.24)	13 (20.63)	0.703
Blood glucose (mmol/L)	4.88±0.56	4.87±1.46	0.973	4.94±0.55	4.84±0.45	0.359
Cholesterol (mmol/L)	4.85±1.06	5.56±1.35	<0.001	4.63±1.29	5.70±1.18	<0.001
Triglyceride (mmol/L)	1.39±0.36	1.38±0.29	0.904	1.42±0.35	1.36±0.29	0.391
HDL-CH (mmol/L)	1.32±0.15	1.32±0.12	0.999	1.34±0.15	1.31±0.12	0.307
LDL-CH (mmol/L)	2.80±1.01	2.77±0.80	0.881	2.90±0.98	2.73±0.80	0.381
Folic acid (ng/ml)	13.55±1.94	10.47±2.10*	<0.001	13.19±2.11#	10.49±2.15	<0.001
Vitamin B12 (Pg/ml)	421.25±83.54	350.40±105.67*	0.003	409.04±94.76#	352.65±104.67	0.015
hs-CRP (mg/L)	4.06±1.99	3.91±1.80	0.728	4.33±1.98	3.78±1.77	0.186

Hcy – homocysteine; UA – uric acid; VMCI – vascular mild cognitive impairment; SVD – small vessel disease; CHD – coronary heart disease; BMI – body mass index; HDL-CH – high-density lipoprotein cholesterol; LDL-CH – low-density lipoprotein cholesterol; hs-CRP – high-sensitivity C-reactive protein; VitB12 – vitamin B12; * P<0.05 compared with the low-Hcy group; # P<0.05 compared with the low-UA group.

Table 3. Correlations of serum Hcy and UA levels with serum levels of cholesterol, folic acid, and vitamin B12 in VMCI patients with cerebral SVD.

	Hcy		UA	
	r	P	r	P
Cholesterol	0.422	<0.001	0.414	<0.001
Folic acid	−0.465	<0.001	0.457	<0.001
Vitamin B12	−0.225	0.031	0.219	0.036

Hcy – homocysteine; UA – uric acid; VMCI – vascular mild cognitive impairment; SVD – small vessel disease.

Logistic regression analysis

With VMCI as a dependent variable, and with indicators related to VMCI (Hcy, UA, CH, FOA, and VitB12) as independent variables, binary logistic regression analysis was performed

(Table 5). The results revealed that both serum Hcy and UA levels were risk factors for VMCI in cerebral SVD patients (both P<0.05).

Table 4. Correlations of serum Hcy and UA levels with MoCA total scores and subscores of VMCI patients with cerebral SVD.

MoCA items	Hcy		UA	
	r	P	r	P
MoCA total score	−0.502	0.003	−0.507	0.027
Object naming	−0.069	0.159	−0.090	0.089
Visuospatial ability and executive function	−0.269	0.017	−0.270	0.002
Abstract thinking	−0.160	0.083	−0.143	0.101
Language ability	−0.343	0.021	−0.369	0.018
Attention and calculation ability	−0.384	0.022	−0.165	0.019
Orientation	−0.165	0.076	−0.146	0.091
Delayed recall	−0.267	0.032	−0.269	0.026

CMVI – vascular mild cognitive impairment; MoCA – Montreal Cognitive Assessment; Hcy – homocysteine; UA – uric acid; SVD – small vessel disease.

Table 5. Logistic regression analysis.

Factor	B	S.E.	Wald	df	Sig.	Exp (B)	95%CI
Cholesterol	0.078	0.190	0.167	1	0.683	1.081	0.744~1.570
Folic acid	−0.140	0.109	1.664	1	0.197	0.869	0.703~1.075
Vitamin B12	0.013	0.003	18.790	1	<0.0001	0.987	0.982~0.993
Hcy	1.548	0.697	4.927	1	0.026	4.702	1.199~18.445
UA	3.569	0.827	18.648	1	<0.0001	35.499	7.025~179.391

Hcy – homocysteine; UA – uric acid; S.E. – standard error; Sig. – significance; 95%CI – 95% confidence interval.

Discussion

Both serum Hcy and UA levels are reported to be associated with cardiovascular diseases in clinical practice. Therefore, this study evaluated the diagnostic values of serum Hcy and UA levels for predicting VMCI in cerebral SVD patients. The results indicated that serum Hcy and UA levels were associated with serum FOA and VitB12 levels in patients with SVD, and might have a certain predictive value for the occurrence of VMCI in patients with SVD.

The results of this study demonstrate that serum FOA and VitB12 levels in the VMCI group were lower than those in the control and non-VMCI groups. Hcy cannot be obtained directly from food, but it is obtained through the methionine metabolism in liver, kidney, and other tissues after a series of methylation reactions. FOA and VitB12 are cofactors of Hcy metabolism, and the absence of or abnormities in either FOA and VitB12 could lead to a metabolic disorder of Hcy, resulting in accumulation of plasma Hcy [25]. A study performed by McMahon et al. selected 276 healthy people over 65 years old as the healthy group, with 2-year Hcy-lowering treatment containing FOA and VitB12 supplements. It also showed that

plasma Hcy levels were significantly decreased, while the FOA and VitB12 were increased [26,30]. Consistent with these findings, the present study found that compared with the non-VMCI and control groups, serum FOA and VitB12 levels were lower, and serum Hcy and UA levels were higher in the VMCI group. We also found that the serum Hcy and UA levels were negatively correlated with serum FOA and VitB12 levels as shown by Pearson's correlation coefficient analysis.

This study further found that serum Hcy and UA levels in the VMCI group were significantly higher than these in the non-VMCI group. Previous reports revealed that elevated Hcy levels may be an independent risk factor for cognitive impairment. Higher Hcy levels have been found to be associated with more serious degrees of cognitive impairment [27,28]. A novel treatment targeting Hcy via a high dose of supplementary B vitamins might decrease the accelerated rate of brain atrophy in MCI [29]. McMahon et al. reported that the Hcy-lowering treatment could improve cognitive performance, which was achieved with long-term supplementation with FOA and VitB12 [30]. All the above findings indicate that serum Hcy and UA levels might be positively correlated with VMCI, and the present study also proved the Hcy and UA levels could be

affected by serum FOA and VitB12 levels, and are thereby able to predict the occurrence of VMCI in patients with cerebral SVD. To support this finding, MoCA was performed to evaluate the degree of VMCI, and the Pearson's correlation coefficient analysis was applied to analyze the correlations of serum Hcy and UA levels with MoCA scores. In the screening for cognitive impairment in patients with subcortical VCI, MoCA has a higher sensitivity than the Mini-Mental State Examination (MMSE) [31]. Vannorsdall et al. reported significant correlations of serum UA with processing speed, working memory, verbal fluency and memory, and white matter hyperintensities [32]. Results of MoCA and Pearson's correlation coefficient analysis revealed that serum Hcy and UA levels were negatively associated with MoCA total scores, as well as subscores on visuospatial ability and executive function, attention and calculation ability, language ability, and delayed recall.

As confirmed by ROC curves, Hcy and UA levels exhibited high values of area under the curve (AUC), and the sensitivities and specificities of Hcy and UA were also high. This indicated that Hcy and UA may be regarded as reliable indicators of VMCI. Binary logistic regression analysis showed that both serum Hcy and UA levels ares risk factors for VMCI in cerebral SVD patients. The cognitive impairment might be induced by an elevated Hcy level, which is caused by cerebrovascular disease or increased cortical or hippocampal atrophy. Hcy was reported to be a risk factor for vascular cognitive impairment in patients with cerebral infarction, and also an independent risk factor for MCI in the Xinjiang Uygur population [33,34]. It has been shown that high UA levels might be a risk factor for stroke, and the elevated level of UA was correlated with poor prognosis of stroke [35]. UA serves as a natural water-soluble antioxidant in the human body, and it had a certain range of antioxidant properties. High UA levels might have pro-oxidant properties, which easily increases oxidative damage and induces inflammatory response and oxidative stress, leading to endothelial dysfunction and the subsequent development of white matter hyperintensities, which thereby may impair the cognitive function [32,36]. Sehreden et al. found that high UA levels in elderly adults can increase the risk of cognitive decline, resulting in cognitive impairment, which is consistent with the results of the present study [37]. Consequently, serum Hcy and UA levels may serve as predictive factors for VMCI in patients with cerebral SVD.

Conclusions

In summary, these results suggest that serum Hcy and UA levels are positively associated with VMCI in cerebral SVD patients, and might serve as predictive factors for VMCI. However, the Hcy-lowering treatment with supplemental FOA and VitB12 remains to be explored to prevent the incidence of VMCI in patients with cerebral SVD in our future research. Another limitation is the lack of experiments to elucidate the specific mechanism by which Hcy and UA are involved in the occurrence of VMCI, which warrants further study.

Disclosure statement

We declare no conflict of interest.

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