

Addition of $A\beta_{42}$ to Total Cerebral Small Vessel Disease Score Improves the Prediction for Cognitive Impairment in Cerebral Small Vessel Disease Patients

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Purpose: To investigate the associations between concentrations of $A\beta_{40}$ and $A\beta_{42}$ and vascular cognitive impairment (VCI) in cerebral small vessel disease (CSVD) patients and evaluate the value of combination of levels of $A\beta_{40}$ or $A\beta_{42}$ and the total CSVD score in predicting VCI.

Patients and Methods: A total of 199 CSVD patients were divided into VCI group and non-VCI group according to the criteria of VCI. Demographic data, MRI markers of CSVD, blood pressure, vascular risk factors, laboratory markers, and serum $A\beta_{40}$ and $A\beta_{42}$ concentration were collected. Univariate analysis was performed with the Student's *t*-test, Mann-Whitney *U*-test or Chi-square test. Variables with $P < 0.10$ in univariate analysis were then included in multivariate analysis that used a backward stepwise logistic regression model. The predictive values were assessed with receiver operating characteristic (ROC) curve.

Results: VCI was determined in 112 CSVD patients (56.3%). Hyperlipidemia (OR: 1.618, 95% CI: 1.265–3.049), the total CSVD score (OR: 1.414, 95% CI: 1.213–2.278) and serum $A\beta_{42}$ concentration (OR: 1.401, 95% CI: 1.212–1.946) were independent risk factors for VCI in CSVD patients with adjustment for age, education years, diabetes and fasting blood-glucose (FBG). The area under curves (AUCs) were 0.640 (SE: 0.040, 95% CI: 0.563–0.718), 0.733 (SE: 0.035, 95% CI: 0.664–0.802) and 0.827 (SE: 0.030, 95% CI: 0.768–0.887), respectively, for the total CSVD score, serum $A\beta_{42}$ concentration and their combination applied in predicting VCI in CSVD patients. *Z* test demonstrated that the AUC of combination prediction was significantly higher than individual prediction (0.827 vs 0.640, $Z = 3.740$, $P < 0.001$; 0.827 vs 0.733, $Z = 2.039$, $P = 0.021$).

Conclusion: Combination of $A\beta_{42}$ and total CSVD score could significantly elevate the predictive value of cognitive impairment in CSVD patients.

Keywords: $A\beta_{40}$, $A\beta_{42}$, vascular cognitive impairment, cerebral small vessel disease, total cerebral small vessel disease score

Introduction

Cerebral small vessel disease (CSVD) is a syndrome induced by intracranial small vessel lesions, which manifests as a series of changes in neuropathology, neuroimaging, cognitive function, sphincter dysfunctions, psychiatric disorders, and gait disorder, etc.^{1,2} Its typical brain magnetic resonance imaging (MRI) markers mainly include white matter hyperintensities (WMH), cerebral microbleeds (CMBs), lacunar infarction (LI) and enlarged perivascular spaces (EPVS).^{1,2} CSVD is one of the

most common causes of vascular cognitive impairment (VCI) and can lead to vascular dementia (VaD) in severe cases.³ Patients with a first-ever lacunar infarction present cognitive impairment (mainly executive dysfunction) in more than half of the cases and more than 55% of the patients meet the criteria for mild cognitive impairment of the vascular type.⁴ VaD is the end-stage of cognitive impairment and its therapeutic outcome is poor. VCI is the early stage of VaD and can be prevented, and moreover, its progression can be slowed or even reversed.^{5,6}

The amyloid β ($A\beta$) is derived from a proteolytic processing of the amyloid precursor protein through the activation of β - and γ -secretase.⁷ The $A\beta$ mainly includes $A\beta_{40}$ and $A\beta_{42}$ isoforms, and most of the $A\beta$ deposited in the brain is $A\beta_{42}$.⁸ Investigations on association between $A\beta$ levels and Alzheimer's disease (AD) have reported contradictory results, with some reporting decreased $A\beta_{40}$ and $A\beta_{42}$ levels in mild cognitive impairment and AD whereas others have reported elevated levels in AD.

Most CSVD patients have two or more MRI markers at the same time, and cognitive impairment is usually the interaction result of multiple lesions.⁹ Recent studies have employed the total MRI cerebral small vessel disease score to evaluate the severity of CSVD.¹⁰ This score is more precise due to synthesizing the type and amount of MRI markers.¹¹ Moreover, it has been demonstrated to have a significant association with cognitive performance.^{12–14} In this paper, the associations between concentrations of $A\beta_{40}$ and $A\beta_{42}$ and VCI in CSVD patients were analyzed, and the value of combination of the total CSVD score and concentrations of $A\beta_{40}$ or $A\beta_{42}$ in predicting VCI was evaluated.

Patients and Methods

Patients

Two-hundred and five consecutive CSVD patients were recruited at Department of Neurology, Tianjin Teda Hospital between July 2017 and June 2020. All patients had brain MRI markers of CSVD (WMH, CMBs, LI and EPVS) and were clinically diagnosed with CSVD according to the criteria of Trial of Org 10,172 in Acute Stroke Treatment.¹⁵ Exclusion criteria included: 1) extra-intracranial large artery stenosis $\geq 50\%$; 2) cortical nonlacunar infarcts, subcortical nonlacunar infarcts or cardio embolic source infarcts; 3) cerebral hemorrhage; 4) presence of other diseases which could affect

cognitive function, such as Alzheimer's disease (AD), Parkinson's disease, traumatic brain injury and congenital mental retardation; 5) presence of mental diseases such as serious anxiety, depression or schizophrenia; 6) difficulties in evaluation of cognitive function due to hearing and visual impairments. This study was performed in accordance with the Declaration of Helsinki and permitted by the Ethics Committee of Tianjin Teda Hospital. Informed consent was provided by patients or family members.

Patient Characteristics

The following variables were collected: 1) demographic data (age, sex, years of education); 1) MRI markers of CSVD (WMH, CMBs, LI and EPVS); 3) blood pressure (systolic blood pressure and diastolic blood pressure); 4) vascular risk factors (drinking, smoking, body mass index [BMI], hypertension, hyperlipidemia, atrial fibrillation and diabetes); and 5) laboratory markers at admission (fasting blood-glucose [FBG], triacylglycerol [TG], total cholesterol [TC], high density lipoprotein cholesterol [HDL-C] and low density lipoprotein cholesterol [LDL-C]).

Neuropsychological Assessment

Two neurologists performed neuropsychological assessment with Montreal Cognitive Assessment (MoCA) and clinical dementia rating (CDR) after unified training. VCI was diagnosed according to the criteria proposed by Geriatric Neurology Group, Chinese Society of Geriatrics and Clinical Practice Guideline for Cognitive Impairment of Cerebral Small Vessel Disease Writing Group: 1) patients or their caregivers reported a decline in subjective cognitive function that affected or did not affect life independence; 2) neuropsychological tests indicated cognitive impairment in one or more cognitive domain, and the judgment basis was MoCA score < 26 points and CDR score ≥ 0.5 points; and 3) cognitive impairment was associated with CSVD according to imaging features and medical history.¹⁶ According to the criteria of VCI, all CSVD patients were divided into VCI group and non-VCI group.

Determination of the Total CSVD Score

The total CSVD score was calculated through counting the presence of each of the four MRI markers of CSVD, with 1 point applied for the presence of each of WMH, CMBs, LI and EPVS. The presence of CMBs or LI was defined as the presence of one or more foci; the presence of WMH

was defined as either irregular periventricular hyperintensity extending into the deep white matter (Fazekas score 3) and/or (early) confluent deep WMH (Fazekas score 2 or 3); and the presence of moderate to severe basal ganglia EPVS was counted if it was grade 2–4. Therefore, the total CSVD score ranged from 0 to 4. Two radiologists determined the total CSVD score of each patient without knowing the results of neuropsychological assessment, and they should discuss and reach an agreement in case of disagreement.

Detection of $A\beta_{40}$ and $A\beta_{42}$ Concentrations

Fasting venous blood samples were collected for all patients on admission, and centrifuged for 15 minutes at 3500 r/min. The serum was then immediately frozen and stored at -80°C . The concentrations of $A\beta_{40}$ and $A\beta_{42}$ were detected using commercially available enzyme-linked immunosorbent assay kits (Thermo Fisher Scientific, Waltham, MA, USA). Detection was performed in an independent laboratory, and testers were blinded to MRI and clinical data.

Statistical Analysis

Statistical analysis was conducted using the SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) and significance was set at $P<0.05$. Quantitative data were assessed with Kolmogorov–Smirnov test for their distribution. Data with normal distribution were described with mean \pm standard deviation, and data without normal distribution were described with median (M) and interquartile range (IQR). Qualitative data were described with percentages or ratios (%). Univariate analysis was performed with the Student's t -test, Mann–Whitney U -test or Chi-square test. Variables with $P<0.10$ in univariate analysis were then included in multivariate analysis that used a backward stepwise logistic regression model. The predictive values of the total CSVD score, $A\beta$ concentrations and their combination were assessed with receiver operating characteristic (ROC) curve. Z test was employed to compare area under curve (AUC).

Results

General Data

A total of 225 CSVD patients were recruited during the study period. 17 cases were excluded because the quality of their MRI images was unqualified, and 9 cases were

excluded because they could not cooperate to complete the neuropsychological tests. Finally, 199 cases were included in this analysis. They included 107 males (53.8%) and 92 females (46.2%) with a mean age of (69.03 ± 7.79) years old. Among them, 146 cases (73.4%) demonstrated LI, 94 cases (47.2%) demonstrated WMH, 83 cases (41.7%) demonstrated EPVS, and 65 cases (32.7%) demonstrated CMBs. Thirty-one cases (15.6%) had 0 point of the total cerebral small vessel disease score, 44 cases (22.1%) had 1 point, 37 cases (18.6%) had 2 points, 53 cases (26.6%) had 3 points, and 34 cases (17.1%) had 4 points. VCI was determined in 112 cases (56.3%).

Analysis of Risk Factors for VCI

According to univariate analysis (Table 1), age, diabetes, hyperlipidemia, FBG, the total CSVD score and serum $A\beta_{42}$ concentration were significantly different between VCI group and non-VCI group ($P<0.05$), and the other variables were not ($P>0.05$). Multivariate analysis was performed with the occurrence of VCI or not as the dependent variable (occurrence =1, not occurrence =0) and the variables with $P<0.1$ in univariate analysis as the independent variables including age, education years, diabetes, hyperlipidemia, FBG, the total CSVD score and serum $A\beta_{42}$ concentration. The results demonstrated that hyperlipidemia (OR: 1.618, 95% CI: 1.265–3.049), the total CSVD score (OR: 1.414, 95% CI: 1.213–2.278) and serum $A\beta_{42}$ concentration (OR: 1.401, 95% CI: 1.212–1.946) were independent risk factors for VCI in CSVD patients with adjustment for age, education years, diabetes and FBG.

Analysis of Predictive Value

The predictive values of the total CSVD score, serum $A\beta_{42}$ concentration and their combination were evaluated with ROC curves. Their AUCs were 0.640 (SE: 0.040, 95% CI: 0.563–0.718), 0.733 (SE: 0.035, 95% CI: 0.664–0.802) and 0.827 (SE: 0.030, 95% CI: 0.768–0.887), respectively (Figure 1). According to Z test, the AUC of combined prediction was significantly higher than individual prediction (0.827 vs 0.640, $Z=3.740$, $P<0.001$; 0.827 vs 0.733, $Z=2.039$, $P=0.021$). Their clinical utility indexes were demonstrated in Table 2. The positive predictive value was 69.0%, 75.3% and 82.9%, respectively for the total CSVD score, serum $A\beta_{42}$ concentration and their combination, and the negative predictive value was 53.6%, 61.8% and 77.3%, respectively.

Table 1 Results of Univariate Analysis Between VCI Group and Non-VCI Group

Variables	All CSVD Patients (n=199)	VCI Group (n=112)	Non-VCI Group (n=87)	t/Z/ χ^2	P
Demographic data					
Age (years old, mean \pm standard)	69.03 \pm 7.79	70.08 \pm 7.98	67.68 \pm 7.54	2.171	0.034
Male (n, %)	107 (53.8%)	62 (55.4%)	45 (51.7%)	0.260	0.610
Education years (years, mean \pm standard)	6.78 \pm 3.49	6.37 \pm 3.32	7.31 \pm 3.70	-1.859	0.072
Vascular risk factors (n, %)					
Drinking	67 (33.7%)	41 (36.6%)	26 (29.9%)	0.991	0.320
Smoking	78 (39.2%)	47 (42.0%)	31 (35.6%)	0.824	0.364
Hypertension	114 (57.3%)	67 (59.8%)	47 (54.0%)	0.673	0.412
Hyperlipidemia	60 (30.2%)	41 (36.6%)	19 (21.8%)	5.071	0.024
Atrial fibrillation	22 (11.1%)	12 (10.7%)	10 (11.5%)	0.030	0.862
Diabetes	75 (37.7%)	50 (44.6%)	25 (28.7%)	5.276	0.022
Blood pressure (mmHg, mean \pm standard)					
Systolic blood pressure	143.72 \pm 15.14	144.26 \pm 15.18	143.02 \pm 15.09	0.574	0.549
Diastolic blood pressure	83.92 \pm 10.95	84.18 \pm 10.41	83.59 \pm 11.64	0.371	0.694
Laboratory markers (mmol/L, mean \pm standard)					
TC	4.13 \pm 1.10	4.17 \pm 1.19	4.08 \pm 0.99	0.582	0.547
TG	1.56 \pm 0.84	1.62 \pm 0.90	1.48 \pm 0.76	1.189	0.258
LDL-C	2.57 \pm 1.06	2.63 \pm 1.14	2.48 \pm 0.95	1.012	0.305
HDL-C	1.23 \pm 0.44	1.19 \pm 0.42	1.29 \pm 0.47	-1.559	0.176
FBG	6.85 \pm 2.81	7.30 \pm 2.85	6.26 \pm 2.76	2.599	0.011
MRI markers of CSVD (n, %)					
LI	146 (73.4%)	85 (75.9%)	61 (70.1%)	0.837	0.360
WMH	94 (47.2%)	57 (50.9%)	37 (42.5%)	1.374	0.241
CMBs	65 (32.7%)	34 (30.4%)	31 (35.6%)	0.619	0.431
EPVS	83 (41.7%)	44 (39.3%)	39 (44.8%)	0.619	0.432
A β ₄₀ (pg/mL, mean \pm standard)	19.82 \pm 8.94	20.47 \pm 9.05	18.98 \pm 8.79	1.171	0.262
A β ₄₂ (pg/mL, mean \pm standard)	14.81 \pm 7.80	16.38 \pm 8.56	12.79 \pm 6.82	3.293	0.002
Total CSVD score (M, IQR)	2 (2)	3 (2)	1 (2)	-3.470	0.001
Distribution of total CSVD score (n, %)				12.710	0.013
0 point	31 (15.6%)	12 (10.7%)	19 (21.8%)		
1 point	44 (22.1%)	19 (17.0%)	25 (28.7%)		
2 points	37 (18.6%)	21 (18.8%)	16 (18.4%)		
3 points	53 (26.6%)	36 (32.1%)	17 (19.5%)		
4 points	34 (17.1%)	24 (21.4%)	10 (11.5%)		

Discussion

In our study, serum A β ₄₂ levels were higher in CSVD patients with VCI than without VCI, and A β ₄₀ levels were not statistically different. Moreover, multivariate analysis showed that the total CSVD score and serum A β ₄₂ levels were independently associated with VCI in CSVD patients.

Previous studies have shown that elevated levels of A β ₄₀ and A β ₄₂ are associated with WMH and LI.^{17–20} This may be involved in multiple mechanisms. Firstly, excessive A β results in deposition in the adventitia and media of arteries and cortical arterioles, which can be

further promoted by Apoe4 isoform that contributes to the transformation of A β oligomers from β sheet.²¹ Secondly, fibrillary deposition of A β in the vessel wall can lead to loss of vascular smooth muscle tone, obliteration of the vessel lumina and endothelial damage, which is responsible for cerebrovascular damage and hypoperfusion.²⁰ Thirdly, hypoperfusion or decreased cerebral blood flow may promote the production of A β through upregulating the expression of amyloid- β protein precursor in endothelial cells and thereby results in its secretion in the peripheral circulation.²² Fourthly, soluble A β may enhance endothelin-1 induced vasoconstriction

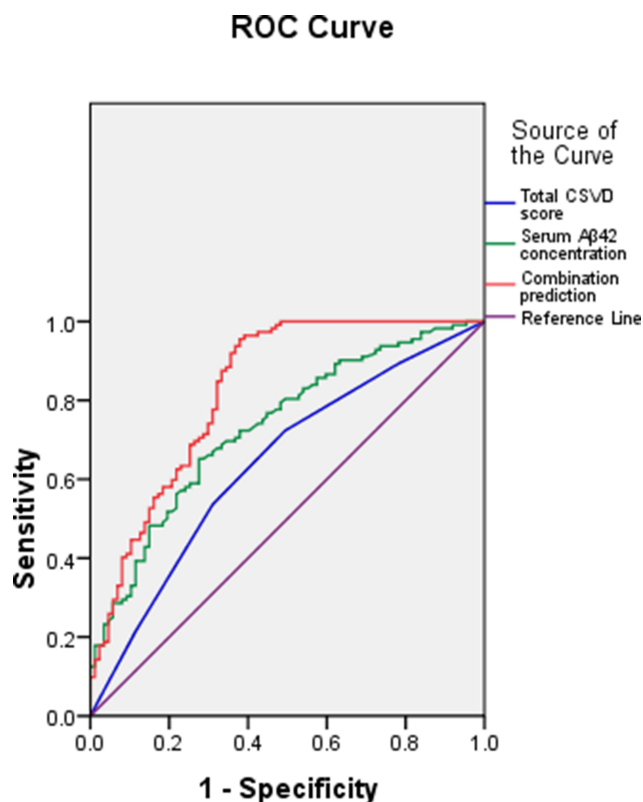


Figure 1 ROC curves of the total CSVD score, serum A β_{42} concentration and their combination.

and thereby influence cerebral vasoreactivity. This alteration can influence brain regions, which limits collateral circulation leading to WMH and LI.²³ In addition to WMH and LI, A β levels have been reported an association with CMBs.²⁴

With respect to cognition, it has been shown that elevated A β levels may induce cortical thinning and decreased grey matter density in temporal lobes, which can cause cognitive dysfunction via disrupting important cognitive networks.^{25,26} However, investigations on association between A β levels and AD have yielded controversial results. Llado-Saz et al indicated that the elevated A β_{40}

level was correlated with decreased information processing speed, poor memory and cognitive decline among cognitively normal adults.²⁷ Hilal et al investigated plasma A β levels in two independent cohorts of the Rotterdam Study.²⁴ The results showed that elevated A β_{40} levels, A β_{42} levels and A β_{40} /A β_{42} ratio were related to increasing microbleeds and lacunar counts. Moreover, elevated A β_{40} levels and A β_{40} /A β_{42} ratio were significantly correlated with large volumes of WMH. For cognition, elevated A β_{40} levels and A β_{40} /A β_{42} ratio were associated with poor performance on cognitive test. Mayeux et al detected plasma A β_{40} and A β_{42} levels of 530 individuals participating in an epidemiologic study on association between aging and dementia at different time points.²⁸ Their results demonstrated that plasma A β_{40} and A β_{42} levels increased with age. Plasma A β_{40} and A β_{42} levels were elevated in some patients before and during the early stages of AD but decline thereafter. Seppälä et al demonstrated that the low plasma A β_{42} level was associated with cognitive decline in a population-based cohort including 52 cognitively impaired and 217 controls.²⁹ Chouraki et al investigated plasma A β_{40} and A β_{42} levels in a community-based cohort under ongoing surveillance for AD (the Framingham cohort).¹⁷ The results demonstrated that decreased plasma A β_{42} levels and A β_{42} /A β_{40} ratio were correlated with risk of dementia and AD, but plasma A β_{40} levels were not. Hansson et al investigated plasma A β_{40} and A β_{42} levels in two independent cohorts of patients with mild cognitive impairment (MCI) and age-matched controls.³⁰ The results showed that decreased A β_{42} levels in CSF were correlated with risk of incident AD. The inconsistency between our results and some previous results might be associated with different participants and different timing of A β detection.

Multiple MRI markers of CSVD have been confirmed to have a significant correlation with cognitive impairment.^{12–14} WMH and LI are associated with

Table 2 Clinical Utility Indexes of the Total CSVD Score, A β_{42} Concentration and Their Combination for Predicting VCI in CSVD Patients

	Best Cut-Off	Sensitivity	Specificity	Accuracy	False Positive Rate	False Negative Rate	Positive Predictive Value	Negative Predictive Value	Youden Index
Total CSVD score	2	72.3%	50.6%	60.3%	31.0%	46.4%	69.0%	53.6%	0.23
Serum A β_{42} concentration (pg/mL)	12.53	65.2%	72.4%	68.3%	24.7%	38.2%	75.3%	61.8%	0.38
Combination prediction		82.1%	78.2%	80.4%	17.1%	22.7%	82.9%	77.3%	0.60

executive dysfunction, working memory disturbances and decreased information processing speed,^{31–36} and CMBs are associated with decreased information processing speed and executive dysfunction.^{37,38} The total CSVD score is a new scoring method proposed in recent years. It can be used to evaluate the total burden of CSVD through synthesizing the type and amount of MRI markers.¹¹ The total CSVD score can assess the impact of CSVD on cognitive function more precisely compared with individual MRI marker of CSVD. In the general population, community-dwelling older people, memory clinic population, first lacunar infarction patients and hypertension patients, the total CSVD score is associated with cognition.^{9,39,40} Moreover, it could be used to predict the cognitive decline in hypertension patients over 4 years, especially in executive function.⁴¹

In this study, we further evaluated the value of the total CSVD score, serum A β ₄₂ levels and their combination in predicting VCI in CSVD patients. The AUC of the total CSVD score in predicting VCI in CSVD patients was 0.640 with the best cut-off of 2, and serum A β ₄₂ levels was 0.733 with the best cut-off of 12.53 pg/mL. The AUC of their combination was 0.827 with a sensitivity of 82.1% and a specificity of 78.2%, significantly higher than individual prediction. Therefore, their combination could be applied in prediction of VCI in CSVD patients.

The limitation of the study is that the potential role of cerebral atrophy in the cognitive impairment of patients in the study sample has not been evaluated and it is a fact of recent interest in the study of cognitive impairment in small vessel cerebrovascular disease.⁴²

Conclusion

The total CSVD score and serum A β ₄₂ concentration were independent risk factors of VCI in CSVD patients. Combination of A β ₄₂ and total CSVD score could elevate the predictive value of cognitive impairment in CSVD patients.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; agreed on the journal to which the article will be submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest for this work.

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