

Serum Retinoic Acid Level and The Risk of Poststroke Cognitive Impairment in Ischemic Stroke Patients

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Background: Retinoic acid (RA), an active metabolite of vitamin A, possesses enormous protective effects on vascular systems. It may also be positively related to good functional outcome after ischemic stroke. However, whether circulating RA concentration is associated with poststroke cognitive impairment (PSCI) remains unclear. This study aimed to detect the association between RA level and PSCI among patients with first-ever acute ischemic stroke. *Methods:* Two hundred and 61 consecutive patients were prospectively recruited during March 2018 and March 2019. Serum RA concentration was measured at admission for all patients. We also performed cognitive function examination using the Montreal Cognitive Assessment (MoCA) at admission and at every follow-up visit. Patients with MoCA score less than 26 were identified as developing PSCI. *Results:* The median serum RA level was 2.0 ng/mL (interquartile range, 1.1-3.2 ng/mL) after admission. Patients diagnosed as PSCI at admission, 1-month and 3-month were 53 (20.3%), 91 (34.6%), and 141 (54.0%), respectively. Univariate analysis showed that reduced RA level was correlated with PSCI at 3-month ($P = .003$), but not at admission ($P = .416$) and 1-month poststroke ($P = .117$). After adjusting for all potential confounders, the odds ratio for the lowest tertile of RA, compared with the highest tertile, was 1.97 (95% confidence interval, 1.01-3.83, $P = .046$) for PSCI at 3 months. Furthermore, multiple-adjusted spline regression model further confirmed the dose-response relationships between RA level and 3-month PSCI ($P < .001$). *Conclusions:* Decreasing serum RA level might be associated with 3-month PSCI in ischemic stroke patients.

Key Words: Retinoic acid–ischemic stroke–cognitive function–poststroke cognitive impairment

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Introduction

Stroke has been ranked as the first leading cause of mortality and long-term disability in China.¹ Poststroke cognitive impairment (PSCI) is a common and important complication after stroke, with prevalence ranging widely from 20% to 80%,^{2,3} among which 20% to 30% of patients with PSCI will develop dementia.⁴ It has been confirmed that PSCI could result in a loss of independence and increased mortality, higher risk of recurrent stroke and aggravated economic burden.⁵⁻⁷ However, the potential pathophysiological mechanisms involved in PSCI remained unclear. Also, multiple factors have been found to contribute to the development of PSCI, including increased age, gender, family history, genetic predisposition, poor educational status, and vascular comorbidities, which are not readily amenable to prevention and treatment.⁸ Accordingly, it is necessary to detect novel risk

factors of PSCI that may assist the selection of patients for aggressive monitoring and therapeutic interventions.

Retinoic acid (RA) is a major metabolite of vitamin A, including carotenoids and retinyl esters, responsible for growth and development. Its broad biologic effects are exerted through binding with members of the nuclear receptor family, such as retinoic acid receptor and retinoid X receptor, and modulating specific gene cassettes.^{9,10} Previous studies suggested the RA and its relevant nuclear receptor signaling on vascular protection, metabolic syndrome, and cardiovascular disease.^{11,12} Moreover, decreasing RA was found to be an independent predictor for long-term poor prognosis of after ischemic stroke.¹³ Data from animal studies showed that decreased cerebral infarction volume was obtained with 9-cis-retinoic acid pretreatment.¹⁴ In addition, functional recovery and endogenous repair were all found favorable with administration of RA,¹⁵ all probably contributing to an increased synaptic plasticity following ischemic stroke. Therefore, we speculated that circulating RA level might be a prognostic biomarker relating to PSCI. However, it is still unclear whether lower RA level is a cause or consequence of PSCI. The aim of this study is to prospectively investigate the relationship between serum RA and risk of PSCI in a cohort of Chinese patients who initially presented with ischemic stroke.

Methods

Subjects and Study Design

From March 2018 to March 2019, consecutive patients with the first-ever acute ischemic stroke were screened for inclusion in our study. All patients were admitted in the Affiliated Brain Hospital of Guangzhou Medical University, Changping Hospital and Jiangsu Provincial Second Chinese Medicine Hospital. Patients meeting the following criteria were eligible to participate in our study: acute ischemic stroke within 7 days of stroke onset with age more than 18 years. Participants were excluded if the following criteria were identified: (1) severe neurological deficit, aphasia or dysarthria, life expectancy less than 3-month; (2) Alzheimer's disease, Parkinson disease, psychiatric disorders known to influence cognitive function, a pre-existing cognitive impairment according to the Informant Questionnaire on Cognitive Decline in the Elderly, a screening instrument validated in Chinese, scoring 3.4 or more¹⁶; (3) transient ischemic attack, hemorrhagic stroke, traumatic brain injury, malignant tumor, active or chronic inflammatory disorders, and major medical illness. We also excluded subjects treated with intravenous thrombolysis and/or endovascular therapy during hospitalization. All patients or their legally acceptable representative provided written informed consent. The ethics committee and the research board of each hospital approved the study protocol.

Clinical Data Collection

After admission, the following information was collected: demographic characteristics (including age, gender, and education status), traditional risk factors (including hypertension, diabetes, hyperlipidemia, coronary heart disease, and smoking) and previous medication (including antiplatelet therapy, stain therapy, and antihypertension therapy). Moreover, blood pressure, time from onset to admission, baseline neurological deficit, and stroke subtype were also recorded. Neurological deficit was assessed by certified neurologist using National Institutes of Health Stroke Scale (NIHSS).¹⁷ Stroke subtype was classified according to TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria.¹⁸

Serum RA Level Measurement

Blood samples were obtained from each subject in the morning after admission. The specimens were centrifuged at 1500 g for 10 minutes and the isolated serum frozen at -80°C for later analysis. RA concentration was measured using commercially available enzyme-linked immunosorbent assay kits (catalog no. MBS705877; MyBioSource) according to the manufacturers' instructions. This assay was highly sensitive and specific for the detection of human serum RA. The standard enzyme-linked immunosorbent assay curve range for serum RA level was .625–10.0 ng/mL. The coefficient of variation for the inter-assay replicate samples was less than 8%.

Follow-Up and Cognitive Function Evaluation

All eligible patients were conducted the Montreal Cognitive Assessment (MoCA) at admission, 1-month and 3-month after symptoms onset by trained neurologists who were blinded to the laboratory results and clinical data. The MoCA evaluates the following cognitive domains: visuospatial/executive functions, naming, memory, attention, language, abstraction and orientation. Previous studies demonstrated that people with less than 12 years of education tended to have worse performance on the MoCA. To correct for education level effects, 1 point was added for participants with education less than 12 years on their total MoCA score.¹⁹ According to previous studies,¹⁹⁻²¹ patients with total MoCA score less than 26 were diagnosed as PSCI.

Statistical Analysis

The statistical analysis was performed using SPSS version 23.0 (SPSS Inc., Chicago, IL) and R statistical software version 3.4.2. Continuous variables were presented as means \pm SD or median (interquartiles), and categorical variables were expressed as percentage. Differences in baseline variables stratified by tertile of RA level were determined using χ^2 , analysis of variance, or Kruskal-Wallis where appropriate. Logistic regression analysis was used to estimate the

risk of PSCI by calculating odds ratio (OR) and 95% confidence interval (CI). We performed 2 multiple adjusted logistic regression models. Model 1 adjusted for age, sex, and education status. Model 2 included the factors in model 1 as well as hypertension, NIHSS score, white matter lesions, and homocysteine level. We also used the spline regression models to provide more precise estimates and explore the shape of association between serum RA and PSCI, fitting a restricted cubic spline function with 3 knots (at the 5th, 50th, and 95th percentiles). The level of statistical significance was set at $P < .05$.

Results

During March 2018 to March 2019, 261 consecutive patients (140 male) included in the final analysis (flow chart of patient inclusion was showed in Fig 1). The baseline characteristics of the 261 patients were presented according to the tertile of RA level (Table 1). The average age of the patient sample was 66.4 ± 9.3 years (from 42 to 87 years old). The median serum RA level was 2.0 ng/mL, with tertile as follows: less than 1.5 ng/mL (first tertile); 1.5-2.7 ng/mL (second tertile); and more than 2.7 ng/mL (third tertile). Decreasing RA level showed a significant association with age ($P = .030$), hypertension ($P = .003$), diabetes mellitus ($P = .001$), smoking ($P = .044$), PSCI at 3 months ($P = .003$), NIHSS score ($P = .013$), total cholesterol ($P = .012$), Hs-CRP ($P = .001$), homocysteine ($P = .003$), and fasting blood-glucose level ($P = .027$).

Patients diagnosed as PSCI at admission, 1-month and 3-month were 53 (20.3%), 91 (34.6%), and 141 (54.0%),

respectively. Univariate analysis showed that reduced RA level was associated with PSCI at 3-month ($P = .003$), but not at admission ($P = .416$) and 1-month ($P = .117$). Table 2 demonstrated the baseline characteristics according to patients with and without PSCI at 3 months. Compared with patients without PSCI at 3-month, those with it were older ($P = .016$), more likely to have lower education level ($P = .027$), hypertension ($P = .004$), white matter lesions ($P = .050$), higher NIHSS score ($P = .023$), increased homocysteine level ($P = .034$), and decreased retinoic acid level ($P = .001$).

As shown in Table 3, serum RA level exhibited significant associations with 3-month PSCI. After adjusted for age, gender, education status, hypertension, NIHSS score, white matter lesions, and homocysteine level, the binary logistic analysis showed that lower RA level was an independent predictor for PSCI at 3-month (OR, .77; 95% CI, .64-.92; $P = .005$). The adjusted OR (95% CI) for the lowest tertile of RA was 1.97 (1.01-3.83; $P = .046$) for PSCI compared with the highest tertile. Furthermore, multiple-adjusted spline regression model further confirmed the dose-response relationships between RA level and 3-month PSCI ($P < .001$; Fig. 2).

Discussion

In the present study, we found that decreasing serum RA level at baseline was independently associated with increasing risk of the PSCI at 3 months after ischemic stroke. This association was independent of established risk factors such as age, gender, education status, hypertension, and severity of stroke. And multiple-adjusted

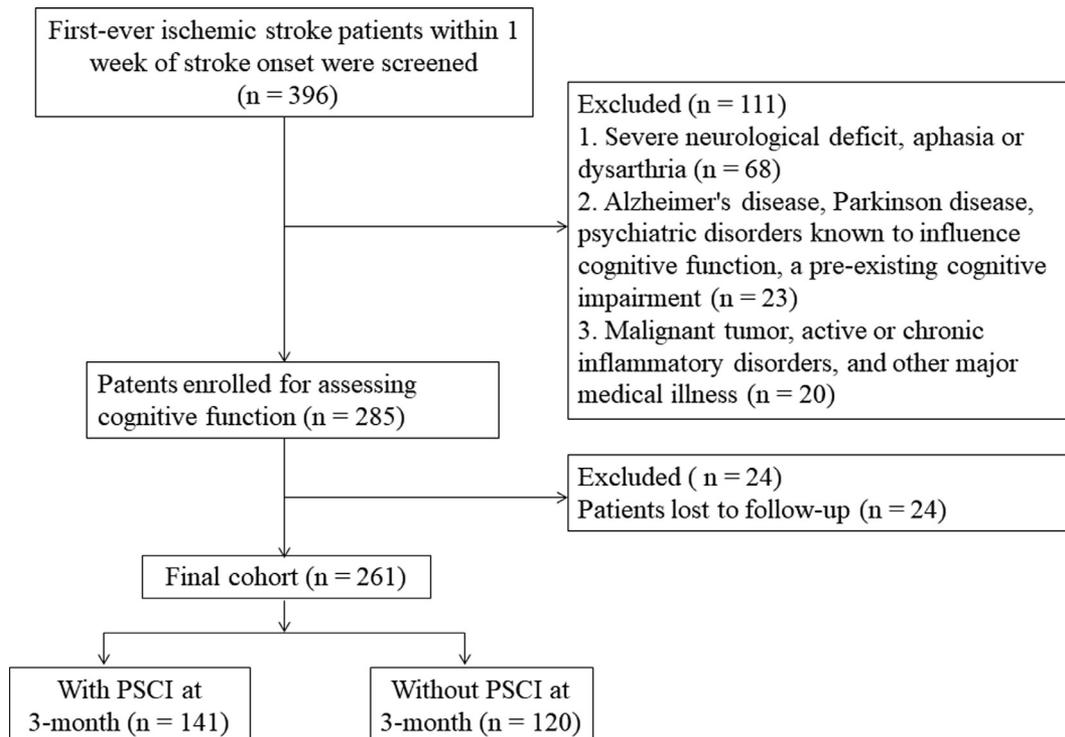


Figure 1. Flow chart of patient inclusion. PSCI, poststroke cognitive impairment.

Table 1. Characteristics of the study population stratified by the retinoic acid tertiles

Variables*	Retinoic acid, ng/mL				P value
	Total (n = 261)	<1.5 (n = 87)	1.5-2.7 (n = 87)	>2.7 (n = 87)	
Demographic characteristics					
Age, year	66.4 ± 9.3	68.3 ± 9.2	66.3 ± 10.1	64.6 ± 8.2	.030
Male, n (%)	140 (53.6)	52 (59.8)	42 (48.3)	46 (52.9)	.310
Education <12 years, n (%)	156 (59.8)	53 (60.9)	53 (60.9)	50 (57.5)	.866
Vascular risk factors, n (%)					
Hypertension	145 (55.6)	60 (69.0)	47 (54.0)	38 (43.7)	.003
Diabetes mellitus	65 (24.9)	30 (34.5)	25 (28.7)	10 (11.5)	.001
Hyperlipidemia	40 (15.3)	15 (17.2)	14 (18.4)	9 (10.3)	.281
Coronary heart disease	31 (11.9)	13 (14.9)	12 (13.8)	6 (6.9)	.207
Smoking	96 (36.8)	41 (47.1)	26 (29.9)	29 (33.3)	.044
Clinical features					
Systolic blood pressure, mm Hg	137.8 ± 16.4	137.6 ± 14.0	138.7 ± 18.8	137.1 ± 16.2	.812
Diastolic blood pressure, mm Hg	80.9 ± 10.3	82.8 ± 9.9	80.3 ± 10.2	79.4 ± 10.7	.071
Time from onset to admission, d	3.0 (1.0, 4.0)	3.0 (2.0, 4.0)	3.0 (1.0, 4.0)	3.0 (1.0, 4.0)	.452
NIHSS, score	5.0 (2.0, 7.0)	5.0 (3.0, 8.0)	5.0 (3.0, 7.0)	3.0 (2.0, 7.0)	.013
White matter lesions, n (%)	97 (37.2)	37 (42.5)	34 (39.1)	26 (29.9)	.204
Previous antiplatelet therapy, n (%)	81 (31.0)	31 (35.6)	29 (33.3)	21 (24.1)	.222
Previous stain therapy, n (%)	67 (25.7)	23 (26.4)	27 (31.0)	17 (19.5)	.217
Previous antihypertension therapy, n (%)	84 (32.2)	24 (27.6)	32 (36.8)	28 (32.2)	.431
MoCA score at admission	27.0 (26.0, 28.0)	27.0 (25.0, 28.0)	27.0 (26.0, 28.0)	27.0 (26.0, 28.0)	.531
PSCI at admission, n (%)	53 (20.3)	21 (24.1)	18 (20.7)	14 (16.1)	.416
MoCA score at 1-month	26.0 (23.0, 28.0)	26.0 (23.0, 28.0)	26.0 (23.0, 28.0)	27.0 (24.0, 28.0)	.334
PSCI at 1-month, n (%)	91 (34.9)	37 (42.5)	30 (34.5)	24 (27.6)	.117
MoCA score at 3-month	25.0 (21.0, 27.5)	23.0 (21.0, 26.0)	25.0 (21.0, 28.0)	26.0 (22.0, 28.0)	.013
PSCI at 3-month, n (%)	141 (54.0)	59 (67.8)	45 (51.7)	37 (42.5)	.003
Stroke subtypes, n (%)					
Large artery atherosclerosis	117 (44.8)	40 (46.0)	44 (50.6)	33 (37.9)	.572
Cardioembolism	51 (19.5)	16 (18.4)	15 (17.2)	20 (23.0)	
Small artery occlusion	73 (28.0)	24 (27.6)	20 (23.0)	29 (33.3)	
Others	20 (7.7)	7 (8.0)	8 (9.2)	5 (5.7)	
Laboratory data					
Total cholesterol, mmol/L	4.0 ± 1.0	4.3 ± 1.0	3.9 ± 1.0	3.8 ± 1.0	.012
Triglyceride, mmol/L	1.4 (1.1, 1.8)	1.5 (1.1, 1.5)	1.3 (1.1, 1.8)	1.3 (0.9, 1.7)	.087
High-density lipoprotein, mmol/L	1.1 ± 0.2	1.0 ± 0.3	1.1 ± 0.2	1.1 ± 0.2	.287
Low-density lipoprotein, mmol/L	2.4 (2.0, 2.9)	2.3 (2.0, 2.8)	2.5 (2.1, 3.0)	2.2 (1.7, 3.0)	.107
Hs-CRP, mg/L	5.3 (2.5, 9.8)	8.4 (2.9, 10.5)	4.7 (2.4, 9.6)	4.1 (2.0, 7.0)	.001
Homocysteine, umol/L	14.7 ± 5.2	16.3 ± 5.4	13.9 ± 4.0	14.2 ± 5.7	.003
Fasting blood-glucose, mmol/L	5.9 ± 2.5	6.3 ± 2.7	6.1 ± 2.7	5.4 ± 1.9	.027

Abbreviations: Hs-CRP, hypersensitive C-reactive protein; MoCA, Montreal Cognitive Assessment; NIHSS, National Institutes of Health Stroke Scale; PSCI, poststroke cognitive impairment.

*Continuous variables were expressed as mean ± SD or median (interquartile range). Categorical variables were expressed as number (percentage).

spline regression model further confirmed a negative linear dose-response relationship between them. These findings suggested that serum RA might be a potential biomarker for cognitive impairment after ischemic stroke.

Previous epidemiological studies on PSCI showed that the incidence rates vary from 20% to 80% (3). In Asia, it is proposed that the prevalence reached up to 69.8% at 3 months after stroke according to the study conducted in South Korea proceeding in 12 hospitals with 620 ischemic stroke patients enrolled.²² While in China, a prevalence of 37%-72% of cognitive impairment was confirmed at 3

months after stroke.^{20,23} Here we reported a 54% of PSCI occurrence at 3-month poststroke, which is similar to previous data detected in Chinese patients. Differences in the case mix of study populations, the discrepancy in PSCI definition, and the interval time between symptoms onset and cognitive function assessment could account for the large variations in reported rates. It has been recognized that the MoCA is an effective and brief tool for detecting cognitive impairment, and is better suited than the minimal state examination in mild cognitive impairment detection among people aged over 60.^{24,25} As MoCA has a

Table 2. Characteristics of the patients with and without PSCI at 3-month

Variables	With PSCI (n = 141)	Without PSCI (n = 120)	P value
Demographic characteristics			
Age, year*	67.7 ± 9.3	64.9 ± 9.0	.016
Male, n (%)	75 (53.2)	65 (54.2)	.875
Education <12 years, n (%)	93 (66.0)	63 (52.5)	.027
Vascular risk factors, n (%)			
Hypertension	90 (63.8)	55 (45.8)	.004
Diabetes mellitus	36 (25.5)	29 (24.2)	.799
Hyperlipidemia	22 (15.6)	18 (15.0)	.893
Coronary heart disease	19 (13.5)	12 (10.0)	.387
Smoking	58 (41.1)	38 (31.7)	.144
Clinical features			
Systolic blood pressure, mm Hg*	138.4 ± 16.0	137.4 ± 17.0	.742
Diastolic blood pressure, mm Hg*	80.5 ± 10.3	81.3 ± 10.9	.544
Time from onset to admission, day*	3.0 (2.0, 4.0)	3.0 (1.0, 4.0)	.307
NIHSS, score*	5.0 (3.0, 8.0)	4.0 (2.0, 6.0)	.023
White matter lesions, n (%)	60 (42.6)	37 (30.8)	.050
Previous antiplatelet therapy, n (%)	47 (33.3)	34 (28.3)	.384
Previous stain therapy, n (%)	38 (27.0)	29 (24.2)	.608
Previous antihypertension therapy, n (%)	46 (32.6)	38 (31.7)	.869
Admitted to nursing home after discharge, n (%)	9 (6.4)	13 (10.8)	.197
Stroke subtypes, n (%)			
Large artery atherosclerosis	68 (48.2)	49 (40.8)	
Cardioembolism	27 (19.1)	24 (20.0)	
Small artery occlusion	35 (24.8)	38 (31.7)	
Others	11 (7.8)	9 (7.5)	
Laboratory data			
Total cholesterol, mmol/L*	4.1 ± 1.1	3.9 ± 1.0	.213
Triglyceride, mmol/L*	1.4 (1.0, 1.8)	1.4 (1.1, 1.8)	.515
High-density lipoprotein, mmol/L*	1.1 ± 0.2	1.1 ± 0.2	.971
Low-density lipoprotein, mmol/L*	2.4 (2.0, 2.9)	2.4 (1.9, 2.9)	.780
Hs-CRP, mg/L*	5.3 (2.7, 8.9)	5.5 (2.3, 11.0)	.668
Homocysteine, umol/L*	15.4 ± 5.3	14.1 ± 4.9	.034
Fasting blood-glucose, mmol/L*	5.9 ± 2.5	5.9 ± 2.4	.871
Retinoic acid, ng/mL*	1.9 (0.8, 2.8)	2.4 (1.6, 3.9)	.001
Retinoic acid tertiles, n (%)			.003
First tertile	59 (41.8)	28 (23.3)	
Second tertile	45 (31.9)	42 (35.0)	
Third tertile	37 (26.2)	50 (41.7)	

Abbreviations: Hs-CRP, hypersensitive C-reactive protein; NIHSS, National Institutes of Health Stroke Scale; PSCI, poststroke cognitive impairment.

*Continuous variables were expressed as mean ± SD or median (interquartile range). Categorical variables were expressed as number (percentage).

sensitivity of 90% and a specificity of 87% when a cutoff score of 26 is used,¹⁹ our present study defined the PSCI as patients with total MoCA score <26.

RA, a major metabolite of retinol in diet, belongs to the retinoid class of chemical compounds. Experimental studies confirmed that RA plays essential and pleiotropic roles in organogenesis, including having distinct effects on neurogenesis and angiogenesis.^{26,27} In terms of stroke, animal studies suggested that RA had favorable effects: reduction of infarct volume and improvement in neurologic function.^{14,28} From bench to bedside, Tu et al found that decreased circulating level of RA was associated with increased risk of all-cause

and cardiovascular disease mortality in a cohort of patients with first-incident acute ischemic stroke.¹³ However, the data supporting the potential role of RA in the presence of PSCI in human populations is limited. In the present study, we provide the first clinical evidence demonstrating that serum RA is a significant protective factor for cognitive function, independent of vascular risk factors and stroke severity.

The pathophysiological mechanisms of the association between circulating RA level and cognitive function might be partly explained by blood-brain barrier (BBB) status. The intact BBB is essential in maintaining a stabilized milieu for synaptic and neuronal functions. BBB

Table 3. Logistic regression analysis for the association of retinoic acid level with PSCI at 3-month

Variables	OR (95% CI)	P value
Model 1		
Retinoic acid (continuous)	0.70 (0.58-0.83)	.001
Retinoic acid (tertiles)		
First tertile	2.85 (1.53-5.29)	.001
Second tertile	1.44 (0.80-2.63)	.648
Third tertile	Reference	
Model 2		
Retinoic acid (continuous)	0.77 (0.64-0.92)	.005
Retinoic acid (tertiles)		
First tertile	1.97 (1.01-3.83)	.046
Second tertile	1.23 (0.66-2.30)	0-.519
Third tertile	Reference	

Abbreviations: CI, confidence interval; OR, odds ratio; PSCI, poststroke cognitive impairment.

Model 1 adjusted for age, sex, and education status.

Model 2 adjusted for age, sex, education status, hypertension, NIHSS score, white matter lesions, and homocysteine level.

dysfunction may cause damage of the white matter and be related to a progression of cognitive impairment.^{29,30} As the administration of RA could ameliorate the BBB disruption following ischemic stroke in rats,³¹ we assumed that higher RA level may mediate the cognitive function by maintaining the integrity of BBB. Furthermore, the

neuroinflammatory response could also be mitigated with RA, which might lead to less hippocampal cell death and better behavioral recovery.³² Some studies also found that RA can improve neurobehavioral outcomes through attenuating glia-associated oxidative stress.^{33,34}

This prospective study was conducted with a homogeneous population of ischemic stroke patients, standardized protocols, rigid quality control procedures in data collection and cognitive function evaluation, all of which makes this group appropriate for examining the association between serum RA and the risk of PSCI. However, our study has several limitations. Firstly, patients with aphasia or dysarthria, and severe neurological deficit were excluded, as well as patients who lost to follow-up, which might result in selection bias and an underestimation of the actual PSCI incidence. Secondly, the metabolism of RA was affected by many other factors, such as retinol dehydrogenase 10, retinaldehyde dehydrogenase, and cytochrome P450. Thus, the effects of these confounding factors cannot be excluded from this study. Finally, we only conduct baseline measurements of serum RA concentration after stroke onset and therefore cannot clarify the variability of the RA level during the course of ischemic stroke. Therefore, the data and results should be interpreted with caution.

In summary, our study demonstrated that lower serum RA concentration was associated with increased risk of

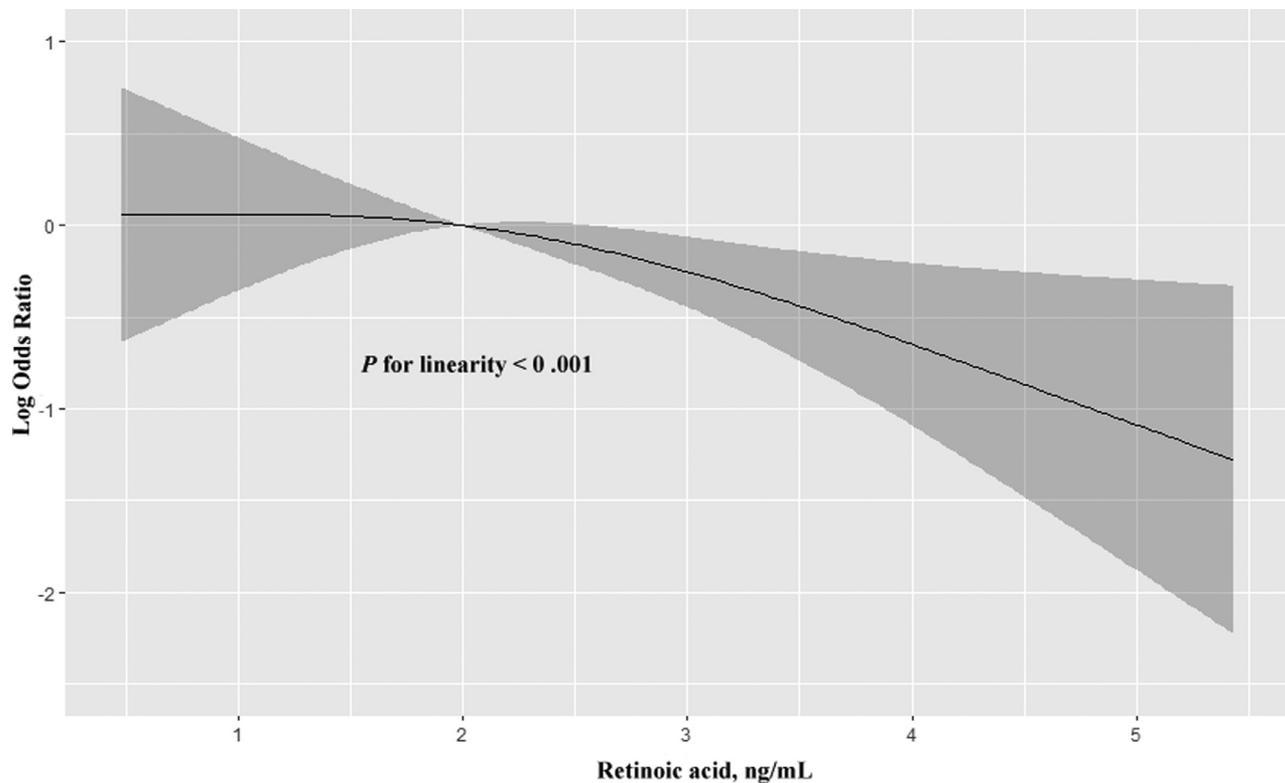


Figure 2. Association of serum RA level with risk of PSCI at 3 months. Odds ratio and 95% confidence intervals derived from restricted cubic spline regression, with knots placed at the 5th, 50th, and 95th percentiles of the distribution of serum RA. The reference point for serum RA is the midpoint (2.0 ng/mL) of the reference group from categorical analysis. PSCI, poststroke cognitive impairment.

3-month PSCI in a cohort of patients with ischemic stroke. Further large sample and well-controlled studies are needed to verify and extend our findings. In addition, for patients with ischemic stroke who had a decreasing RA level, whether supplementing with RA or vitamin A would be beneficial for cognitive impairment prevention remain to be determined with long-term controlled clinical trials.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

Declaration of Competing Interest

The authors do not have any conflicts of interest to declare.

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