Asian Journal of Psychiatry 46 (2019) 87–91

Contents lists available at ScienceDirect

Asian Journal of Psychiatry

journal homepage: www.elsevier.com/locate/ajp

# Association between serum retinoic acid levels and risk of post-stroke depression in patients with ischemic stroke

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ARTICLE INFO

*Keywords:*
Retinoic acid
Post-stroke depression
Ischemic stroke
Hamilton depression scale

ABSTRACT

Previous studies suggest that retinoic acid (RA) can exert neuroprotective function in ischemic stroke. However, its role in post-stroke depression (PSD) has still been unclear. We sought to investigate the relationship between circulating RA levels and PSD in patients with ischemic stroke. From September 2018 to March 2019, we prospectively screened patients with ischemic stroke who were hospitalized within 7 days of symptoms onset. RA levels were measured after admission. All patients were followed up at 3 months after stroke. Diagnosis of PSD was made in line with the Chinese version of Structured Clinical Interview of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition criteria. PSD risk was estimated using multivariable regression models. In total, 352 ischemic stroke patients were enrolled for the final analysis. Up to 3 months after symptoms onset, 102 subjects experienced PSD. PSD patients showed significantly lower RA levels at baseline as compared to non-PSD patients. In univariate logistic analysis, reduced levels of RA was a significant predictor of PSD. These results were further confirmed in multivariate regression additionally controlled for possible relevant confounders. Our study shows that decreased serum RA levels at admission might be associated with 3-month PSD in ischemic stroke patients.

## 1. Introduction

Post-stroke depression (PSD) is recognized as a common and serious neuropsychiatric disorder that affecting approximately one third of ischemic stroke survivors (Tang et al., 2005; Hackett and Pickles, 2014; Liu et al., 2018). Epidemiological studies demonstrate that PSD may interfere with stroke recovery and is associated with stroke severity and higher recurrence rate, cognitive impairment, and mortality (Yuan et al., 2012; Ayerbe et al., 2013b, 2014; Ojagbemi et al., 2014). Accordingly, it is important to early identify and manage those stroke survivors at high risk of developing PSD (Loubinoux et al., 2012; Robinson and Jorge, 2016). However, the potential etiological mechanisms of PSD remain unknown.

Retinoic acid (RA), the retinoid class of chemical compounds, is a major metabolite of vitamin A in the diets (von, 2012). In the clinical study, RA was reported to be neuroprotective in acute ischemic stroke patients and may contribute to stroke outcome (Tu et al., 2019). In addition, the molecular effects of RA in central nervous system have been explored in several diseases, including stroke and Alzheimer's disease (Ahlemeyer et al., 2001; Ashok et al., 2019; Kim et al., 2013). RA may mitigate neuro-inflammatory response, suppress cell death and promote behavioral recovery (Kim et al., 2013). Data from another *in vivo* experiment found that RA can improve neurobehavioral outcomes through attenuating glia-associated oxidative stress (Ahlemeyer et al., 2001). As a growing body of evidence suggest the involvement of neuro-inflammation and oxidative stress in the pathophysiology of PSD (Spalletta et al., 2006; Nabavi et al., 2015), we further hypothesized that the RA level may be mechanistically related to PSD. However, the potential role of RA on the development of PSD has not yet been determined. Our aim in this prospective study was therefore to evaluate the possible association between serum RA levels and the risk of PSD in a Chinese cohort sample.

## 2. Methods

### 2.1. Study population

Patients were hospitalized in Suzhou No.9 People's Hospital from

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https://doi.org/10.1016/j.ajp.2019.09.038
Received 30 July 2019; Received in revised form 30 September 2019; Accepted 30 September 2019

September 2018 to March 2019. Subjects older than 18 years with first-ever ischemic stroke within 7 days of onset were screened for the study upon hospital admission. Patients with unconsciousness, aphasia, severe neurological deficits, pre-stroke diagnosis of any psychiatric illness, malignant tumor, thyroid disease, autoimmune disease, immunosuppressive therapy, active or chronic inflammatory disorders, severe renal disease and hepatic disease were excluded. The study protocol was approved by the local Ethical Committee of Suzhou No.9 People's Hospital. Informed consents were obtained from all participants.

### 2.2. Collection of clinical data

All of the participants had face-to-face interviews with trained neurologists. Baseline characteristics on demographics (including age, sex, and years of education), vascular risk factors (including hypertension, diabetes mellitus, hyperlipidemia, and current smoking), medical histories, blood pressure, body mass index, stroke severity and stroke etiology were recorded. Severity of stroke was measured by the National Institutes of Health Stroke Scale (NIHSS) (Goldstein and Samsa, 1997) at admission. Stroke subtypes were classified according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria (Adams et al., 1993). We also estimated the volume of the infarction using the DWI based Alberta Stroke Program Early CT (DWI-ASPECT) (Lassalle et al., 2016). The DWI-ASPECT score was dichotomized as 0–7vs. 8–10.

### 2.3. Sample collection and RA measurement

With informed consents, peripheral blood samples were obtained in EDTA tubes and were collected within 24 h after admission. The specimens were centrifuged at 1500 *g* for 10 min and the isolated serum was stored at −80 °C before being analyzed. RA levels were measured using commercially available enzyme-linked immunosorbent assay kits according to the manufacturer's instructions (Cat. MBS705877, MyBioSource, San Diego, CA).RA concentrations were determined induplicate in serum aliquots that had undergone 1 or 2 freeze-thaw cycles. No significant cross-reactivity or interference between human RA and other analogs was observed. The coefficient of variation for the inter-assay replicate samples was < 8%. All samples were measured by the same laboratory technician who was blinded to clinical data.

### 2.4. Neuropsychiatric assessment and diagnosis of PSD

At follow-up of 3 months, neuropsychiatric assessments were performed by trained psychiatrists who were blinded to the laboratory results. The 17-item Hamilton Depression Scale (HAMD) was used to screen for depression symptoms. Patients were further scored by the Chinese version of the Structured Clinical Interview for DSM-IV for diagnosis of PSD if HAMD score was > 7 (Zhang et al., 2017). Furthermore, we used the Hamilton Anxiety Rating Scale and Mini-Mental State Examination to assess the anxiety symptoms and cognitive function in all patients.

### 2.5. Statistical analysis

All data were statistically analyzed using the Statistical Package for the Social Sciences (SPSS 23.0; Chicago, IL, USA). All continuous variables were presented as mean ± SD or median (interquartile range). Comparisons between groups were performed using chi-square, t-test, one-way ANOVA, or Kruskal–Wallis tests as appropriate. Univariable and multivariable logistic regression models were used to assess the prognostic value of serum RA, where RA was used as a categorical variable with patients in the fourth quartile as the reference category. Multivariable analyses were first adjusted for age, sex and educational status (Model 1), additionally adjusted for systolic blood pressure and diabetes mellitus (Model 2), and additionally adjusted for all variables (including age, sex, educational status, systolic blood pressure, diabetes mellitus, baseline NIHSS score, white matter lesions, silent lacunar infarction, DWI-ASPECT 0–7,Hs-CRP and High-density lipoprotein levels; Model 3). Two-sided $P < 0.05$ was considered statistically significant.

## 3. Results

Overall, 352ischemic stroke patients (196 male; mean age, 63.4 ± 9.5 years) were included for the final analysis. Study recruitment profile was shown in Fig. 1. The median serum RA level was 2.7 ng/mL, with quartile levels as follows: quartile 1 (< 1.6 ng/mL), quartile 2 (1.6 ng/mL–2.6 ng/mL), quartile 3 (2.7 ng/mL–4.4 ng/mL), and quartile 4 (> 4.4 ng/mL). Table 1 demonstrated the baseline data of the study population according to quartile of RA. Decreasing RA levels showed a significant correlation with age ($P = 0.005$), diabetes mellitus ($P = 0.041$), coronary heart disease ($P = 0.002$), baseline

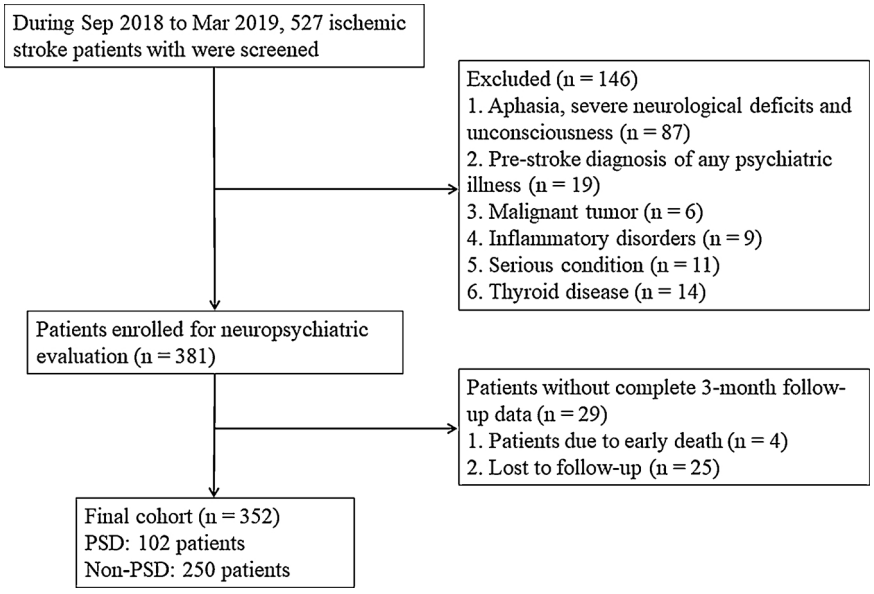


**Fig. 1.** Flow chart of patient inclusion.

**Table 1**
Clinical and demographic characteristics of the patients according to the retinoic acid quartiles.

| Variables | Quartile 1 (< 1.6, ng/mL) | Quartile 2 (1.6–2.6, ng/mL) | Quartile 3 (2.7–4.4, ng/mL) | Quartile 4 (> 4.4, ng/mL) | *P* value |
|---|---|---|---|---|---|
| No. of patients | 87 | 89 | 90 | 86 | |
| Age, year | 64.9 ± 9.0 | 65.2 ± 8.8 | 62.5 ± 9.2 | 61.2 ± 10.0 | 0.005 |
| Male, n (%) | 40 (46.0) | 58 (65.2) | 50 (55.6) | 48 (55.8) | 0.107 |
| Education < 12 years, n (%) | 48 (55.2) | 54 (60.7) | 44 (48.9) | 42 (48.8) | 0.326 |
| Current smoking, n (%) | 28 (32.2) | 44 (49.4) | 36 (40.0) | 38 (44.2) | 0.124 |
| Hypertension, n (%) | 64 (73.6) | 61 (68.5) | 68 (75.6) | 56 (65.1) | 0.413 |
| Diabetes mellitus, n (%) | 31 (35.6) | 21 (23.6) | 16 (17.8) | 19 (22.1) | 0.041 |
| Hyperlipidemia, n (%) | 21 (24.1) | 20 (22.5) | 20 (22.2) | 12 (14.0) | 0.347 |
| Coronary heart disease, n (%) | 11 (12.6) | 19 (21.3) | 12 (13.3) | 2 (2.3) | 0.002 |
| Previous antiplatelet therapy, n (%) | 12 (13.8) | 12 (13.5) | 13 (14.4) | 14 (16.3) | 0.954 |
| Previous stain therapy, n (%) | 13 (14.9) | 8 (9.0) | 13 (14.4) | 6 (7.0) | 0.251 |
| Systolic blood pressure, mmHg | 138.8 ± 21.4 | 138.1 ± 16.7 | 137.2 ± 17.4 | 135.8 ± 16.9 | 0.734 |
| Diastolic blood pressure, mmHg | 81.0 ± 10.6 | 83.2 ± 10.2 | 80.9 ± 9.8 | 82.0 ± 9.5 | 0.415 |
| Body mass index, kg/m$^2$ | 25.4 ± 3.4 | 24.8 ± 2.8 | 24.2 ± 3.9 | 24.4 ± 3.6 | 0.062 |
| Baseline NIHSS, score | 6.0 (4.0, 8.0) | 5.0 (2.0, 7.0) | 4.0 (2.0, 6.0) | 3.0 (2.0, 7.0) | 0.001 |
| White matter lesions, n (%) | 39 (44.8) | 39 (43.8) | 49 (54.4) | 33 (38.4) | 0.188 |
| Silent lacunar infarction, n (%) | 49 (56.3) | 45 (50.6) | 44 (48.9) | 43 (50.0) | 0.762 |
| DWI-ASPECT 0–7*, n (%) | 33 (42.3) | 45 (50.6) | 33 (39.3) | 16 (19.0) | 0.002 |
| Hamilton Anxiety Rating Scale, score | 7.0 (6.0,10.0) | 8.0 (6.0,12.0) | 7.0 (5.5,10.0) | 7.0 (6.0, 9.0) | 0.207 |
| Mini-Mental State Examination, score | 26.0 (23.0,28.0) | 27.0 (25.0,28.0) | 27.0 (25.0,28.0) | 26.0 (24.0,28.0) | 0.092 |
| Hamilton Depression Scale, score | 7.0 (4.0,17.0) | 6.0 (4.0,14.0) | 5.0 (4.0,7.0) | 5.0 (4.0,8.0) | 0.003 |
| Post-stroke depression, n (%) | 42 (48.3) | 27 (30.3) | 17 (18.9) | 16 (18.6) | 0.001 |
| Ischemic stroke subtypes, n (%) | | | | | 0.162 |
| Atherothrombotic infarction | 37 (42.5) | 45 (50.6) | 41 (45.6) | 32 (37.2) | |
| Cardioembolic infarction | 22 (25.3) | 15 (16.9) | 16 (17.8) | 14 (16.3) | |
| Lacunar infarction | 21 (24.1) | 20 (22.5) | 25 (27.8) | 36 (41.9) | |
| Other types of infarction | 7 (8.0) | 9 (10.1) | 8 (8.9) | 4 (4.7) | |
| Laboratory data | | | | | |
| Fasting blood-glucose, mmol/L | 5.5 ± 1.9 | 5.6 ± 1.8 | 5.2 ± 1.3 | 5.2 ± 1.2 | 0.163 |
| Homocysteine, umol/L | 15.6 ± 8.6 | 15.2 ± 7.0 | 16.1 ± 6.2 | 15.1 ± 7.6 | 0.776 |
| Hs-CRP, mg/L | 4.0 (1.0, 6.3) | 4.0 (1.2, 7.0) | 3.0 (1.0, 7.2) | 3.0 (1.5, 5.7) | 0.497 |
| Total cholesterol, mmol/L | 4.1 ± 1.1 | 4.1 ± 1.0 | 3.9 ± 1.0 | 4.0 ± 1.1 | 0.429 |
| Triglyceride, mmol/L | 1.4 (1.1, 1.9) | 1.3 (1.0, 1.7) | 1.4 (0.9, 1.9) | 1.3 (1.0, 1.8) | 0.409 |
| High-density lipoprotein, mmol/L | 1.0 ± 0.2 | 1.0 ± 0.3 | 1.0 ± 0.2 | 1.0 ± 0.2 | 0.474 |
| Low-density lipoprotein, mmol/L | 2.3 (1.9, 3.0) | 2.4 (1.8, 2.9) | 2.1 (1.8, 2.9) | 2.5 (2.0, 3.1) | 0.172 |

Abbreviations: DWI-ASPECT, DWI based Alberta Stroke Program Early CT; Hs-CRP, Hyper-sensitive C-reactive protein; NIHSS, National Institutes of Health Stroke Scale.

* Data is unavailable in 21 patients.

NIHSS score ($P = 0.001$), DWI-ASPECT 0–7($P = 0.002$), HAMD score ($P = 0.003$), and PSD ($P = 0.001$).

Up to 3 months after stroke onset, 102 patients (28.9%) experienced PSD. Comparisons of baseline characteristics between patients with and without PSD were illustrated in Table 2. Compared with patients without PSD, those with it were older ($P = 0.003$), had higher prevalence of education < 12 years ($P = 0.045$), more likely to develop diabetes mellitus ($P = 0.043$), white matter lesions ($P = 0.023$), silent lacunar infarction ($P = 0.025$), DWI-ASPECT 0–7 ($P = 0.001$), and had higher NIHSS score ($P = 0.025$) and Hs-CRP level ($P = 0.023$). Also, PSD patients had significantly lower level of RA at baseline as compared to non-PSD patients (median RA levels, 1.9 ng/mL *vs* 2.9 ng/mL, $P = 0.001$).

Table 3 summarized the results of the binary logistic regression of the PSD. In univariate regression analysis, the first quartile of RA level (fourth quartile used as the reference value) was identified as a significant predictor for PSD (odds ratio 4.08, 95% confidence intervals 2.06–8.12) in patients with ischemic stroke. After controlling for age, sex, educational status, systolic blood pressure, diabetes mellitus, baseline NIHSS score, stroke subtypes, white matter lesions, silent lacunar infarction, DWI-ASPECT 0–7, Hs-CRP and high-density lipoprotein levels, the association between circulating RA levels and PSD remained statistically significant (Model 3, *P* for liner trend = 0.013).

## 4. Discussion

The present observational study demonstrated the significant association between serum RA levels and PSD. Lower circulating RA level may be an independent predictor of PSD, independent of established conventional risk factors. Therefore, it may be a useful and novel therapeutic target for the treatment of PSD.

Currently, despite the preexisted vast literatures, it remains difficult to determine the true incidence rates of PSD, possibly due to the different study designs, diagnostic and psychiatric assessment methods, time of neuropsychiatric evaluation, and source of subject samples. A prior meta-analysis of 50 clinical studies, which included 20,293 patients, reported that the pooled PSD prevalence was approximately 30% at any time point within 5 years (Ayerbe et al., 2013a). Our study demonstrated that the prevalence of PSD was 28.9% at 3 months, which was in agreement with the results of recent studies (Gu et al., 2015; Zhang et al., 2017).

There was no significant relationship between MMSE score and PSD, which was not in accordance with previous studies (Narushima et al., 2003; Hackett and Anderson, 2005; Ayerbe et al., 2013b). Naiushima, et al. reported that the MMSE score of PSD patient was generally lower than those who weren't depressed (Narushima et al., 2003). This may be partially explained by differences of study population and methods. In our study, we found that patients with PSD had higher infarct volumes and increased stroke severity, which were negatively associated with RA levels. Therefore, we hypothesized that RA may cause 3-month PSD through affecting stroke severity. Nonetheless, RA levels at admission were independently associated with PSD after adjustment for potential variables (including DWI-ASPECT score and baseline NIHSS score). Therefore, other potential causal mechanisms may be involved.

Although the biological mechanism by which decreased RA levels affect PSD is still unclear, several biological mechanisms are noted.

**Table 2**
Comparison of baseline characteristics between patients with and without PSD.

| Variables | With PSD (n = 102) | Without PSD (n = 250) | *P* value |
|---|---|---|---|
| Age, year | 65.8 ± 9.2 | 62.6 ± 9.5 | 0.003 |
| Male, n (%) | 54 (52.9) | 142 (56.8) | 0.509 |
| Education < 12 years, n (%) | 63 (61.8) | 125 (50.0) | 0.045 |
| Current smoking, n (%) | 39 (38.2) | 107 (42.8) | 0.430 |
| Hypertension, n (%) | 72 (70.6) | 177 (70.8) | 0.968 |
| Diabetes mellitus, n (%) | 34 (33.3) | 57 (22.8) | 0.043 |
| Hyperlipidemia, n (%) | 17 (16.7) | 56 (22.4) | 0.229 |
| Coronary heart disease, n (%) | 17 (16.7) | 27 (10.8) | 0.131 |
| Previous antiplatelet therapy, n (%) | 16 (15.7) | 35 (14.0) | 0.683 |
| Previous stain therapy, n (%) | 10 (9.8) | 30 (12.0) | 0.556 |
| Systolic blood pressure, mmHg | 140.3 ± 20.1 | 136.3 ± 17.2 | 0.061 |
| Diastolic blood pressure, mmHg | 81.6 ± 10.1 | 81.7 ± 10.0 | 0.997 |
| Body mass index, kg/m$^2$ | 24.8 ± 4.5 | 24.5 ± 3.0 | 0.706 |
| Baseline NIHSS, score | 5.0 (3.0, 8.0) | 5.0 (2.0, 7.0) | 0.007 |
| White matter lesions, n (%) | 56 (54.9) | 104 (41.6) | 0.023 |
| Silent lacunar infarction, n (%) | 62 (60.8) | 119 (47.6) | 0.025 |
| DWI-ASPECT 0–7*, n (%) | 50 (53.8) | 77 (32.4) | 0.001 |
| Hamilton Anxiety Rating Scale, score | 7.5 (6.0,12.0) | 7.0 (6.0, 9.0) | 0.080 |
| Mini-Mental State Examination, score | 26.0 (23.0,28.0) | 27.0 (24.0, 28.0) | 0.112 |
| Ischemic stroke subtypes, n (%) | | | 0.897 |
| Atherothrombotic infarction | 47 (46.1) | 108 (43.2) | |
| Cardioembolic infarction | 19 (18.6) | 48 (19.2) | |
| Lacunar infarction | 27 (26.5) | 75 (30.0) | |
| Other types of infarction | 9 (8.8) | 19 (7.6) | |
| Ischemic area, n (%) | | | 0.536 |
| Frontal lobe | 24 (23.5) | 46 (18.4) | |
| Parietal lobe | 8 (7.8) | 27 (10.8) | |
| Basal ganglia | 27 (26.5) | 79 (31.6) | |
| Posterior fossa | 16 (15.7) | 44 (17.6) | |
| Other | 27 (26.5) | 54 (21.6) | |
| Laboratory data | | | |
| Fasting blood glucose, mmol/L | 5.3 ± 1.7 | 5.4 ± 1.5 | 0.709 |
| Homocysteine, umol/L | 15.0 ± 6.2 | 15.7 ± 7.7 | 0.381 |
| Hs-CRP, mg/L | 4.7 (1.2, 7.1) | 3.2 (1.0, 6.0) | 0.023 |
| Total cholesterol, mmol/L | 4.0 ± 1.1 | 4.0 ± 1.1 | 0.858 |
| Triglyceride, mmol/L | 1.5 (1.1, 1.8) | 1.3 (1.0, 1.8) | 0.088 |
| High-density lipoprotein, mmol/L | 1.0 ± 0.3 | 1.1 ± 0.2 | 0.084 |
| Low-density lipoprotein, mmol/L | 2.5 (1.9, 3.1) | 2.3 (1.8, 2.9) | 0.266 |
| Retinoic acid, ng/mL | 1.9 (1.2, 3.8) | 2.9 (1.9, 4.7) | 0.001 |
| Retinoic acid, n (%) | | | 0.001 |
| Quartile 1 | 42 (41.2) | 45 (18.0) | |
| Quartile 2 | 27 (26.5) | 62 (24.8) | |
| Quartile 3 | 17 (16.7) | 73 (29.2) | |
| Quartile 4 | 16 (15.7) | 70 (28.0) | |

Abbreviations: DWI-ASPECT, DWI based Alberta Stroke Program Early CT; Hs-CRP, Hyper-sensitive C-reactive protein; NIHSS, National Institutes of Health Stroke Scale; PSD, Post-stroke depression.

* Data is unavailable in 21 patients.

Firstly, growing evidence suggests that cerebral inflammatory response may promote depression progression (Lotrich, 2015). It is already known that acute stroke triggers widespread neuroinflammation, which is characterized by rapid up-regulation of pro-inflammatory cytokines, disrupting blood-brain-barrier and inducing neurodegeneration (Kriz and Lalancette-Hébert, 2009; Jin et al., 2013). Previous studies show that RA could improve blood-brain barrier integrity and decrease inflammatory responses of macrophages, contributing to less hippocampal cell death and better behavioral recovery (Kim et al., 2013; Kong et al., 2015). Therefore, RA may be able to inhibit neuroinflammation-related depression. Secondly, oxidative stress causes damage to lipids, proteins, DNA, and mitochondria and eventually results in neurodegeneration and depression stemming from oxidative stress-related neurotoxicity (Ng et al., 2008; Smaga et al., 2015). RA has multiple antioxidant roles including the scavenging of free radicals and reactive oxygen species, and the preservation of SOD protein level (Ahlemeyer et al., 2001). Thus, the antioxidant characteristics of RA may protect against the development of PSD. In addition, RA signaling plays an important role in the establishment of neurotransmitter systems (Zieger and Schubert, 2017), which is involved in the pathophysiology of PSD (Fang and Cheng, 2009; Loubinoux et al., 2012; Robinson and Jorge, 2016). This also provides the basis for a possible causal correlation between RA and PSD.

However, some limitations in this study should be acknowledged. First, the study was performed in one stroke center, limiting the generalizability of the results to the general population. Second, patients with aphasia, severe neurological deficits or a serious condition were excluded, as well as patients who failed to assess neuropsychiatric assessment, which might lead to an underestimation of the actual incidence of PSD. Third, serum levels of RA were only measured within first 24 h after admission and, hence, this study yielded no data regarding when and how long biomarkers were changed in these patients. It is necessary to conduct a further longitudinal study assessing how RA level changes over time after stroke to provide better prognostic information. Finally, our study did not collect information on nutritional status, which may influence circulating RA status. As was mentioned above, our study should be considered preliminary. Further prospective studies with larger cohorts of subjects are necessary to confirm this association.

In summary, the present study shows a negative relationship between circulating RA levels at admission and the risk of 3-month PSD in a cohort of patients with acute ischemic stroke. Furthermore, for ischemic stroke patients who had a reducing level of RA, whether supplementation of RA or vitamin A may offer a potential prevention or therapeutic target for PSD should be further detected with randomized clinical trials.

## Data availability

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

## Funding source

None.

## Financial disclosure

This work is not financially supported by any project.

**Table 3**
Odds ratio for PSD according to the RA quartiles.

| | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | *P* for linear trend |
|---|---|---|---|---|---|
| Number of PSD | 42/87 | 27/89 | 17/90 | 16/86 | |
| RA levels | < 1.6, ng/mL | 1.6–2.6,ng/mL | 2.7–4.4, ng/mL | > 4.4, ng/mL | |
| Unadjusted model | 4.08 (2.06–8.12) | 1.91 (0.94–3.86) | 1.03 (0.48–2.17) | Reference | 0.001 |
| Model 1 | 4.32 (2.13–8.75) | 1.96 (0.95–4.03) | 1.04 (0.47–2.21) | Reference | 0.001 |
| Model 2 | 3.52 (1.74–7.11) | 1.58 (0.76–3.26) | 0.98 (0.46–2.13) | Reference | 0.007 |
| Model 3 | 2.34 (1.08–5.06) | 1.11 (0.49–2.48) | 0.63 (0.26–1.51) | Reference | 0013 |

Abbreviations: PSD, Post-stroke depression; RA, Retinoic acid.

## Contributors

ZD: designed the study, conducted statistical analysis, and wrote the draft of the manuscript. WS: conducted statistical analysis and acquired data. HD: acquired data. MX: acquired data. JF: manuscript revision. CQ: acquired data. YL: conceived and designed the study, conducted statistical analysis and supervised this study.

## Declaration of Competing Interest

All the authors declare that there is no conflict of interest.

## Acknowledgments

We express our gratitude to all the researchers and patients who participated in this study.

## References

Adams Jr., H., Bendixen, B., Kappelle, L., Biller, J., Love, B., Gordon, D., et al., 1993. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in acute stroke treatment. Stroke 24, 35–41.

Ahlemeyer, B., Bauerbach, E., Plath, M., Steuber, M., Heers, C., Tegtmeier, F., et al., 2001. Retinoic acid reduces apoptosis and oxidative stress by preservation of SOD protein level. Free Radic. Biol. Med. 30, 1067–1077.

Ashok, A., Naaz, S., Kota, L.N., Sen, S., Purushottam, M., Faruq, M., et al., 2019. Does retinoic acid reverse cell cycle dysregulation in Alzheimer's disease lymphocytes? Asian J. Psychiatr. 39, 174–177.

Ayerbe, L., Ayis, S., Crichton, S., Wolfe, C., Rudd, A., 2013a. The natural history of depression up to 15 years after stroke: the South London Stroke Register. Stroke 44, 1105–1110.

Ayerbe, L., Ayis, S., Wolfe, C., Rudd, A., 2013b. Natural history, predictors and outcomes of depression after stroke: systematic review and meta-analysis. Br. J. Psychiatry 202, 14–21.

Ayerbe, L., Ayis, S., Crichton, S., Wolfe, C., Rudd, A., 2014. The long-term outcomes of depression up to 10 years after stroke; the South London Stroke Register. J Neurol Neurosurg Psychiatry 85, 514–521.

Fang, J., Cheng, Q., 2009. Etiological mechanisms of post-stroke depression: a review. Neurol. Res. 31, 904–909.

Goldstein, L., Samsa, G., 1997. Reliability of the National Institutes of Health Stroke Scale. Extension to non-neurologists in the context of a clinical trial. Stroke 28, 307–310.

Gu, Y., Han, B., Wang, L., Chang, Y., Zhu, L., Ren, W., et al., 2015. Low serum levels of uric acid are associated with development of poststroke depression. Medicine (Baltimore) 94, e1897.

Hackett, M., Anderson, C., 2005. Predictors of depression after stroke: a systematic review of observational studies. Stroke 36, 2296–2301.

Hackett, M., Pickles, K., 2014. Part I: frequency of depression after stroke: an updated systematic review and meta-analysis of observational studies. Int. J. Stroke 9, 1017–1025.

Jin, R., Liu, L., Zhang, S., Nanda, A., Li, G., 2013. Role of inflammation and its mediators in acute ischemic stroke. J. Cardiovasc. Transl. Res. 6, 834–851.

Kim, J., Yu, K., Jeong, J., Lee, N., Lee, J., Jeong, Y., et al., 2013. All-trans-retinoic acid rescues neurons after global ischemia by attenuating neuroinflammatory reactions. Neurochem. Res. 38, 2604–2615.

Kong, L., Wang, Y., Wang, X., Wang, X., Zhao, Y., Wang, L., et al., 2015. Retinoic acid ameliorates blood-brain barrier disruption following ischemic stroke in rats. Pharmacol. Res. 99, 125–136.

Kriz, J., Lalancette-Hébert, M., 2009. Inflammation, plasticity and real-time imaging after cerebral ischemia. Acta Neuropathol. 117, 497–509.

Lassalle, L., Turc, G., Tisserand, M., Charron, S., Roca, P., Lion, S., et al., 2016. ASPECTS (Alberta stroke program early CT score) assessment of the perfusion-diffusion mismatch. Stroke 46, 2553–2558.

Liu, Z., Cai, Y., He, J., 2018. High serum levels of 8-OHdG are an independent predictor of post-stroke depression in Chinese stroke survivors. Neuropsychiatr. Dis. Treat. 14, 587–596.

Lotrich, F., 2015. Inflammatory cytokine-associated depression. Brain Res. 1617, 113–125.

Loubinoux, I., Kronenberg, G., Endres, M., Schumann-Bard, P., Freret, T., Filipkowski, R., et al., 2012. Post-stroke depression: mechanisms, translation and therapy. J. Cell. Mol. Med. 16, 1961–1969.

Nabavi, S., Dean, O., Turner, A., Sureda, A., Daglia, M., Nabavi, S., 2015. Oxidative stress and post-stroke depression: possible therapeutic role of polyphenols? Curr. Med. Chem. 22, 343–351.

Narushima, K., Chan, K., Kosier, J., Robinson, R., 2003. Does cognitive recovery after treatment of poststroke depression last? A 2-year follow-up of cognitive function associated with poststroke depression. Am. J. Psychiatry 160, 1157–1162.

Ng, F., Berk, M., Dean, O., Bush, A., 2008. Oxidative stress in psychiatric disorders: evidence base and therapeutic implications. Int. J. Neuropsychopharmacol. 11, 851–876.

Ojagbemi, A., Akinyemi, R., Baiyewu, O., 2014. Cognitive dysfunction and functional limitations are associated with major depression in stroke survivors attending rehabilitation in Nigeria. Neuro. Rehabilitation 34, 455–461.

Robinson, R., Jorge, R., 2016. Post-stroke depression: a review. Am. J. Psychiatry 173, 221–231.

Smaga, I., Niedzielska, E., Gawlik, M., Moniczewski, A., Krzek, J., Przegaliński, E., et al., 2015. Oxidative stress as an etiological factor and a potential treatment target of psychiatric disorders. Part 2. Depression, anxiety, schizophrenia and autism. Pharmacol. Rep. 67, 569–580.

Spalletta, G., Bossù, P., Ciaramella, A., Bria, P., Caltagirone, C., Robinson, R., 2006. The etiology of poststroke depression: a review of the literature and a new hypothesis involving inflammatory cytokines. Mol. Psychiatry 11, 984–991.

Tang, W.K., Chan, S.S., Chiu, H.F., Ungvari, G.S., Wong, K.S., Kwok, T.C., et al., 2005. Poststroke depression in Chinese patients: frequency, psychosocial, clinical, and radiological determinants. J. Geriatr. Psychiatry Neurol. 18, 45–51.

Tu, W., Qiu, H., Zhang, Y., Cao, J., Wang, H., Zhao, J., et al., 2019. Lower serum retinoic acid level for prediction of higher risk of mortality in ischemic stroke. Neurology 92, e1678–e1687.

Von, L.J., 2012. Provitamin A metabolism and functions in mammalian biology. Am. J. Clin. Nutr. 96, 1234S–1244S.

Yuan, H., Wang, C., Zhang, N., Bai, Y., Shi, Y., Zhou, Y., et al., 2012. Poststroke depression and risk of recurrent stroke at 1 year in a Chinese cohort study. PLoS One 7, e46906.

Zhang, X., Tang, Y., Xie, Y., Ding, C., Xiao, J., Jiang, X., 2017. Total magnetic resonance imaging burden of cerebral small-vessel disease is associated with post-stroke depression in patients with acute lacunar stroke. Eur. J. Neurol. 24, 374–380.

Zieger, E., Schubert, M., 2017. New insights into the roles of retinoic acid signaling in nervous system development and the establishment of neurotransmitter systems. Int. Rev. Cell Mol. Biol. 330, 1–84.