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The association between circulating Hcy and Lp-PLA2 levels and poststroke depression

A meta-analysis

Yongjun Tao, MD[a], Wenmin Wang, MD[a], Jiang Zhao, BD[a], Xiaohui Xu, BD[a], Jinfeng Ke, MD[a], Xiaoyong Ke, MD[a,*]

Abstract

Objective: To analyze the correlation between circulating homocysteine (Hcy) and lipoprotein-associated phospholipase A2 (Lp-PLA2) levels and poststroke depression (PSD).

Materials and methods: Chinese (Chinese National Knowledge Infrastructure, Wanfang, and VIP) and English (PubMed, EMBASE, MEDLINE, and Cochrane Library) databases on the correlation between circulating Hcy and Lp-PLA2 and PSD were collected. Meta-analysis was performed to compare the distinctions in circulating Hcy and Lp-PLA2 levels between PSD and non-PSD groups. Meta-analysis was conducted by using STATA 15.0 software.

Results: A total of 20 literatures were included in this study. The level of circulating Lp-PLA2 in the PSD group was obviously higher than that in the non-PSD group (weighted mean differences: 2.75, 95%CI: 0.10–5.39, $P = .002$), which was an independent predictor of PSD (effect size = 0.05, 95%CI: 0.03, 0.07, $P < .001$). The level of circulating Hcy in the PSD group was obviously higher than that in the non-PSD group (weighted mean differences = 1.41, 95%CI: 1.01, 1.81, $P < .001$), which was an independent influencing factor for the occurrence of PSD (effect size = 0.07, 95%CI: 0.04, 0.09, $P = .011$).

Conclusion: Circulating Hcy and Lp-PLA2 levels are linked to the development of PSD, and can be applied as predictive or diagnostic indicators.

Abbreviations: ES = effect size, Hcy = homocysteine, Lp-PLA2 = lipoprotein-associated phospholipase A2, PSD = poststroke depression, WMD = weighted mean differences.

Keywords: correlation, homocysteine, lipoprotein-associated phospholipase A2, poststroke depression

1. Introduction

Stroke is the second leading cause of death and the first leading cause of disability in the world, and the focus of prevention and treatment of cardiovascular and cerebrovascular diseases worldwide, resulting in a heavy disease burden.[1,2] About 70% of the patients who survived stroke had sequelae or complications, such as hemiplegia, aphasia, swallowing dysfunction, balance disorder, poststroke depression, etc, which required systematic rehabilitation.[3–5] Depression is a common complication of stroke, namely post stroke depression (PSD). PSD is a series of mental symptoms, physical symptoms and complex emotional disorders complicated with cerebrovascular disease. The main clinical manifestations are persistent depression, thinking disorders, mental retardation and reduced will activity. In severe cases, there may be behaviors such as weariness, despair, and suicide.[6] Studies have shown that the incidence of PSD in stroke patients is about 10.5–35.6%, which is specifically affected by diagnostic criteria.[7] It can occur at various stages after the onset of the disease, mostly within 1 year after the onset of the disease, with the highest within 3 months.[8] PSD can seriously affect the effects of poststroke treatment and rehabilitation, reduce patients' quality of life, lead to or aggravate poststroke disability, and affect patients' cognitive function recovery.[9] Early prediction or diagnosis of PSD and reasonable treatment and rehabilitation measures are of great significance to guarantee the effect of neurological recovery in poststroke patients. Recent studies have shown that levels of circulating homocysteine (Hcy) and lipoprotein-associated phospholipase A2 (Lp-PLA2) in early postmortem stroke patients are linked to the development of PSD. Both of them may be of great value in the prediction, diagnosis, treatment and follow-up of PSD,[10,11] but there is still a lack of evidence-based medical evidence. In this study, a meta-analysis was conducted to investigate the correlation between circulating Hcy and Lp-PLA2 levels and PSD occurrence.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] *Department of Neurology, Taizhou Municipal Hospital, Taizhou, Zhejiang, China.*

** Correspondence: Xiaoyong Ke, Department of Neurology, Taizhou Municipal Hospital, Taizhou, Zhejiang 318000, China (e-mail: kxy12300@126.com).*

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2. Materials and methods

This study was written according to the PRISMA 2020 checklist.[12]

2.1. Inclusion criteria

(1) Study design: case–control study. (2) Study subjects: stroke patients, including ischemic stroke and hemorrhagic stroke, 18 years old at least. (3) The diagnostic criteria of PSD are described. (4) At least one of the following parameters was described: (a) circulating Lp-PLA2 levels in PSD and non-PSD groups; (b) multivariate analysis of the effects of circulating Lp-PLA2 levels on PSD; (c) circulating Hcy levels in PSD and non-PSD groups.

2.2. Exclusion criteria

(1) For duplicate reports of the same study population, literature with the maximum sample volume was enrolled in this case. (2) Failure to report the research results or the results do not meet the requirements. (3) The design method is not clear and the reliability is insufficient; (4) reviews, case reports, animal tests; (5) full texts cannot be obtained.

2.3. Literature search

Search Chinese (Chinese National Knowledge Infrastructure, Wanfang, and VIP) and English (PubMed, EMBASE, MEDLINE, and Cochrane Library) databases, and the time period for conducting the search was from their inception to December 2022. Key words: homocysteine/Hcy; lipoprotein-associated phospholipase A2/Lp-PLA2; post stroke depression/PSD.

2.4. Literature screening and data extraction

Two researchers conducted literature screening independently, and data extraction will be carried out for the included literature. If there is any disagreement, a third researcher will be consulted. A data collection table was developed for the authors, year of publication, sample size, number of PSD cases, number of non-PSD cases, circulating Hcy levels, circulating Lp-PLA2 levels, and analysis results of influencing factors.

2.5. Literature quality evaluation

The Newcastle-Ottawa Scale (NOS) was applied for literature quality evaluation. The full score of this scale was 9, and the score ≥ 7 was considered as high-quality literature.[13]

2.6. Statistical analysis

STATA 15.0 software was applied for data analysis. The quantitative indicators (circulating Hcy and Lp-PLA2 levels) were weighted mean difference (WMD) as effect statistics. Effect size (ES) was applied as the effect statistic in the results of multi-factor analysis. Cochrane Q test was applied for literature heterogeneity analysis. $P > .1$ or $I^2 < 50\%$: fixed-effects model, $P < .1$ and $I^2 > 50\%$: random-effects model. Egger test was applied to calculate publication bias, and funnel plots were drawn to observe publication bias.

2.7. Ethics and dissemination

Ethic approval was not required because this study only involved published data.

3. Results

3.1. Basic information

The study included a total of 20 papers that met the inclusion and exclusion criteria, 14 in Chinese and 6 in English (Fig. 1). Twenty papers included a total of 3714 stroke patients, 1560 with PSD and 2245 with non-PSD.[10,11,14–31] Twenty papers had NOS scores of 4–9, 12 papers had ≥7, and the percentage of high-quality literature was 60%. The basic characteristics of the literature are shown in Table 1.

3.2. Meta-analysis results

3.2.1. Correlation of circulating Lp-PLA2 with PSD. Three papers described distinctions in circulating Lp-PLA2 levels between the PSD and non-PSD groups. Meta-analysis revealed that circulating Lp-PLA2 levels were obviously higher in the PSD group than in the non-PSD group (WMD = 2.75, 95% CI: 0.10–5.39, $P = .002$), as shown in Figure 2. All the above-mentioned literature also described the results of multivariate analysis of the effect of circulating Lp-PLA2 levels on PSD, with no heterogeneity between studies ($I^2 = 9.9\%$, $P = .329$). The results of the fixed-effects model analysis revealed that circulating Lp-PLA2 levels were an independent influence on PSD (ES = 0.05, 95% CI: 0.03–0.07, $P < .001$), as shown in Figure 3.

3.2.2. Correlation of circulating Hcy with PSD. Seventeen papers reported distinctions in circulating Hcy levels between the PSD and non-PSD groups. Meta-analysis revealed obviously higher circulating Hcy levels in the PSD group than in the non-PSD group (WMD = 1.41, 95% CI: 1.01–1.81, $P < .001$), as shown in Figure 4. Ten publications reported the results of multivariate analysis of circulating Hcy levels on the occurrence of PSD. Heterogeneity existed between studies ($I^2 = 81.4\%$, $P < .001$). Random effects model analysis revealed that circulating Hcy was an independent influence on PSD (ES = 0.07, 95% CI: 0.04–0.09, $P = .011$) (Fig. 5).

3.3. Publication bias

The funnel plot of the difference in circulating Hcy levels between PSD and non-PSD patients is shown in Figure 6, which shows symmetrical, and Egger test shows that the parameters are significant ($P < .05$), implying the existence of publication bias. Egger test results show that the parameters of the difference in circulating Lp-PLA2 level difference, circulating Lp-PLA2 level on PSD occurrence multivariate analysis results, and circulating Hcy level on PSD occurrence multivariate analysis results parameters were not significant, implying that there is no publication bias.

4. Discussion

PSD is intimately linked to the medium- and long-term prognosis of stroke patients, which can affect the way stroke patients cope, hinder neurological and motor recovery, and increase the risk of deterioration. Studies have shown that PSD is linked to disability 5 years after stroke onset, which increases the incidence and severity of disability and reduces quality of life.[32] The presence of suicidal ideation is obviously higher in patients with PSD than in stroke patients without PSD and is an independent risk factor for death in stroke patients.[33] In recent years, the prevention and treatment of PSD has received increased attention in stroke treatment and rehabilitation clinics, and early prediction, diagnosis and intervention are the focus in the field of neurology and rehabilitation. The current study set out to investigate the early prediction and diagnosis of PSD and to evaluate the correlation between circulating

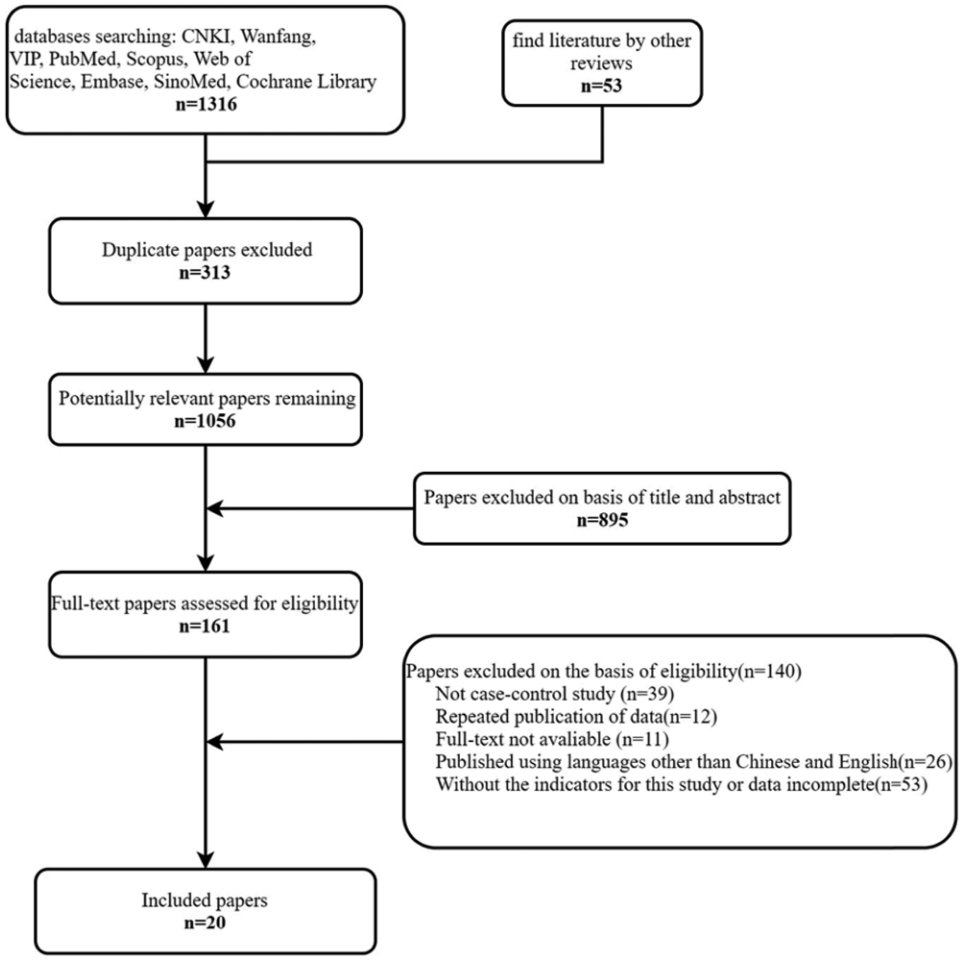

Figure 1. Literature search and screening process.

Table 1

Basic characteristics of the included literature.

Author	Year	Sample	PSD	Non-PSD	Outcomes	NOS
Zhang B	2020	100	32	68	a, b	4
Song J	2022	121	30	91	c, d	6
Wang L	2021	300	99	201	c, d	7
Li YQ	2020	408	162	246	c	6
Ji YH	2015	327	165	162	c	7
Li X	2020	110	40	70	c, d	6
Zhu JY	2021	200	100	100	c	5
He X	2016	213	81	132	c	7
Yang CM	2016	185	75	110	c, d	8
Wang HP	2013	198	102	96	c	5
Ding N	2014	100	41	59	c	8
Liu C	2013	87	49	38	c	7
Tu WJ	2012	82	62	20	c	8
Yan XX	2022	146	73	73	a, b, c, d	6
Zhu SZ	2019	76	46	30	a, b	7
Li Yan	2017	238	65	173	c, d	8
Pascoe MC	2012	149	33	116	d	7
Zhang JY	2022	212	81	131	c	9
Zhao HL	2020	236	55	181	c, d	8
Cheng LS	2018	226	69	157	c, d	6

(a) Circulating Lp-PLA2 levels in PSD and non-PSD groups; (b) multivariate analysis of the effects of circulating Lp-PLA2 levels on PSD; (c) circulating Hcy levels in PSD and non-PSD groups; (d) multivariate analysis of the effects of circulating Lp-PLA2 levels on PSD.

Hcy = homocysteine , Lp-PLA2 = lipoprotein-associated phospholipase A2, PSD = poststroke depression.

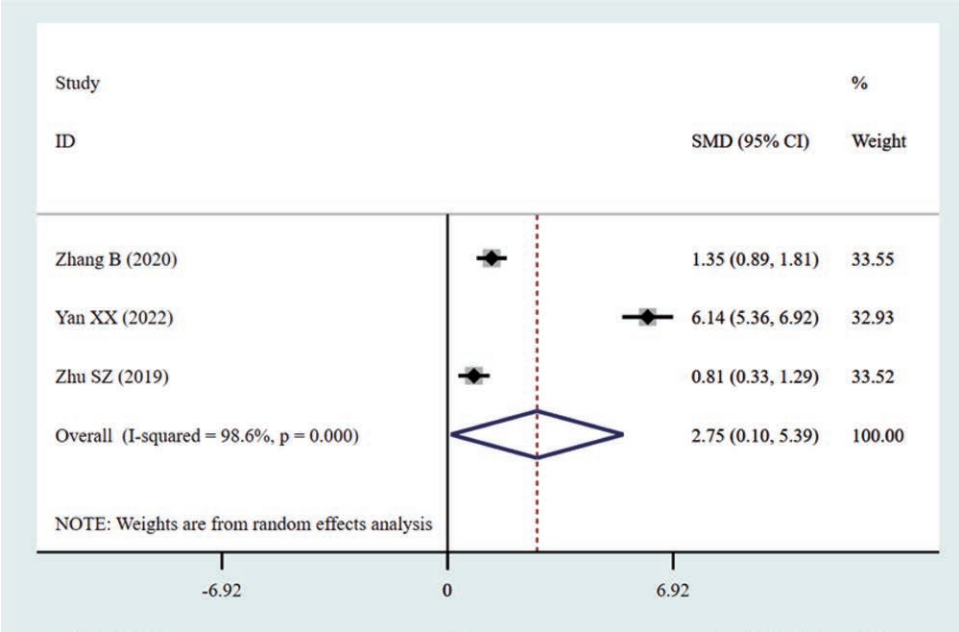

Figure 2. Distinctions in circulating Lp-PLA2 levels between PSD and non-PSD patients. Lp-PLA2 = lipoprotein-associated phospholipase A2, PSD = post-stroke depression.

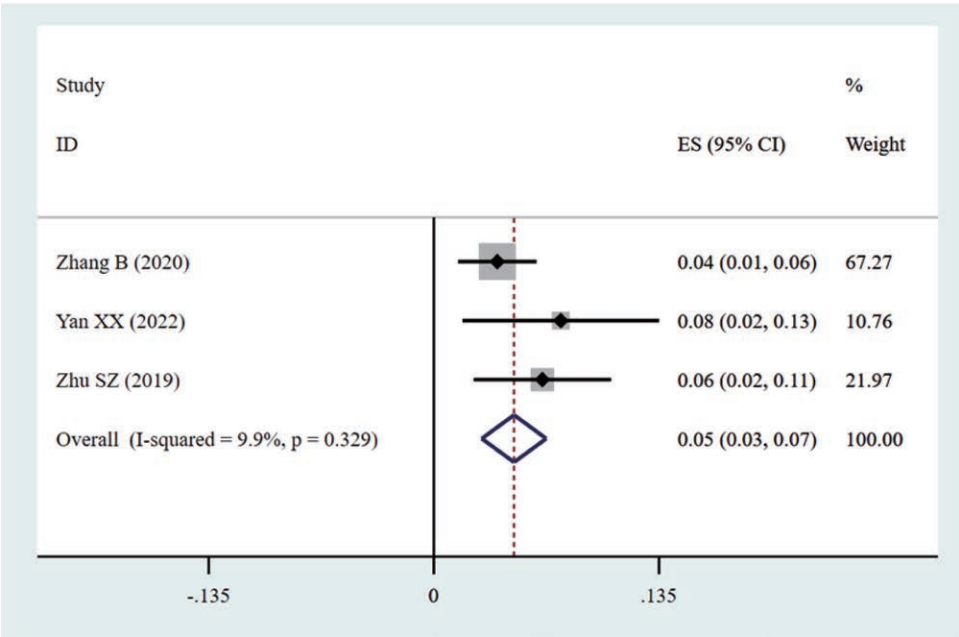

Figure 3. Results of multivariate analysis of correlation between Lp-PLA2 and PSD. Lp-PLA2 = lipoprotein-associated phospholipase A2, PSD = poststroke depression.

Hcy, Lp-PLA2, and the occurrence of PSD. The present study revealed that circulating Hcy and Lp-PLA2 increased obviously in patients with PSD relative to those without PSD in the early post-onset period, and both were independent influencing factors for PSD, implying that both could assist in the early prediction and diagnosis of PSD.

After stroke onset, ischemic and hypoxic lesions become degenerative, edematous, and necrotic, with a strong inflammatory response and oxidative stress damage, both of which can contribute to the development of PSD. On the one hand, inflammatory factors can affect neurotransmitter quantity, function, and transport by acting on monoamine neurotransmitters; on the other hand, inflammatory factors can activate the hypothalamus, pituitary, and adrenal glands and promote cortisol secretion, which can lead to neuronal damage through cytotoxic effects, thus promoting the development of depression.[34] In addition, inflammatory factors can also affect the expression levels of some neurotrophic factors, diminish neurological plasticity, and impede the recovery of its function.[35] PLA2 is a catalytic phosphatidylglycerol molecule hydrolase, which is the rate-limiting enzyme for the production of many active substances such as arachidonic acid, platelet-activating factor, and prostaglandins. As a non-calcium-dependent catalytic serine lipase, Lp-PLA2 is involved in the metabolism of LDL

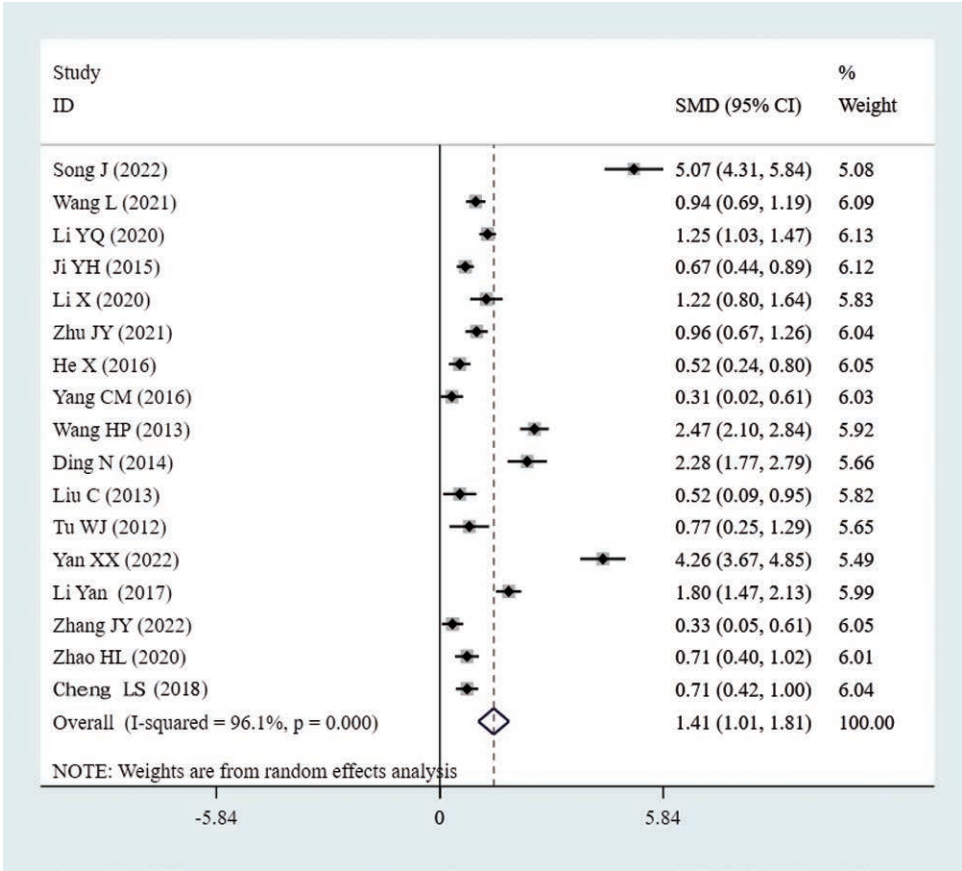

Figure 4. Distinctions in circulating Hcy levels between PSD and non-PSD patients. Hcy = homocysteine, PSD = poststroke depression.

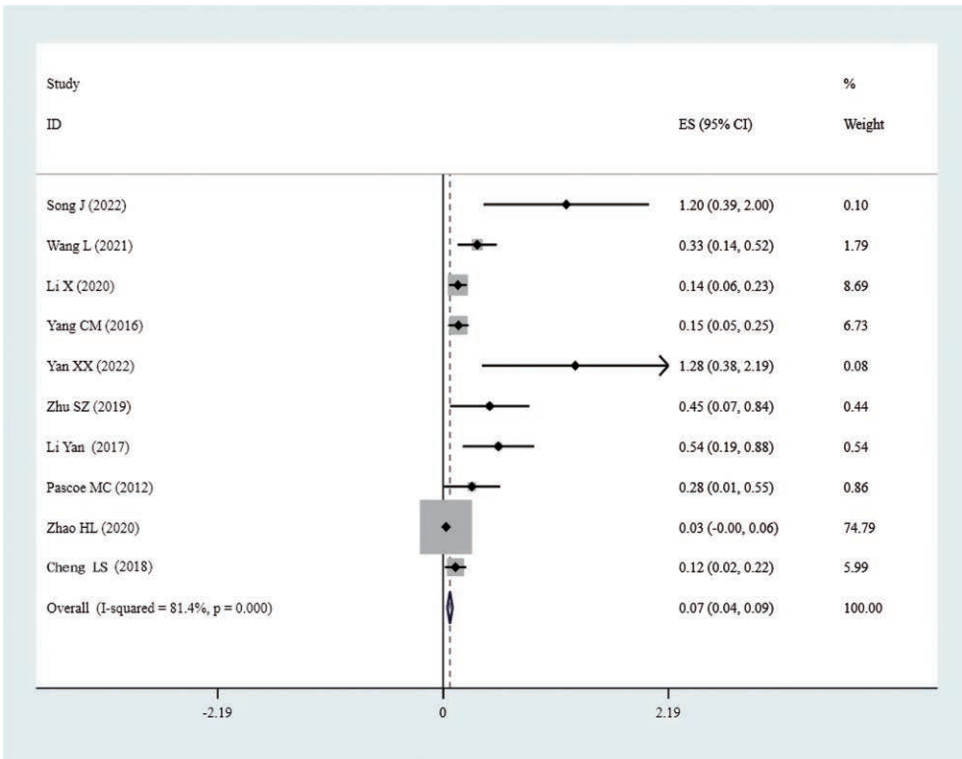

Figure 5. Multivariate analysis of the correlation between Hcy and PSD. Hcy = homocysteine, PSD = poststroke depression.

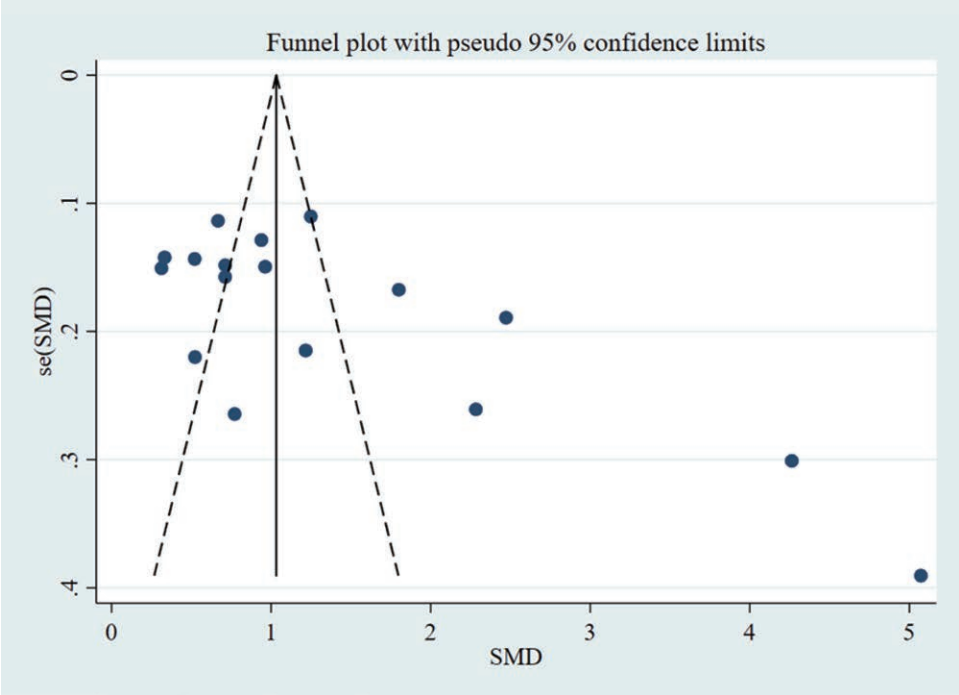

Figure 6. Funnel plot of the difference in circulating Hcy levels between PSD and non-PSD patients. Hcy = homocysteine, PSD = poststroke depression.

to pro-inflammatory mediators and is a novel inflammatory marker. Lp-PLA2 catalyzes the hydrolysis of glycerophospholipid diacyl lipid bonds in lipoproteins and cell membranes.[36,37] The present study revealed that circulating Lp-PLA2 levels were higher in patients with PSD in the early poststroke phase, and multivariate analysis revealed that it was an independent predictor of PSD, implying that patients with high Lp-PLA2 levels are more likely to develop PSD and that it can be applied as a predictor of PSD. Recent studies have also shown that Lp-PLA2 is positively correlated with the degree of neurological deficits in patients with PSD and correlated with the severity of depression,[14,26] further implying its close relationship with the occurrence and progression of PSD.

Hcy is a sulfur-containing amino acid produced by the demethylation of methionine, which is linked to the development of various diseases such as hypertension, type 2 diabetes, and chronic kidney disease. High Hcy can promote the development of atherosclerosis and is an essential risk factor for ischemic stroke.[38] Atherosclerotic plaque rupture and thrombosis are the direct causes of cerebral infarction, and a higher proportion of cerebral infarction emboli originate from carotid atheromatous plaque rupture. Studies have shown that serum Hcy levels are positively correlated with the progression of carotid atherosclerotic lesions, and its possible involvement in carotid atherogenesis and progression.[39] The main mechanisms by which hyper-Hcy promotes atherogenesis and progression include the following[40,41]: (1) cause or aggravate vascular endothelial dysfunction and injury; (2) induce proliferation and migration of vascular smooth muscle cells and promote their calcification; (3) promote platelet aggregation, reduce fibrinogen lysis efficiency and aggravate hypercoagulable state. Therefore, Hcy is widely considered as a biomarker for stroke occurrence and regression. The results of the present analysis revealed that Hcy is linked to the occurrence of PSD, it can be applied as a predictor of PSD, and dynamic monitoring of Hcy has positive significance for the prevention and treatment of PSD. Hcy may contribute to the development of PSD through the following mechanisms[42]: (1) Hcy under normal conditions can generate S adenosylmethionine, which possesses antidepressant effects. In stroke patients, circulating Hcy is abnormally elevated and methylation is inadequate, resulting in reduced S adenosylmethionine production. (2) High Hcy may promote oxidative stress and aggravate neurological damage, and may also aggravate depressive symptoms by affecting neurotransmitters.

In conclusion, circulating Hcy and Lp-PLA2 levels in stroke patients are linked to the occurrence of PSD, and they can be applied as markers for PSD prediction, diagnosis, and monitoring. However, the present study has some restrictions: the literature linked to Lp-PLA2 is insufficient, with only 3 articles, and more studies are needed to provide evidence to support it; most of the literature originated from mainland China, which is not representative enough; the literature included in the correlation analysis of Hcy and PSD has publication bias.

Author contributions

Conceptualization: Yongjun Tao, Wenmin Wang, Jiang Zhao, Xiaohui Xu, Jinfeng Ke, Xiaoyong Ke.
Data curation: Yongjun Tao, Wenmin Wang, Xiaohui Xu, Xiaoyong Ke.
Formal analysis: Yongjun Tao, Wenmin Wang, Jiang Zhao, Xiaohui Xu, Jinfeng Ke, Xiaoyong Ke.
Funding acquisition: Wenmin Wang.
Investigation: Yongjun Tao, Jiang Zhao, Xiaohui Xu, Jinfeng Ke.
Methodology: Wenmin Wang, Xiaoyong Ke.
Project administration: Yongjun Tao, Jiang Zhao, Xiaoyong Ke.
Resources: Wenmin Wang, Jinfeng Ke, Xiaoyong Ke.
Software: Yongjun Tao, Xiaohui Xu.
Supervision: Yongjun Tao, Jiang Zhao, Jinfeng Ke.
Validation: Yongjun Tao, Xiaoyong Ke.
Writing – original draft: Yongjun Tao.
Writing – review & editing: Xiaoyong Ke.

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