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Increased C-Reactive Protein in Patients with Post-Stroke Depression: A Meta-analysis of Cohort Study

ABSTRACT

Background: Pathophysiological mechanisms and related biological markers for post-stroke depression (PSD) are unknown. Some studies have noted that C-reactive protein (CRP) is activated in the serum of PSD patients. We aim to quantitatively summarize the concentrations of CRP in PSD patients compared to non-PSD patients.

Methods: Original studies evaluating the association between CRP and PSD were searched in 4 specific databases from the establishment of the databases to March 2023. RevMan 5.20 and Stata 11.0 statistical software were used for meta-analysis. Publication bias was tested by Egger's test. The CRP level were combined by standardized mean difference (SMD) with 95% confidence interval (CI).

Results: A total of 43 relevant literatures were retrieved, while 13 cohort studies were collected. The heterogeneity test result of the level of CRP in patients with PSD vs. non-PSD was ($Q = 98.38$, $P < .001$, $I^2 = 88\%$). The combined value of the estimated effect was [SMD = 0.34, 95% CI (0.12-0.56); $P = .003$]. Sensitivity analysis indicated that no study had a remarkable influence on the result of the pooled estimate. Egger's test was used to test the bias and the result was (Egger's test, $P = .548$), suggesting that there was no publication bias, and the results were credible. We found that different depression evaluation criteria ($P = .035$) and stroke types ($P = .024$) were considered as influencing factors for potential sources of heterogeneity.

Conclusion: In conclusion, compared to those without depressive symptoms, patients with post-stroke depression have higher concentrations of CRP in the blood.

Keywords: CRP, post-stroke depression, ischemic stroke, meta-analysis

Introduction

Stroke is a complex neurological syndrome caused by a large area of cerebral hypoxia or hemorrhage caused by acute bleeding rupture or obstruction of blood vessels in the brain. Stroke patients' insufficient blood supply and oxygen supply to the brain will cause headache, vomiting, and other clinical manifestations. Long-term ischemia and hypoxia will further damage brain function, and cause paralysis, coma, and brain death. Stroke is characterized by high morbidity, a high disability rate, a high mortality rate, and a high recurrence rate.[1] According to the Chinese Stroke Prevention and Treatment Report in 2019,[2] the lifetime risk of stroke in China is estimated to be about 39.9%, ranking first in the world. Post-stroke depression (PSD) is one of the most common syndromes with a high incidence rate after a stroke. The researchers reported that[3] the incidence rate of PSD was about 31% and could occur at any time within 5 years after a stroke. A study on PSD incidence rate 90 days after a stroke in different races in the United States[4] showed that the incidence of PSD in Mexican Americans and non-Hispanic whites was 30.4% and 20.7%, respectively. This difference was mainly related to sociodemographic factors, disease factors, and especially education. A review of the epidemiology of stroke in Europe[5] reported that 30% to 50% of stroke patients experienced depressive symptoms within the first year after a stroke. Previous studies have confirmed that PSD can increase post-stroke mortality and have a

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negative impact on the survival rate of stroke survivors. Post-stroke depressed patients experience[6] more severe dysfunction, longer hospital stay, poorer rehabilitation outcomes, lower quality of life, and higher mortality in the first year after a stroke compared with the non-depressed stroke patients. Results of an analysis of post-stroke survivors showed a positive correlation between stroke and depression.[7] The results of a study in Iran showed that nearly half of the Iranian stroke patients had PSD. Depressed mood led to decreased treatment compliance and eventually worsened the patient's condition.[8] Therefore, early prediction and recognition of PSD is particularly important.[9,10]

In a recent meta-analysis evaluating the relationship between PSD and the risk of stroke recurrence and mortality, Cai et al[11] included 15 prospective cohort studies with a follow-up period of 1 to 15 years, including a total of 250 294 participants. The results confirmed that PSD was significantly related to elevated mortality among stroke survivors. The results of another meta-analysis on early PSD, namely, the occurrence of depressive symptoms within 3 months after a stroke, and the risk of mortality[12] also confirm that early PSD has a negative impact on the survival rate of stroke patients, but this result is also influenced by gender. Post-stroke depression has also been found to be related to the recurrence rate of stroke, and Sibolt et al[13] have reported that PSD is associated with an increase in the recurrence rate of ischemic stroke (hazard ratio (HR) = 1.68, 95% confidence interval (CI) = 1.07-2.63). At the same time, however, the research results of Ayerbe et al[14] showed that PSD at 3 months was not associated with the risk of all types of stroke recurrence (HR = 0.98, 95% CI = 0.60-1.62).

C-reactive protein (CRP) is a key biomarker for testing the degree of systemic inflammatory reaction.[15] It is a highly conserved protein in phylogeny, commonly found in vertebrates and invertebrates, which also involves systemic inflammatory responses. C-reactive protein synthesis can rapidly increase within hours of tissue injury or infection.[16] A large number of studies[17-21] have shown that CRP is closely related to depression. The study by Kuo et al[22] shows that elevated levels of CRP in the body are associated with an increased history of stroke and the risk of stroke events. At the same time, CRP can also serve as one of the factors affecting the prognosis of acute ischemic stroke.[23,24] The research results of Noonan and other researchers[25] suggest that the CRP concentration in stroke patients is higher than that in healthy individuals within 18 months after a stroke, but this change is not associated with the diagnosis of depression.

Therefore, the level of CRP may be valuable in the diagnosis of PSD and the prognosis of the disease. However, whether there is a difference in CRP levels between PSD patients and non-PSD patients in the acute stage of a stroke is still controversial, and the results of cohort studies on the correlation between CRP concentration and PSD in the acute phase of a stroke are often inconsistent. In this current meta-analysis, we aim to quantitatively investigate the level of CRP of PSD patients compared to non-PSD patients.

MAIN POINTS

- *Differences in depression evaluation criteria and stroke types are fundamentally explained by the high heterogeneity in this meta-analysis.*
- *Higher blood concentrations of CRP in post-stroke depression (PSD) are compared with patients without depressive symptoms.*
- *The level of CRP is important for the diagnosis of PSD and the prognosis of the disease.*

Materials and Methods

Search Strategy

Four unique databases (See Figure 1) were retrieved, and the search strategy is as follows: (C Reactive Protein OR hypersensitive C-reactive protein [hs-CRP]) AND (Strokes OR Cerebrovascular Accident OR Cerebrovascular Accidents OR Post-stroke depression). The retrieval time is through March 2023. Concurrently, the references of relevant reviews were searched manually in the 4 databases to ensure that no articles were omitted, and the original studies published in the literature are also statistically reviewed. The study protocol has not been registered.

Study Selection

Studies which meet the following criteria as well as an information specialist utilizing the PICO framework[26] were identified to be eligible for inclusion: (1) the study patients in the original article were clinically diagnosed as PSD; (2) studies employed patients with PSD as the interventions; (3) studies employed patients with non-PSD as controls; (4) original article contents should include accurately comprehensive statistical data: Sample size, CRP concentration (mean, standard deviation). Exclusion criteria: (1) non-clinical study; (2) incomplete literature data; (3) repeated reports of literature; (4) not find clear outcome observation indicators. Only English language articles were applied.

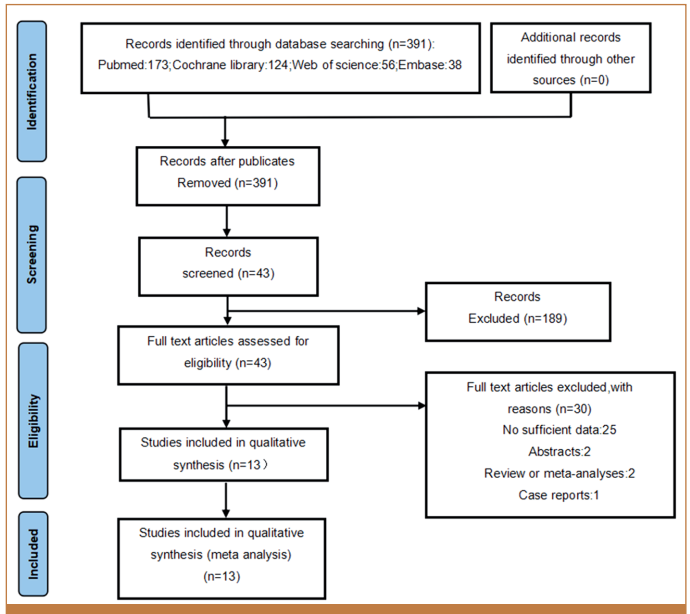

Figure 1. Flow chart of the literature search and study selection. Meta-regression was performed to explore potential sources of heterogeneity using Stata software. We found that different depression evaluation criteria (P = .035) and stroke types (P = .024) were considered as influencing factors for potential sources of heterogeneity.

Table 1. General Characteristics and Information of the Included Studies

Author and Year	Country	Type of Stroke	Stroke Assessment	Depression Assessment	n		CRP Level [Mean (SD), mg/dL]	
					PSD	Non-PSD	PSD	Non-PSD
Cheng SY 2014[29]	China	AIS	WHO-MONICA	DSM-IV (HAMD-17)	70	139	1.47 (1.48)	1.17 (2.51)
Kang Y 2021[41]	China	Ischemic stroke	CT/MRI	Hamilton adulteration scale-24 (HAMD-24) scores ≥ 8	67	96	6.19 (1.00)	4.75 (0.54)
Kowalska K 2020[30]	Poland	Ischemic stroke or TIA	/	DSM-IV (PHQ-9 ≥ 10)	82	224	1.6 (2.23)	1.04 (2.17)
Li Y 2017[32]	China	AIS	CT/MRI	DSM-IV (HAMD-17)	65	173	1.01 (1.1)	0.86 (1.34)
Li YT 2014[31]	China	AIS	WHO-MONICA	DSM-IV	44	147	2.68 (7.49)	1.33 (3.8)
Lu X 2020[33]	China	AIS	WHO-MONICA	BDI-FS ≥ 13	76	234	0.96 (0.74)	0.68 (0.63)
Wang Q 2018[34]	China	AIS	CT/MRI	HAMD-17 ≥ 7	45	107	2.68 (3.01)	3.28 (8.77)
Yang RR 2016[35]	China	AIS	WHO-MONICA	DSM-IV (HAMD-17)	69	157	1.53 (1.1)	1.23 (2.71)
Yin J 2018[36]	China	AIS	MRI	DSM-IV (HAMD-24 ≥ 8)	241	357	3.47 (3.75)	3.94 (8.69)
Yue W 2014[37]	China	AIS	WHO-MONICA	DSM- III- R (HAMD)	60	184	2.14 (3.95)	1.1 (1.53)
Zhang W 2018[38]	China	AIS	WHO-MONICA	DSM- III- R (HAMD)	74	151	1.64 (2.66)	0.82 (1.11)
Zhao H 2020[40]	China	AIS	WHO-MONICA	DSM-IV (HAMD-17 ≥ 8)	55	181	1.52 (1.25)	1.06 (2.03)
Zhu L 2016[39]	China	AIS	/	DSM-IV (HAMD-17 ≥ 7)	56	140	8.86 (12.56)	4.68 (13.51)

AIS, acute ischemic stroke; BDI-FS, Beck Depression Inventory Fast Screen; DSM, Diagnostic and Statistical Manual of Mental Disorders; HAMD, Hamilton Rating Scale for Depression; PHQ-9, Patient Health Questionnaire 9 items; TIA, transient ischemic attack; WHO-MONICA, The World Health Organization Multinational Monitoring of Trends and Determinants in Cardiovascular Disease; CT/MRI, Computed Tomography/Magnetic Resonance Imaging; PSD, post-strokedepression; CRP, C-reactive protein.

Literature Quality Evaluation and Data Extraction

Literature was screened by 2 reviewers independently based on the inclusion and exclusion criteria. If there is a disagreement, the 2 reviewers discuss and negotiate with a third participant to resolve it. We aim to extract the following data: age of subjects and controls, the number of cases and controls, outcomes (the level of CRP) as well as the name of the first author, the time of publication.

The Newcastle–Ottawa Scale[27] was employed to assess the methodological quality of the included papers. Notably, the study reported median and range estimation have been converted to the mean and standard deviation based on Hozo et al.[28]

Statistical Analysis

RevMan version 5.30 software (Cochrane Collaboration, Plano Texas, TX, USA) was implemented to conduct meta-analysis. The effect estimates were pooled by standardized mean difference (SMD) with 95% CI regarding the level of complement C3. The heterogeneity of the researches collected in this meta-analysis was calculated using Cochran *Q* test and I^2 test. Meanwhile, if *P* is <.10, it was indicated that there was heterogeneity across the included studies, so a random effect model was conducted to combine the merged SMD with 95% CI; otherwise, a fixed-effect model was employed. Notably, sensitivity analysis was conducted to test if the results of the meta-analysis are robust. Funnel plot and forest plots were made by using RevMan 5.20 software, and sensitivity analysis and Egger's test were analyzed by Stata 11.0 statistical software (Stata Corp.; USA).

Results

Study Characteristics and Quality Assessment

A total of 43 papers were screened from the 4 databases based on inclusion and exclusion criteria. Finally, 13 prospective cohort studies[29-41] were collected, including 1004 cases in the PSD group and 2290 in the control group. All of the included studies evaluated the association between CRP and PSD. The flow chart of literature screening was shown in Figure 1. The basic information of the 4 included literatures are shown in Table 1 specifically. The outcome of research quality assessment using Newcastle–Ottawa Scale showed that the quality of enrolled studies was moderate to high with a score of 5-7. The Newcastle–Ottawa Scale of included literature is shown in Table 2.

Heterogeneity Test and Estimated Effect Analysis

The heterogeneity test result of the level of CRP in patients with PSD vs. Non-PSD was ($Q = 98.38$, $P < .001$, $I^2 = 88\%$). It was considered that the heterogeneity among the studies was not small, so the random effect model was used to analyze. The combined value of the estimated effect was [SMD = 0.34, 95% CI (0.12-0.56); $P = .003$]. Figures 2 and 3 are forest plot and funnel plot, respectively.

Sensitivity Analysis

Notably, sensitivity analysis was conducted to analyze the stablity of this meta-analysis. The outcomes showed that each study had no significant influence on the conclusion of the pooled effect regarding primary outcomes, suggesting that the robustness of the primary outcome is robust in this meta-analysis (Figure 4).

Bias Analysis

The funnel plot showed that all points were evenly distributed and symmetrical. Egger's test was used to test the bias of this study. The result was (Egger's test, $P = .548$), suggesting that there was no publication bias, and the results were credible.

Meta-regression

Meta-regression was conducted to explore potential heterogeneity using Stata software. We found that different depression evaluation criteria ($P = .035$) and stroke types ($P = .024$) were considered as influencing factors for potential sources of heterogeneity (Figure 1).

Table 2. Study Quality Assessment Based on the Newcastle–Ottawa Scale

Author, Year	Selection				Comparability of Cases	Outcome			
	Adequate Case Definition	Representative of Cases	Selection of Controls	Definition of Controls	and Controls on the Basis of Design of Analysis	Ascertainment of Exposure	Same Method of Ascertainment for Cases and Controls	Non-response Rate	Score
Cheng SY 2014[29]	Yes	Yes	Yes	Yes	Yes	Yes	No	No	6
Kang Y 2021[41]	Yes	Yes	Yes	Yes	Yes	No	Yes	No	6
Kowalska K 2020[30]	Yes	Yes	Yes	Yes	No	No	Yes	No	5
Li Y 2017[32]	Yes	Yes	Yes	Yes	No	No	Yes	No	5
Li YT 2014[31]	Yes	Yes	Yes	No	Yes	Yes	Yes	No	6
Lu X 2020[33]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	6
Wang Q 2018[34]	Yes	Yes	No	Yes	No	Yes	Yes	No	5
Yang RR 2016[35]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7
Yin J 2018[36]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	6
Yue W 2014[37]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
Zhang W 2018[38]	Yes	Yes	Yes	Yes	Yes	No	Yes	No	6
Zhao H 2020[40]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
Zhu L 2016[39]	Yes	Yes	Yes	Yes	Yes	No	Yes	No	6

Discussion

Correlation of C-Reactive Protein Concentrations with Depression After Stroke

Post-stroke depression is an emotional disorder that occurs after a stroke. In addition to conventional symptoms such as physical activity disorders and speech impairments, it also includes low mood, decreased interest, sleep disorders, decreased appetite, difficulty concentrating, and in severe cases, it can even manifest as hallucinations, suicidal tendencies, and other symptoms. Among all the complications of stroke, the global incidence rate of PSD is about 30%.[3] It has seriously affected the prognosis of stroke patients and has brought adverse effects on individuals, families, and the whole society. The CRP is one of the most common biomarkers to evaluate the degree of inflammation.[15] It is a phylogenetically highly conserved protein that is ubiquitous in vertebrates versus invertebrates and is involved in the systemic inflammatory response. C-reactive protein synthesis can rapidly increase[16] within a few hours of tissue injury or infection. A large number of studies[17,18,20,21,46] showed that CRP is closely related to depression; CRP concentrations were associated with depression, and a meta-analysis found that the degree of depression and CRP concentrations were positively associated in both hospital admissions and in the community.[22] Ford et al[43] analysis found that male patients with severe depression were strongly associated with elevated CRP concentrations. And Kuo et al's study[44] showed that increased CRP levels in vivo were associated with an increased risk of stroke history and stroke events. At the same time, CRP can also be used as one of the factors affecting the prognosis of acute ischemic stroke.[23,24] The results of Noonan et al[45] investigators suggest that CRP concentrations in stroke patients are higher than those in healthy groups within 18 months after a stroke, but this change does not affect the diagnosis of depression. However, the results obtained in cohort studies of PSD syndrome and CRP concentrations are often inconsistent, so we chose CRP level as the preferred measure. This meta-analysis included 13 moderate-to-high-quality documents that met the inclusion criteria, which evaluated on the relationship between serum CRP levels and the occurrence of PSD in patients with acute stroke. A total of 3294 patients with acute stroke were included, including 1004 patients with PSD. The incidence rate of PSD was 30.48%, which was basically consistent with the epidemiological survey results of the previous PSD incidence rate.[3] Of the 13 studies, 12 were from China and 1 was from Poland. Kowalska et al[30] found that elevated CRP levels are closely linked to depressive symptoms that occur 8 days after a stroke. However, if depressive symptoms occur 3 months after a stroke, the same conclusion no longer exists. The research results of Yang et al[35] show that when the serum hs-CRP concentration in the acute phase of a stroke is $\geq$ 0.85 mg/dL, the risk of patients being diagnosed with PSD at 6 months after a stroke significantly increases. The results of sensitivity analysis and publication bias analysis confirmed the stability and reliability of this conclusion.

Sarfo et al[46] conducted a study on post-stroke patients at a comprehensive neurological clinic in Ghana, Africa, where a total of 200 cases were collected. The patients were evaluated for depressive symptoms using both the Center for Epidemiologic Studies Depression Scale (CES-D) and the Geriatric Depression Scale (GDS) from the Center for Epidemiologic Studies. The results showed that 78.5% and 42.5%

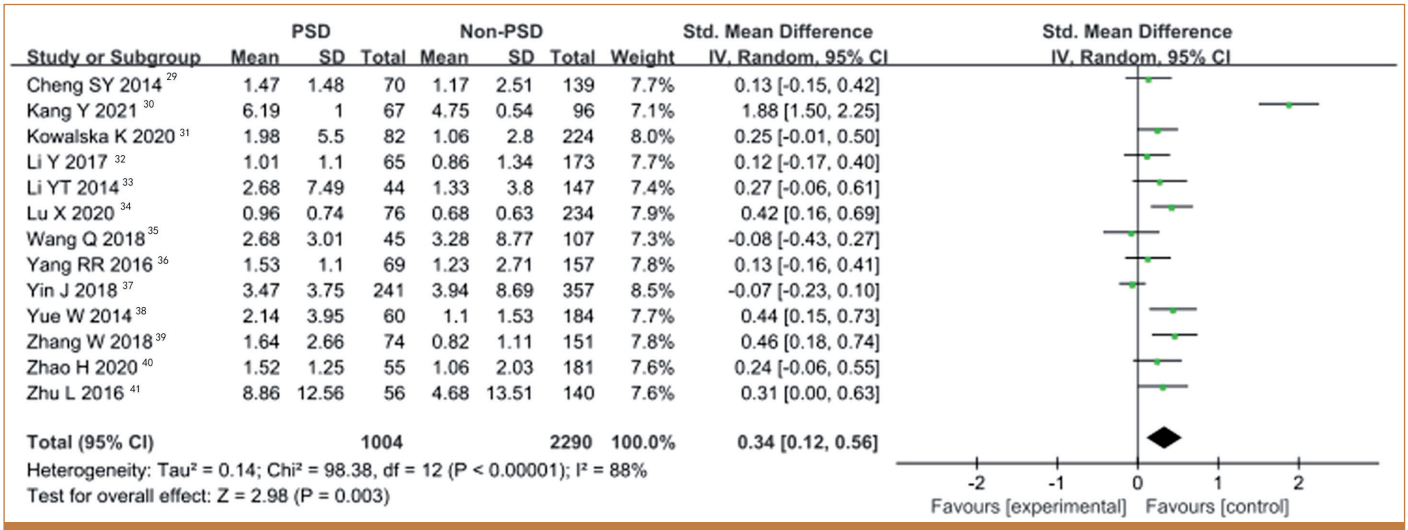

Figure 2. The forest plot of the level of CRP in patients with PSD vs. non-PSD. The result of the heterogeneity test was ($Q = 98.38$, $P < .001$, $I^2 = 88\%$). The combined value of the estimated effect was [SMD = 0.34, 95% CI (0.12-0.56); $P = .003$]. CRP/(mg/dL). CRP, C-reactive protein; PSD, post-stroke depression.

of the patients were evaluated as having depression by CES-D and GDS respectively, and 36.5% of the patients were assessed to have depression symptoms by both scales. In another study conducted in Jordan, a Western Asian country,[47] 198 stroke patients hospitalized in 9 hospitals across the country were included, and 76% of post-stroke patients were reported to have depression, with severe depression affecting as many as 51.6%.

In a review of PSD, Robinson et al[48] summarized the factors affecting PSD, including genetic factors, social and demographic factors, history of mental illness, severity and location of stroke, as well as the presence of functional and cognitive impairments. The meta-analysis results from Taylor-Rowan et al[49] showed that the probability of developing depression after stroke significantly increased for patients with a history of depression before stroke, while Mitchell et al.'s[50] meta-analysis confirmed the above factors as predictors of the risk of PSD. When stroke occurs in the dominant hemisphere, stroke patients develop aphasia, or there is a history of depression or mental illness in the family, the risk of depression in stroke patients will be significantly increased. Good family and social support can reduce the incidence of PSD to some extent.

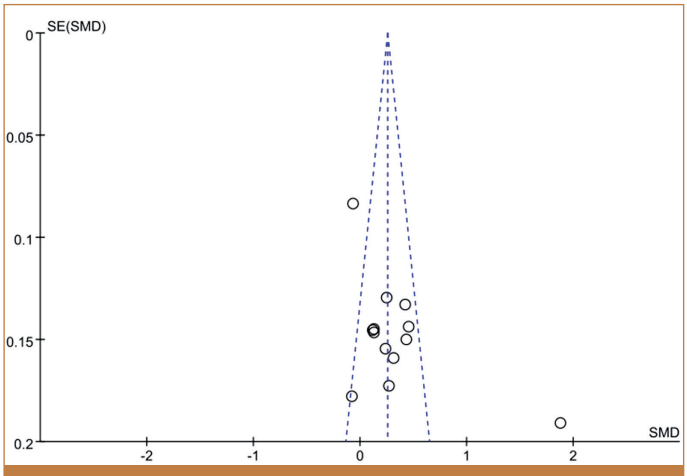

Figure 3. The funnel plot of the level of CRP in patients with PSD vs. non-PSD. CRP, C-reactive protein; PSD, post-stroke depression; SMD, standardized mean difference.

Increased C-Reactive Protein Concentration in the Acute Phase of Stroke Suggests Depression

A large number of studies have confirmed that the pathophysiology of PSD is a complex process involving multiple factors and is the result of the comprehensive effects of biological, psychological, social, and other aspects.[51] The understanding of PSD in modern medicine mostly focuses on 2 major aspects: biological mechanisms and social and psychological mechanisms. Neurotransmitters such as 5-hydroxytryptamine (5-HT), norepinephrine, and acetylcholine have extensive biological activity and play an important role in the development of PSD. In addition, the increase in inflammatory factors leads to inflammatory reactions, extensive activation of indoleamine 2,3-dioxygenase in the cerebral cortex and basal ganglia, reduction of 5-HT production, and PSD production.[5253,54] After a stroke, a large number of inflammatory factors are produced in patients. Animal experiments have confirmed that the antidepressant fluoxetine can play a neuroprotective role in the ischemic brain through anti-inflammatory effects, which can reduce the formation of infarction and alleviate the clinical manifestations of cerebral infarction.[55] At the same time, the hyperactivity of the HPA axis is also related to the intensification of inflammatory reactions.[56] A large amount of glucocorticoids is released, resulting in neuronal atrophy and apoptosis, and decreased neural plasticity.[57,58] In addition, as an excitatory neurotransmitter widely present in the central nervous system, glutamic acid levels in the blood of stroke patients during the acute phase have been proven by multiple studies to be an independent risk factor for PSD. Post-stroke depression is one of the most common emotional disorders after a stroke, and researchers have been working to find reliable biological markers for it. Some potential biomarkers that have been previously reported include brain-derived neurotrophic factor, 5-HT, noncoding RNA, and inflammatory markers such as interleukin 6, Tumor Necrosis Factor Alpha (TNF-α), neutrophil-to-lymphocyte

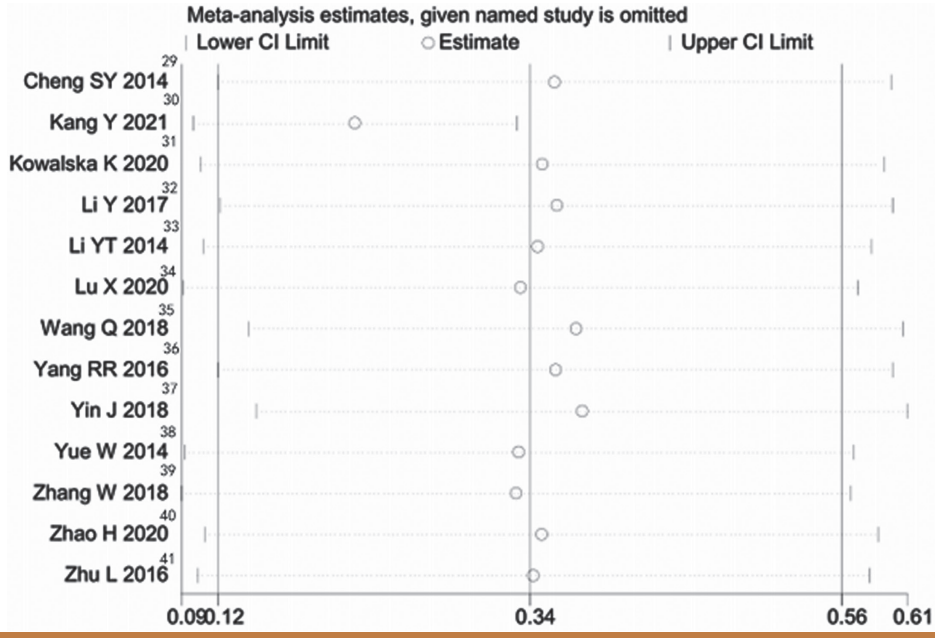

Figure 4. The sensitivity analysis of the enrolled study. No study had a significant influence on the result of the pooled effect regarding primary outcomes. CI; confidence interval.

ratio (NLR) and platelet-to-lymphocyte ratio (PLR) and others.[59,60,61] Some studies have revealed that the CRP concentration in the acute phase of a stroke is an independent risk factor for PSD; among them, Kowalska et al[30] found that the increase in CRP level in the acute phase was closely related to the depressive symptoms produced at 8 days after a stroke, but if the depressive symptoms appeared at 3 months after a stroke, the same conclusion disappeared. The findings of Yang et al[35] showed that when the serum hs-CRP concentration was 0.85 mg/dL in the acute phase of a stroke, the risk of PSD at 6 months after a stroke increased significantly. In addition,[36] it was confirmed that homocysteine in the acute phase and CRP in the stroke could predict the occurrence of PSD. The results of this meta-analysis confirm this conclusion again. At the same time, PSD has a negative impact on the survival rate of stroke patients,[12,62] so high levels of CRP concentration in the acute phase of a stroke also indicate the possibility of a poor prognosis in patients. Stroke inflammatory response is the main type of nerve injury, and CRP as a highly sensitive acute-phase protein is not only is closely related to the degree of nerve injury in a stroke, but also can reflect the brain microinflammation, is considered to predict acute stroke patients' fatigue,[63] cognitive impairment,[64] death risk, and long-term recovery of.[65] Post-stroke depression is not only a depression caused by factors induced by brain injury but also related to the psychological response mechanism of patients. Some studies have shown that PSD[66] often occurs even in mild strokes. Therefore, the severity of a stroke can be predicted according to the CRP level and PSD occurrence.

At the same time, the high heterogeneity is also worth further exploration. The results of regression analysis indicate that differences in depression evaluation criteria, and stroke types are the underlying reasons for the high heterogeneity in this meta-analysis. The differences in the diagnostic criteria for PSD were noted in various studies. In 10 studies, [29-32,35-40] the depressive symptoms of stroke patients were evaluated according to the Diagnostic and Statistical Manual for Mental Disorders, while the diagnosis of PSD was conducted according to other diagnostic criteria in 3 studies.[33,34,41] Due to differences in the diagnosis of depressive symptoms, the inclusion criteria for PSD patients in various studies are different, which has a significant impact on the heterogeneity of research results. Notably, the inclusion of patient stroke types in the study is also not entirely consistent, with all of the stroke types in 20 studies being acute ischemic stroke, while the other one[30] also includes patients with ischemic stroke or transient ischemic attack.

Limitations

This meta-analysis has the following limitations: First, the results of CRP in patients' blood were tested by various methods. Second, the source of research is not rich enough. Of the 13 studies we included, 12 were from China, which means that more research is needed to demonstrate the universal applicability of the conclusions of this meta-analysis across all ethnic groups. Third, no data were extracted for potential covariates that could be used for the meta-regression analysis. Finally, as a post-stroke emotional disorder, PSD affects approximately 31% of patients with depressive symptoms within 5 years after a stroke. However, in the studies we included, the longest follow-up time is 1 year. Therefore, studies with a longer follow-up time are needed.

In conclusion, compared to those without depressive symptoms, patients with PSD have higher concentrations of CRP in the blood during the acute phase of stroke.

Availability of Data and Materials: *Data to support the findings of this study are available on reasonable request from the corresponding author.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept – W.C., X.W.; Design – W.C., X.W.; Supervision – S.X.; Resources – N/A; Materials – W.C., X.W., S.X.; Data Collection and/or*

Processing – W.C., X.W., S.X.; Analysis and/or Interpretation – S.X.; Literature Search – W.C.; Writing – W.C., X.W., S.X.; Critical Review – S.X.

Declaration of Interests: The authors have no conflict of interest to declare.

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